U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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|---|---|
| **NDA #:** | 21-372 |
| **Supplement #:** | 018 & 019 |
| **Drug Name:** | Aloxi (Palonosetron HCI) Injection |
| **Indication(s):** | Prevention of PONV & CINV |
| **Applicant:** | Helsinn Healthcare SA |
| **Date(s):** | |
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**Keywords:** NDA review, clinical study (pediatrics), non-inferiority

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# 1 EXECUTIVE SUMMARY

The sponsor has submitted two efficacy supplements to fulfill the requirements of Written Requests for pediatric studies of palonosetron hydrochloride I.V. (Aloxi). A single, principle efficacy study was reviewed for the each of two pediatric indications: prevention of post-operative nausea and vomiting (PONV) and prevention of chemotherapy-induced nausea and vomiting (CINV). Both studies were design to demonstrate the non-inferiority of Aloxi to ondansetron.

**Study PALO-10-14 (PONV)**
Study PALO-10-14 did not show Aloxi to be non-inferior to ondansetron for treatment of PONV based on the primary efficacy endpoint of complete response (CR) and a non-inferiority margin of 10%. The treatment difference (palonosetron minus ondansetron) was -4%, and the 95% CI of the difference was (-10.5%, 1.6%).

The sponsor acknowledged that a non-inferiority margin of 10% was not validated for the secondary endpoint comparisons, but the failure of the primary comparison would have precluded any subsequent hypothesis testing regardless.

**Study PALO-10-20 (CINV)**
In Study PALO-10-20, two dose levels of Aloxi (10 mcg/kg and 20 mcg/kg).were compared to ondansetron using a primary endpoint of CR during the Acute Phase (0-24 hours) of the first treatment cycle. Only Aloxi 20 was found to be non-inferior to ondansetron based on a 97.5% CI (as a consequence of the two comparisons) and a margin of 15%. The treatment difference (Aloxi 20 minus ondansetron was 1% and the 95% CI of the difference was (-11%, 13%).

Important secondary endpoints were CR in the Delayed Phase (24-120 hours) and CR in the Overall Phase (0-120 hours). Aloxi 20 showed results numerically similar to ondansetron for these endpoints, however, the non-inferiority margin for secondary endpoint comparisons was not justified and cannot be deemed valid. Thus these results cannot support a clinical benefit claim in the labeling package.

# 2 INTRODUCTION

Palonosetron hydrochloride (Aloxi, 0.25 mg IV)) has been marketed in the U.S. since 2003 for the prevention of chemotherapy induced nausea and vomiting (CINV) in adults following initial and repeated courses of moderately or highly emetogenic chemotherapy (MEC/HEC

Palonosetron hydrochloride 0.075mg was approved for marketing in the U.S. in 2008 for the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours after surgery in adults.

At the pre-sNDA meeting held Dec 4, 2012, the sponsor agreed to submit the applications in accordance with CDISC standards.

## 2.1 Overview

Helsinn Healthcare submitted two efficacy supplements to fulfill the requirements of Written Requests (WR) for pediatric studies of palonosetron I.V., issued by the Agency in 2010. Two

pediatric clinical trials were conducted for the each of two indications: prevention of PONV and prevention of CINV.

NDA 21372/ S-018 proposes the indication for prevention of PONV for up to 24 hours following surgery in patients less than 18 years of age. The sNDA contains clinical trial reports and supporting data for studies PALO-10-14 and PALO-07-29.

NDA 21372/S-019 proposes the indication for prevention of CINV in pediatric patients 1 month and older. It contains study reports and supporting data for studies PALO-10-20 and PALO-99-07.

Studies PALO-10-14 and PALO-10-20 represent adequate and well-controlled studies with inferential statistical analyses, and they will be the focus of the statistical assessment. Studies PALO-07-29C and PALO-99-07 are exploratory studies for efficacy and pharmacokinetics and are not part of this review.

The table below shows a brief description of the two principle studies:

**Table 1: A Brief Description of the Two Pivotal Studies**

| Study Type<br>Study No. | Study Objective(s) | Study Design | Key inclusion criteria | Sample Size<br>Gender<br>Age Range (yrs) | Treatment |
|---|---|---|---|---|---|
| PALO-10-14 | Efficacy and Safety in PONV pediatric patients | Phase 3, multicenter, randomized (1:1), active-controlled, double-blind, double-dummy, parallel group, stratified by age group | Pediatric patients undergoing surgical elective procedures requiring general IV anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia | 670 randomized<br>661 treated<br>400M/261F<br>7.63 y (0.08 - 16.97) | Single IV palonosetron 1 mcg/kg, max 0.075 mg<br><br>Ondansetron IV: 0.1 mg/kg, max 4 mg |

IV=intravenous; M=male; F=female;

| Study Type<br>Study No. | Study Objective(s) | Study Design | Key inclusion criteria | Sample Size<br>Gender<br>Age Range (yrs) | Treatment |
|---|---|---|---|---|---|
| PALO-10-20 | Efficacy, Safety, Tolerability and Pharmacokinetics | Randomized, active-controlled, double-blind, double-dummy, parallel group (3 group), non-inferiority active-control, stratified by age and emetogenicity, repeat cycle. | Pediatric cancer patients full term neonates to <17 years of age receiving MEC or HEC. | 502 randomized<br>494 treated<br>263M/231F<br>0.2-16.9 yrs | Single IV by 15 min infusion<br>palonosetron 10 mcg/kg (max 0.75 mg)<br>palonosetron 20 mcg/kg (max 1.5 mg)<br>ondansetron 0.15 mg/kg 3 single doses (max 32 mg)[c] |

[a]: 71 patients randomized in the double-blind phase, 12 patents assigned in the open-label cohort.
[b]: First 3 mcg/kg IV Palonosetron cohort, then 10 µg/kg IV Palonosetron cohort, in two sequential single rising dose cohorts groups of n=6 each.
[c]: Ondansetron was re-administered 4 hours and 8 hours after the first study dose administration.
IV = intravenous; M = male; F = female; MEC = moderately emetogenic chemotherapy, HEC = highly emetogenic chemotherapy.

### 2.2 Data Sources

All data was supplied electronically by the applicant as SAS transport files and can be found in the CDER electronic document room (EDR):
\\Cdsesub1\evsprod\NDA021372\0295 and \\Cdsesub1\evsprod\NDA021372\0296.

## 3 STATISTICAL EVALUATION

### 3.1 Study PALO-10-14

#### 3.1.1 Study Objectives

The primary objective of this study was to evaluate the efficacy of a single palonosetron IV dose compared to a single ondansetron IV dose in the prevention of postoperative nausea and vomiting (PONV) through 24 hours after surgery in children aged from 0 up to 16 years undergoing elective surgical procedures requiring general intravenous anesthesia.

The secondary objective was to evaluate the safety and tolerability of palonosetron IV in pediatric patients.

#### 3.1.2 Study Design and Endpoints

This was a multicenter, active controlled, double-blind, double-dummy, randomized, parallel group, age stratified, phase 3 study involving 2 study groups receiving intravenous (IV) palonosetron or IV ondansetron standard therapy. The palonosetron dose was 1 mcg/kg (up to a maximum of 0.075 mg based on body weight) and the ondansetron dose was 0.1 mg/kg (up to a maximum dose of 4 mg based on body weight and age).

The target population was pediatric patients aged from 28 days to 16 years with American Society of Anesthesiologists (ASA) physical status I, II or III, who were scheduled to undergo elective surgical procedures categorized in the protocol requiring general intravenous anesthesia and who were scheduled to receive nitrous oxide during the maintenance phase of anesthesia.

A single dose of study drug was administered on Day 1. The planned duration of study participation for an individual patient was a maximum of 32 days, which included screening, treatment with study drug and surgery, visit after surgery, final study visit and a follow-up telephone contact.

Patients were stratified by age groups (<2 years, 2 to <6 years, 6 to <12 years, 12 to <17 years). Within each stratum, patients were randomized prior to study drug administration to receive one of the two treatments. For each age group, patients were randomized to balance over all study sites rather than for individual sites.

**Primary and Secondary Efficacy Endpoints**
The primary efficacy analysis endpoint was the proportion of patients showing Complete Response (CR); defined as no vomiting, no retching (no emetic episodes), and no use of rescue medication

during the first 24 hours postoperatively, starting at T0 (when the patient woke up and was able to show any active reaction).

An emetic episode was defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Regurgitation (for babies) was a physiological event not considered as a vomit.

T0 was defined as the time of start of administration of the most emetogenic chemotherapy agent (highly or moderately emetogenic) on Day 1 of each cycle.

The secondary efficacy analysis endpoints were:

• Proportion of patients with no vomiting.
• Proportion of patients without emetic episode.
• Proportion of patients without antiemetic rescue medication.
• Proportion of patients without nausea (patients aged ≥6 years).
• Time to first vomiting.
• Time to first emetic episode.
• Time to first administration of rescue medication.

The sponsor had not planned an adjustment for the comparisons of the multiple secondary endpoints to control the study-wise type I error rate. In addition, the sponsor acknowledged in the CSR that the 10% non-inferiority margin could not be considered valid for the secondary endpoints. In this review, results for the first four secondary endpoints are presented in a descriptive fashion. Results for the time-to-event endpoints are not considered informative and are not discussed.

**Analysis Populations**
The following analysis populations were defined in the Statistical Analysis Plan (SAP):

- The randomized population included all randomized patients.

- The primary analysis was based on the Full Analysis Set (FAS). The FAS included all randomized patients who received the active study drug, general anesthesia and surgery (evaluable patients). Following the intent-to-treat principle, patients were assigned to the study treatment arm according to their randomized treatment.

- The Per Protocol population was a subset of the FAS. After data cleaning, a blinded review of the data was performed in order to define the violations leading to exclusions from the PP. All per protocol criteria were documented by the sponsor.

- The As-Treated population included all randomized patients who received the active study drug, general anesthesia and surgery (evaluable patients), with each patient being assigned to the treatment actually received.

- The Safety Population (SAF) included all randomized patients receiving at least one study treatment and having at least one post-treatment safety assessment.

### 3.1.3 Statistical Methods

The Agency's Written Request (WR) specified that the study enroll a sufficient number of patients to provide at least 80% power at a (two-sided) alpha level of 5% to reject the null hypothesis that the study drug is inferior to active control drug by more than a 10% non-inferiority margin. The Agency concurred with the study protocol (letter dated 26 April 11). The sponsor incorporated the necessary assumptions for the sample size and to achieve their statistical objective.

The primary efficacy objective was to demonstrate the non-inferiority of palonosetron compared to ondansetron in terms of proportion of patients reporting CR in the time interval 0-24 hours after the patient wakes up ($T_0$).

The null hypothesis ($H_0$) was written as:

$$H_0: CR_{\text{0-24 hr palonosetron}} - CR_{\text{0-24 hr ondansetron}} \leq -10\%$$
$$H_1: CR_{\text{0-24 hr palonosetron}} - CR_{\text{0-24 hr ondansetron}} > -10\%$$

The difference between treatments was analyzed as "palonosetron IV minus ondansetron IV". In order to provide substantial evidence of efficacy, the primary efficacy analyses was to demonstrate rejection of the null hypothesis. The rejection of the null hypothesis was to be demonstrated by showing that the lower confidence bound of the CI of the difference between treatments is greater than -10%.

For the primary efficacy analysis the sponsor calculated the confidence interval (CI) on the FAS using the stratum adjusted Mantel-Haenszel (MH) method with a continuity correction applied. Supportive primary analyses using alternative statistical methods were also conducted. The sponsor did not provide rationale or historical evidence for choosing a margin of 10%. The margin, was however, agreed to by the Agency and is not inconsistent with margins used in adult studies.

In the protocol, the sponsor had stated that although the study is a multicenter study, center would not be included either as a stratification factor in the randomization or as a factor in the analysis. As only one stratification factor (age) was to be applied.

The FAS was the primary population for efficacy analyses. In addition, the primary efficacy endpoint was analyzed for the PP and the "as-treated" populations. Analyses of the secondary efficacy endpoints were performed for the FAS only.

For the primary analysis, values for missing binary outcomes (e.g., presence or absence of retching, vomiting, or nausea), were defined consistent with lack of efficacy.

Planned analyses for secondary endpoints (proportions) were similar to that for the primary endpoint.

**Determination of Sample Size**
The study was planned to enroll 660 patients (330 patients in each treatment arm). The sample size was based on the assumption of a CR rate in the 0-24 hours time interval of 70% in the palonosetron and ondansetron groups. Sponsor stated that for a non-inferiority test using a type I error equal to

0.025 (one sided), a sample size of 330 evaluable patients per group provides a power of 80% to show that the lower bound of the CI of the difference (CR 0-24 hr palonosetron - CR 0-24 hr ondansetron ) is greater than -10%.

### 3.1.4 Study Results

**Number of Subjects**
In total, 670 patients were randomized, of which 9 subjects were not treated due to the occurrence of vomiting prior to study drug administration (143-1026, 143-1044), administration of prohibited anesthetics (161-1153), cancelled surgery (172-1346), respiratory tract obstruction developed during premedication procedures (122-1422), and refusal by the anesthesiologist to follow the protocol (164-1567, 167-1055). A specific reason for not administering study drug was not given for 2 patients (164-1175, 164-1184) randomized to Palonosetron.

**Patient Disposition**
A total of 661 subjects were evaluable (randomized patients who received active study drug, general anesthesia and surgery). Six of the discontinued subjects were from US (4 in the palonosetron arm and 2 in ondansetron arm). The Full Analysis Set (FAS) included 661 patients who received the active study drug (331 palonosetron, 330 ondansetron). Safety Population (SAF) included the same number of patients.

**Table 2: Patient Disposition (Study PALO 10-14)**

| | Palonosetron n=336 | Ondansetron n=334 | |
|---|---|---|---|
| Randomized | 336 (100%) | 334 (100%) | 670 (100%) |
| Not Treated | 5 (1.5%) | 4 (1.2%) | 9 (1.3%) |
| Treated | 331 (98.5%) | 330 (98.8%) | 661 (98.7%) |
| Completer | 326 (97.0%) | 329 (98.5%) | 655 (97.8%) |
| Drop-Outs | 5/331=1.5% | 1/330=0.3% | 6/661=0.9% |
| Reason for Termination | | | |
| Adverse Event | 0 | 1 (0.3%) | 1 (0.1%) |
| Death | 0 | 0 | 0 |
| Protocol Violation | 0 | 0 | 0 |
| Lost to Follow-Up | 4 (1.2%) | 0 | 4 (0.6%) |
| Withdrawal of Consent | 1 (0.3%) | 0 | 1 (0.1%) |
| Lack of Efficacy | 0 | 0 | 0 |

Source: Reviewer

As it is seen in the Table above, more subjects dropped-out of the study in palonosetron arm (1.5%) than in ondansetron (0.3%).

No drop-outs due to lack of efficacy were reported. A total of twenty nine subjects were not included in the per-protocol analyses.

The sponsor determined that for 12 subjects (4 palonosetron and 8 ondansetron) data were potentially un-blinded, and the sponsor identified a modified FAS excluding these subjects for additional sensitivity analysis.

**Demographics and Baseline Characteristics**
The number of patients randomized to each treatment arm and included in the FAS was similar within age groups; however, patient numbers in the FAS were not balanced across age groups. Enrollment was largest in the 2 to 5 years and 6 to 11 years age groups, which included 247 (37.3%) and 234 (35.4%) patients, respectively. The 12 to 16 years age group included 134 (20.3%) patients. The under 2 year age group was the least represented with 46 (7.0%) patients in this age group being included in the FAS.

The study included more males (60.5%) than females (39.5%), and the age ranged from 30 days to 16.9 years. Most patients were white, not Hispanic/Latino (88.8%), white, Hispanic/Latino (6.1%) or Black or African American, not Hispanic/Latino (3.6%). With the exception of 1 Asian patient enrolled in Russia, all non-white patients were enrolled in the US.

The gender distribution for the FAS was 60.5% males and 39.5% females. The percentage of male patients was highest in the under 2 year age group (76.1%) and progressively decreased to 64.8%, 59.4%, and 49.3% in the 2 to 5 years, 6 to 11 years, and 12 to 16 years age groups, respectively. The percentage of males was similar between treatments in each age group except the under 2years age group (81.8% Palonosetron vs. 70.8% Ondansetron).

For each age group, the demographic characteristics were comparable between treatments.

**Analysis of the Primary Efficacy Endpoint**
A summary of FAS, PP and sensitivity analysis of the primary efficacy variable is presented in the Table 3, below. For the primary efficacy endpoint of CR at 24 hours, the lower confidence bound of the CI of the difference in treatment group results was -10.5% and thus statistical non-inferiority of Aloxi to ondansetron based on a non-inferiority margin of 10% was not demonstrated. In addition, the analysis of the PP population, as well as the sensitivity analysis did not support non-inferiority of Aloxi to ondansetron.

In the reviewer's sensitivity analysis, 4 subjects in the Aloxi group who terminated early were assigned as treatment failures, whereas in the FAS analysis, these subjects were counted as successes. The results based on the modified FAS population as well as the results based on the As-treated population are not shown here but are consistent with those based on the FAS.

**Table 3: Analyses of Efficacy (Complete Response), (Study PALO 10-14)**

| Population | Aloxi n/N (%) | Ondansetron n/N (%) | Difference (95% CI ) Aloxi - Ondansetron |
|---|---|---|---|
| FAS | 259/331 (78.3) | 273/330 (82.7) | -4% (-10.5%, 1.6%) |
| PP | 254/320 (79.4) | 262/312 (84.0) | -5% (-10.6%, 1.4%) |
| Sensitivity (drop-outs= no cr) | 255/331 (77.0) | 273/330 (82.7) | -6% (-11.8%, 0.4%) |

Source: Reviewer

The results in Table 3 are consistent with the results presented by the sponsor.

**Analysis of the Secondary Endpoints**
The results for the key secondary endpoints are presented below. The lower bounds of the 95% CI of the difference between the treatment arms ranged from -6% to -10%. As mentioned above, the sponsor had not considered an adjustment for the comparisons of multiple secondary endpoints to control the study-wise type I error rate and recognized that the margin was not valid for hypothesis testing. These comparisons can only be considered exploratory.

**Table 4: Analyses of Secondary Endpoints (Study PALO 10-14)**

| Key Secondary Endpoints | Aloxi n/N (%) | Ondansetron n/N (%) | Difference (95% CI) Aloxi - Ondansetron |
|---|---|---|---|
| No Vomiting | 275/331 (83.1) | 289/330 (87.6) | -4% (-10%, 1%) |
| No Emetic Episode | 265/331 (80.1) | 277/330 (83.9) | -4% (-10%, 2%) |
| No Nausea in Subjects ≥ 6 | 154/185 (83.2) | 150/183 (82.0) | 1% (-6%, 9%) |
| No Rescue Medication | 308/331 (93 | 318/330 (96.4) | -3% (-7%, 0.1%) |

Source: Reviewer

These results are consistent with those of the sponsor.

## 3.2 Study PALO-10-20

### 3.2.1 Study Objectives

The primary objective of this study was to evaluate the efficacy of two different doses of intravenous (IV) Palonosetron, compared to Ondansetron in the prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in pediatric patients receiving Moderately Emetogenic Chemotherapy (MEC) or Highly Emetogenic Chemotherapy (HEC) through 120 hours after the start of chemotherapy in single and repeated chemotherapy cycles.

The secondary objectives of this study were to evaluate the safety and tolerability of IV palonosetron in pediatric patients and to evaluate the pharmacokinetics of IV palonosetron in a subset of pediatric patients receiving MEC or HEC.

### 3.2.2 Study Design and Endpoints

This was a multicenter, active-controlled, double-blind, randomized, parallel group, stratified, double-dummy, phase 3 study involving three study groups receiving palonosetron in two different doses (the lower palonosetron dose was 10 mcg/kg up to a maximum of 0.75 mg and the higher palonosetron dose was 20 mcg/kg up to a maximum dose of 1.50 mg) or ondansetron standard therapy (the ondansetron dose was 0.15 mg/kg given three times (every 4 hours - maximum dose of 32 mg)) for the prevention of CINV. Study drug could be administered for up to four cycles of HEC or MEC.

Patients could remain in the study for up to four chemotherapy cycles. The planned duration of the study was a maximum of 32 days for the first study cycle, which included screening up to 14 days before randomization (up to 7 days for patients aged <2 years), the day of randomization, administration of study drug and chemotherapy (Study Day 1), and the control visits (Study Days 2 to 6). The final Visit was between Day 7 and Day 10, with a follow-up telephone contact between Day

15 and Day 18. The maximum duration of each of the subsequent cycles was 21 days. For patients undergoing multiple cycles the total study duration could be up to 16.5 weeks. Subjects with ongoing AEs at the follow-up visit and subjects who reported a SAE within 30 days after the last study drug administration were to be followed-up as necessary until the AE or SAE resolved or stabilized.

Patients were stratified by emetogenicity (HEC/MEC) and by the following age groups:
• <2 years
• 2 years to <6 years
• 6 years to <12 years
• 12 years to <17 years

Within each stratum, patients were randomized prior to study drug administration to receive one of the three treatments. In order to maintain the blind, patients randomized to either palonosetron dose also received placebo to ondansetron, and patients randomized to receive ondansetron also received placebo to palonosetron. Study treatments were:

Group 1: palonosetron 10 mcg/kg – active palonosetron and placebo to ondansetron
Group 2: palonosetron 20 mcg/kg – active palonosetron and placebo to ondansetron
Group 3: ondansetron – active ondansetron and placebo to palonosetron

Study drug was administered on Day 1 for up to four study cycles. The planned duration of the study was a maximum of 32 days for the first study cycle, which included screening up to 14 days before randomization (up to 7 days for patients aged <2 years), the day of randomization, administration of study drug and chemotherapy (Study Day 1), and the control visits (Study Days 2 to 6). The final Visit was between Day 7 and Day 10, and a follow up telephone contact between Day 15 and Day 18. The maximum duration of each of the subsequent cycles was 21 days. For patients undergoing multiple cycles the total study duration could be up to 16.5 weeks.

The focus of this review is only on the results of the first treatment cycle. Results from subsequent cycles are considered exploratory only.

**Primary and Secondary Efficacy Endpoints**
The primary efficacy analysis endpoint was the proportion of patients showing Complete Response (CR) defined as no vomiting, no retching, and no use of antiemetic rescue medication from 0 to 24 hours (Acute phase) after T0 (start of administration of the most emetogenic chemotherapy) during the first cycle.

The key secondary endpoint was the proportion of patients with CR from 24 to 120 hours (Delayed phase) after $T_0$. The proportion of patients with CR from 0 to 120 hours (Overall Phase) was also evaluated as a secondary endpoint.

Additional secondary endpoints, each defined for the Acute, Delayed and Overall periods, are listed below:

- Proportion of patients without vomiting
- Proportion of patients without emetic episodes
- Proportion of patients without antiemetic rescue medication

- Proportion of patients without nausea (patients aged ≥6 years)
- Time to first vomiting
- Time to first emetic episode
- Time to first administration of antiemetic rescue medication

This review addresses only the primary and key secondary outcomes. Results for the additional secondary endpoints listed above and results for treatment cycles 2-4 are not presented. The reader is referred to the CSR for a summary of these exploratory comparisons.

**Analysis Populations**
The following analysis populations were defined in the SAP:

- The Randomized Population included all randomized patients.

- The FAS included all randomized patients receiving the active study drug and HEC or MEC. Following the intent-to-treat principle, patients were assigned to the study treatment group according to their randomized treatment.

- The Per Protocol (PP) population was a subset of the FAS. After data cleaning, a blinded review of the data was performed in order to define the violations leading to exclusion from the PP. For the purpose of the analysis the PP was defined only for the first cycle.

- The As-Treated population included all randomized patients receiving the active study drug and HEC or MEC (evaluable patients) and each patient was assigned to the treatment actually received.

- The Safety Population (SAF) included all randomized patients receiving at least one study treatment and having at least one post-treatment safety assessment.

### 3.2.3 Statistical Methods

The primary efficacy analysis was based on the proportion of patients showing Complete Response (CR) during the acute phase in the first chemotherapy cycle. To show non-inferiority of palonosetron versus the comparator, at least one of the two doses of palonosetron was to have the lower bound of the two-sided 97.5% confidence interval of the difference in proportions (palonosetron minus ondansetron) greater than -15%.

The choice of 97.5% for the CI was based on a Bonferroni adjustment to account for the two dose-level comparisons.

Indicating $\pi_T$ and $\pi_R$ as the proportions of patients showing CR in the test (palonosetron) and reference (ondansetron) treatments respectively and based on a non-inferiority margin of 15% ($\delta$= -0.15), the sponsor specified the null hypotheses of no difference between treatments as:

$H_{0\ 20\ mcg/kg}$: $\pi_{T\ 20mcg/kg} - \pi_R \leq \delta$

$H_{0\ 10\ mcg/kg}$: $\pi_{T\ 10mcg/kg} - \pi_R \leq \delta$

The null and alternative hypotheses were stated as:

$H_0 = \{H_{0\ 20\ mcg/kg} \cap H_{0\ 10\ mcg/kg}\}$ and

$H_1 = \{H_{1\ 20\ mcg/kg} \cup H_{1\ 10\ mcg/kg}\}$

The -15% margin was based on data from adult studies and was agreed upon in the written request. The stratum adjusted Mantel-Haenszel method was used to compute the confidence interval (CI) of the difference in proportions. If the lower bound of the 97.5% CI of either the difference (CR 0-24h palonosetron 20 mcg/kg - CR 0-24h ondansetron) or the difference (CR 0-24h palonosetron 10 mcg/kg - CR 0-24h ondansetron) was greater than -0.15, then the null hypothesis ($H_0$) was to be rejected.

For the primary efficacy analysis, the two CIs were based on the FAS, using the stratum adjusted Mantel-Haenszel method with correction for continuity. Supportive primary analyses using alternative statistical methods were also conducted by the sponsor but are not presented here..

The key secondary efficacy endpoint was the CR from 24 to 120 hours (Delayed Phase) after T0 during the first cycle. The difference in CR between treatment groups for this period was analyzed using the same approach as for the primary endpoint. However, the non-inferiority margin for this secondary endpoints was not derived from historical data and should be considered exploratory; moreover, no study-wise control of type I error was planned, the statistical results for all secondary endpoints should be considered descriptive only and not supportive of labeling claims.

Missing values for the primary endpoint and for other variables with binary outcomes (e.g., presence or absence of retching, vomiting, or nausea) were to be imputed consistent with lack of efficacy.

**Determination of Sample Size**

The sponsor indicated that a previous pediatric trial showed a possible trend in the difference of efficacy between two palonosetron doses ($3_{mcg/kg}$ and $10_{mcg/kg}$), as well as a possible trend for a dose-efficacy relationship. Based on these observations, the sponsor chose two doses to be tested: 10 mcg/kg and 20 mcg/kg.

The sponsor assumed that in order to demonstrate efficacy of palonosetron, only one of the two doses ($10_{mcg/kg}$ or $20_{mcg/kg}$) needed to be efficacious.

In this non-inferiority trial the computation of the sample size was based on:

- Similar values for the CR rate in palonosetron and ondansetron arms: 60%
- A type I error of 5% (2-sided)
- A type II error of 20% (Power of 80%)
- A non-inferiority margin of -15%

Based on these criteria, the protocol planned to enroll 492 evaluable patients (i.e., 164 patients in each group) undergoing MEC or HEC in the double-blind portion of the study.

### 3.2.4 Study Results

**Number of Subjects Randomized**
Eligible patients were randomized to one of three treatment groups, stratified by emetogenicity (HEC/MEC) and by age (<2 years, 2 to <6 years, 6 to <12 years, and 12 to <17 years). A total of 502 patients were randomized (169 palonosetron 10 mcg/kg, 169 palonosetron 20mcg/kg, 164 ondansetron) and 494 patients were treated with study drug to comprise the Safety population (167 palonosetron 10mcg/kg, 163 palonosetron 20 mcg/kg, and 164 ondansetron.

**Table 8: Number of Subjects in Each Analysis Population (Cycle 1) (Study PALO 10-20)**

| Analysis Population | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron 3x0.15 mg/kg | Total |
|---|---|---|---|---|
| Randomized Population | 169 | 169 | 164 | 502 |
| Full Analysis Set (FAS) | 166 | 165 | 162 | 493 |
| As-treated Population | 166 | 163 | 164 | 493 |
| Per Protocol Population (PP) | 130 | 124 | 124 | 378 |
| Safety Population (SAF) | 167 | 163 | 164 | 494 |
| PK Population | 144 | 137 | 0 | 281 |
| PK Sub-Study Population | 32 | 29 | 0 | 61 |

Source: Sponsor CSR

**Patient Disposition**
Table 9 shows the disposition of subjects in the study.

A total of 502 patients were enrolled and randomly assigned to treatment at 59 sites. Of the 494 patients that received study drug, 167 were included in the palonosetron 10 mcg/kg group, 165 in the palonosetron 20 mcg/kg group and 162 in the ondansetron group.

Study drug was not administered to 8 randomized patients. Reasons were due to vomiting (4 patients), chemotherapy not administered (2 patients), central line infection (1 patient) and incorrect body weight (1 patient).

The percentage of randomized patients completing at least one study cycle was 98.2% for palonosetron 10 mcg/kg, 96.4% for palonosetron 20 mcg/kg, and 97.6% for ondansetron.
A patient was considered to have completed the study if he/she completed Visit 8 of the last initiated cycle. A total of 485 patients completed all initiated study cycles, while 17 patients terminated the study during one of the cycles.

**Table 9: Patient Disposition (Study PALO 10-20)**

| Patients Disposition | Palonosetron 10 mcg/kg (N=169) | Palonosetron 20 mcg/kg (N=169) | Ondansetron 3x0.15 mg/kg (N=164) |
|---|---|---|---|
| Randomized patients | 169 (100%) | 169 (100%) | 164 (100%) |
| Not treated patients | 2 (1.2%) | 4 (2.4%) | 2 (1.2%) |
| Treated patients | 167 (98.8%) | 165 (97.6%) | 162 (98.8%) |
| Patients completing Cycle 1 | 166 (98.2%) | 163 (96.4%) | 160 (97.6%) |
| Patients completing Cycle 2 | 84 (49.7%) | 89 (52.7%) | 86 (52.4%) |
| Patients completing Cycle 3 | 43 (25.4%) | 59 (34.9%) | 44 (26.8%) |
| Patients completing Cycle 4 | 19 (11.2%) | 31 (18.3%) | 19 (11.6%) |
| Patients completing the study | 166 (98.2%) | 160 (94.7%) | 159 (97.0%) |
| Patients prematurely terminating the study[1] | 3 (1.8%) | 9 (5.3%) | 5 (3.0%) |

N = Number of patients

[1] Patients prematurely terminating the study include not treated patients.

Source: Sponsor CSR

**Demographics and Baseline Characteristics**

Patients were enrolled in 59 sites, including 11 sites in the United States, 7 in Russia and 5 in Poland, 4 sites each in Chile, Czech Republic, Romania and Ukraine, 3 sites each in Bulgaria, France, Hungary, and Peru, and 2 sites each in Argentina, Austria, and Serbia as well as 1 site in Estonia and Germany.

The percentage of randomized patients completing at least one study cycle was 98.2% for palonosetron 10 mcg/kg, 96.4% for palonosetron 20 mcg/kg and 97.6% for ondansetron. Death was the reason for study discontinuation in 1 patient in the palonosetron 20 mcg/kg group and 1 in the ondansetron group. Treatment-emergent adverse events (TEAEs) led to discontinuation of 3 patients in the palonosetron 20 mcg/kg group and 2 patients in the ondansetron group (1 in each group was not treated with study drug). The Investigators considered the relationship to study drug unlikely or not related for all AEs that led to premature discontinuation or had fatal outcomes. Consent was withdrawn for 1 patient in the ondansetron group.

The age range was from 64 days to 16.9 years. The FAS included 53.1% of males and 46.9% of females. This distribution was slightly different in the three treatment groups: 53.0% males and 47.0% females in the palonosetron 10 mcg/kg group, 46.1% males and 53.9% females in the palonosetron 20 mcg/kg group, and 60.5% males and 39.5% females in the ondansetron group.

Most patients were classified as White/not Hispanic (86.2%). Other patients were White/ Hispanic (8.9%), White and native Indian/ Hispanic (3.9%), Asian/ not Hispanic (0.4%), Black or African American/ not Hispanic (0.4%) and Latino /Hispanic (0.2%). All Asian/ not Hispanic, Black or African American/ not Hispanic and Latino/ Hispanic patients were enrolled in the palonosetron 10 mcg/kg groups.

No significant differences between the treatment groups for any of the baseline characteristics were observed.

**Analysis of the Primary Efficacy Endpoint**

The primary analysis of efficacy was based on the FAS population. The results for FAS, as-Treated and PP as well as the reviewer's sensitivity analysis are presented in the tables below.

**Table 10: Analyses of Efficacy, Complete Response (Study PALO 10-20)**

| Analysis Populations | Aloxi 10 n/N (%) | Aloxi 20 n/N (%) | Ondansetron n/N (%) |
|---|---|---|---|
| FAS (n=493) | 90/166 (54.2) | 98/165 (59.4) | 95/162 (58.6) |
| As Treated (n=493) | 90/166 (54.2) | 98/163 (60.1) | 95/164 (57.9) |
| PP (n=378) | 78/130 (60.0) | 85/124 (68.6) | 79/124 (63.7) |
| Sensitivity (drop-outs= no cr) | 89/166 (53.6) | 95/163 (58.3) | 93/164 (56.7) |

| Comparisons | Difference (97.5% CI) | | | |
|---|---|---|---|---|
| | FAS | As Treated | PP | Sensitivity |
| Aloxi 10 - Ondan | -4% (-16.5%, 8%) | -4% (-16%, 9%) | -4% (-16%, 8%) | -3% (-15%, 9%) |
| Aloxi 20 - Ondan | 1% (-11%, 13%) | 2% (-10%, 14%) | 5% (-7%, 17%) | 2% (-11%, 14%) |

Source: Reviewer

Aloxi 20 showed non-inferiority to Ondansetron in FAS population based on a -15% margin [1% treatment difference and 97.5% CI (-11%, 13%)]. In the other analyses shown, the non-inferiority criteria were also supportable. The reviewer's sensitivity analysis showed minor differences in both numerator and denominator counts as compared to the FAS analysis. However the reviewer's results are consistent with those presented by the sponsor.

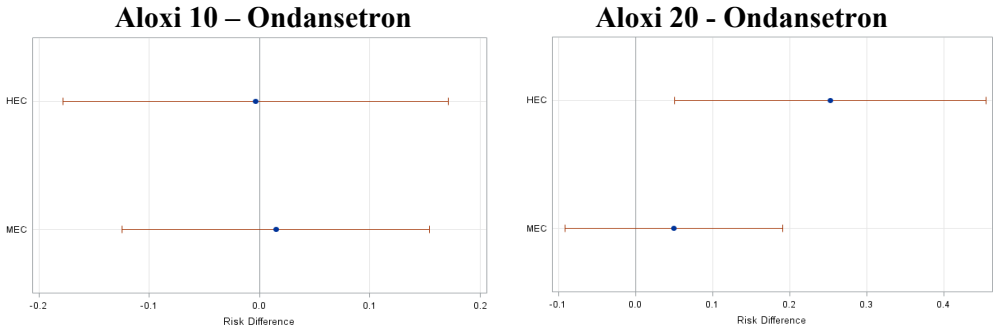
In addition to the primary analyses, I also explored efficacy by emetogenicity level (HEC vs. MEC) which was one of the stratification factors at randomization. The results below are based on the "As treated" population. This table shows slight differences in both numerators and denominators shown in Table 29 of the CSR, which is based on the FAS population..

**Table 11: Complete Response by Emetogenicity, As-treated Population (Study 10-20)**

| | Aloxi 10 n/N (%) | Aloxi 20 n/N (%) | Ondansetron n/N (%) |
|---|---|---|---|
| HEC | 10/52 (19.2) | 22/49 (44.9) | 10/51 (19.6) |
| MEC | 38/114 (33.3) | 42/114 (36.8) | 36/113 (31.9) |
| Comparisons | Difference (97.5% CI) | | |
| | Aloxi 10 - Ondansetron | Aloxi 20 - Ondansetron | |
| HEC | -0.4% (-18%, 17%) | 25% (5%, 46%) | |
| MEC | 1% (-12%, 15%) | 5% (-9%, 19%) | |

Source: Reviewer, based on dataset submitted by the Sponsor.

**Figure 1: 97.5% Confidence Intervals of Treatment Differences in Complete Response by Emetogenicity (Study PALO 1020)**




Source: Reviewer

As it can be observed in the above tables and plots, the Aloxi 20 comparison was consistent with the non-inferiority criteria for both the HEC and MEC subgroups, with better performance indicated for Aloxi 20 in the HEC subgroup. However, these results, and those based on other subgroups should be considered exploratory as the non-inferiority criteria were not based on appropriate historical data.

Analysis of the primary endpoint by the age category is shown in Section 4.2.

The Table below shows the results of the analyses for the key secondary efficacy endpoint, the proportion of patients with CR from 24 to 120 hours (Delayed Phase).

**Table 12: Analyses of Key Secondary Endpoint, Complete Response in the Delayed Phase (Study PALO 10-20**

| | Aloxi 10<br>n/N (%) | Aloxi 20<br>n/N (%) | Ondansetron<br>n/N (%) |
|---|---|---|---|
| CR (Delayed Phase) | 48/166 (29.0) | 64/163 (39.3) | 46/164 (28.1) |
| Comparisons | Difference (97.5% CI) | | |
| Aloxi 10 - Ondansetron | 0.1% (-10%, 12%) | | |
| Aloxi 20 - Ondansetron | 11% (-0.04%, 23%) | | |

Source: Reviewer

For the key secondary endpoint, the lower bounds of the 97.5% CIs of the differences between Aloxi and ondansetron were -10% and -0.04% for Aloxi 10 and Aloxi 20, respectively. Since the non-inferiority margin for the secondary endpoints for both Aloxi doses was not supported by historical studies and agreed to by the Agency (as was done for the primary endpoint) results for all secondary endpoints are exploratory and should not be considered supportive of a clinical benefit claim in the labeling package.

### 3.3 Safety

For evaluation of safety, refer to the Medical Officer's review.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Geographic Region for Study PALO 10-14

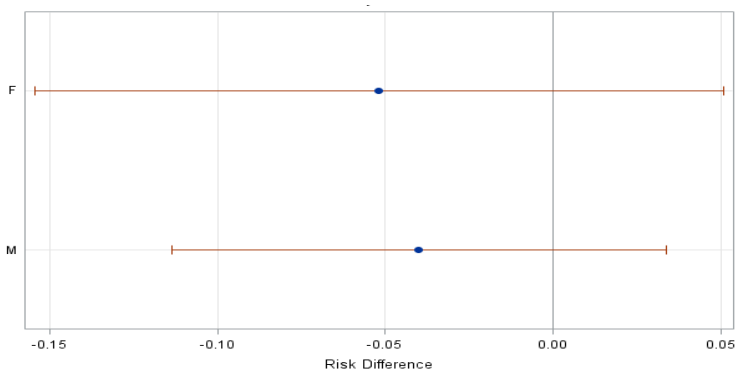
**Analysis by Gender**
Results of the primary efficacy endpoint by gender, age category, race, site and country are shown below in the following tables and plots.

**Table 13: Complete Response by Gender, (Study PALO 10-14)**

| Gender | Aloxi n/N (%) | Ondansetron n/N (%) | Difference (95% CI) Aloxi - Ondansetron |
|---|---|---|---|
| Female | 97/131 (74.1) | 103/130 (79.2) | -5% (-15%, 5%) |
| Male | 162/200 (81%) | 170/200 (85%) | -4% (-11%, 3%) |

Source: Reviewer

**Figure 2: 95% Confidence Intervals of Treatment Differences in Complete Response by Gender (Study PALO 10-14)**




Source: Reviewer

The female and the male sub-populations showed results similar to the primary analysis. The ondansetron rates were numerically higher than those for Aloxi by 4% to 5% and neither subgroup showed results consistent with the proposed non-inferiority criteria.

**Analysis by Race**
A majority (89%) of the subjects were classified in the White subgroup; therefore, a subgroup analysis by race was not conducted.

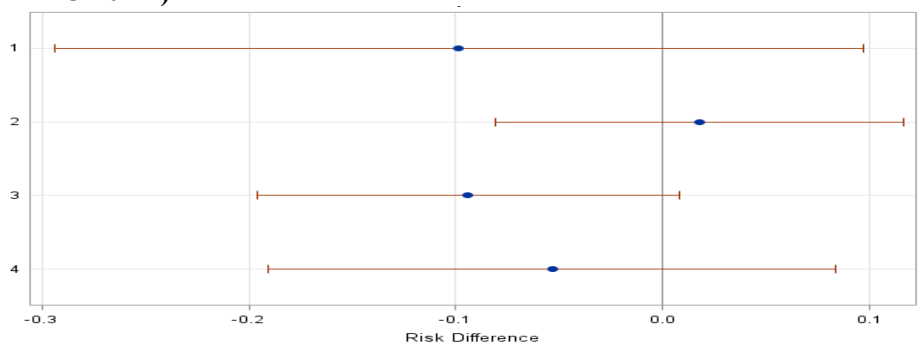
**Analysis by Age**
It can be observed from Table 14 that among the four age groups, only the results for age group "2 to <6" would meet the criteria for non-inferiority, with a lower 95% CI of -8%.

**Table 14: Complete Response by Age Category, (Study PALO 10-14)**

| Age Category (Yrs) | Aloxi n/N (%) | Ondansetron n/N (%) | Difference (95% CI) Aloxi - Ondansetron |
|---|---|---|---|
| < 2 | 18/22 (81.8) | 22/24 (91.7) | -10% (-30%, 10%) |
| 2 to < 6 | 101/124 (81.5) | 98/123 (79.7) | 2% (-8%, 12%) |
| 6 to < 12 | 88/117 (75.2) | 99/117 (84.6) | -9% (-20%, 10%) |
| 12 to 17 | 52/68 (76.5) | 54/66 (81.8) | -5% (-19%, 8%) |

Source: Reviewer

**Figure 3: 95% Confidence Intervals of Treatment Differences in Complete Response by Age (Study PALO 10-14)**




Source: Reviewer

**1 = <2 years**
**2 = 2 to <6 years**
**3 = 6 to <12 years**
**4 = 12 to <17 years**

**Analysis by Geographic Region (Site and Country)**

Thirty-nine centers in 7 countries participated in this study. Thirteen sites had 5 or less subjects. The reviewer conducted an analysis by site, and results did not show any trend reflecting site differences..

The table below show complete response by country. Hungary and Ukraine indicated a result numerically better than observed for the other countries. However, sample sizes are small and the variability of results here are not unexpected.

**Table 15: Complete Response by Country, (Study PALO 10-14)**

| Country | Aloxi n/N (%) | Ondansetron n/N (%) | Difference (95% CI) Aloxi - Ondansetron |
|---|---|---|---|
| Argentina | 5/7 (71.4) | 5/6 (83.3) | -12% (-57%, 33%) |
| Czech Republic | 3/7 (42.9) | 8/13 (61.5) | -19% (-64%, 27%) |
| Hungary | 96/117 (82.1) | 81/102 (79.4) | 3% (-8%, 13%) |
| Poland | 21/28 (75.0) | 20/26 (77.0) | -2% (-25%, 21%) |
| Russia | 22/24 (91.7) | 42/46 (91.3) | 0.4% (-13%, 14%) |
| Ukraine | 56/59 (94.9) | 64/66 (97.0) | -2% (-9%, 5%) |
| USA | 56/89 (62.9) | 53/71 (74.7) | -12% (-26%, 3%) |

Source: Reviewer

### 4.2 Gender, Race, Age, and Geographic Region for Study PALO 10-20

**Analysis by Gender**

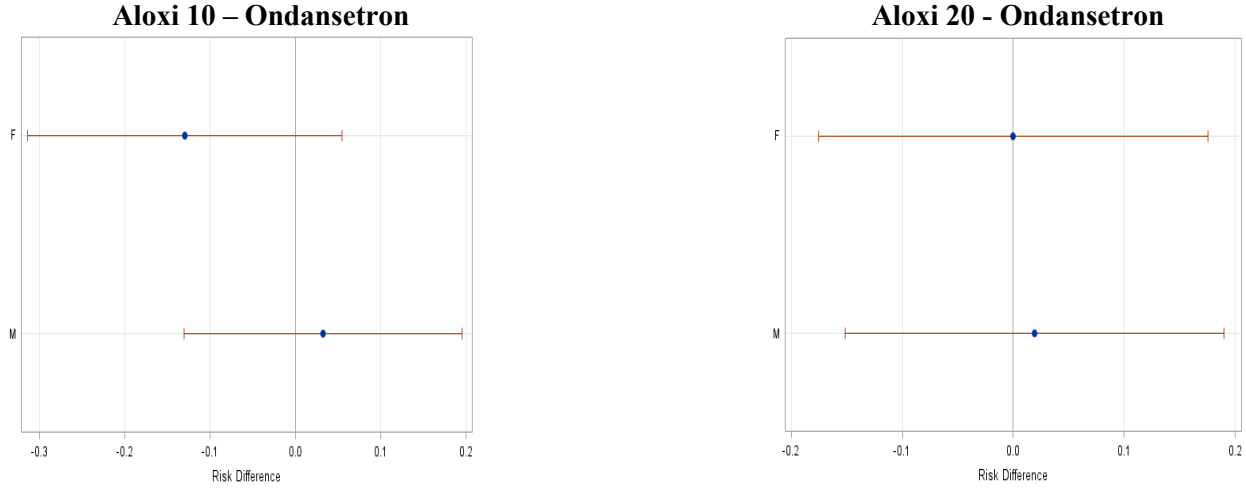
Table 16 shows the results of complete response by gender for study PALO-10-20.

**Table 16: Complete Response by Gender (Study PALO 10-20)**

| | Aloxi 10<br>n/N (%) | Aloxi 20<br>n/N (%) | Ondansetron<br>n/N (%) |
|---|---|---|---|
| Female | 39/77 (50.7) | 56/88 (63.6) | 42/66 (63.6) |
| Male | 51/89 (57.3) | 42/75 (56.0) | 53/98 (54.1) |
| Comparisons | Difference (97.5% CI) | | |
| | Aloxi 10 - Ondansetron | Aloxi 20 - Ondansetron | |
| Female | -13% (-31%, 5%) | 0% (-18%, 18%) | |
| Male | 3% (-13%, 20%) | 2% (-15%, 19%) | |

Source: Reviewer

**Figure 4: 97.5% Confidence Intervals of Treatment Differences in Complete Response by Gender (Study PALO 10-20)**




Source: Reviewer

The Tables and figures above indicate that the CR rate for the male subgroup was numerically higher than that for the female subgroup for both doses of Aloxi. The non-inferiority criteria would appear to be met for the male subgroup, but these subgroup comparisons are exporatory only and not intended to convey a noninferiority conclusion. Moreover, the small sizes of the subgroups preclude clear interpretation.

**Analysis by Race**

More than 90% of the subjects were classified as White; therefore, analysis by race was not conducted.

**Analysis by Age**

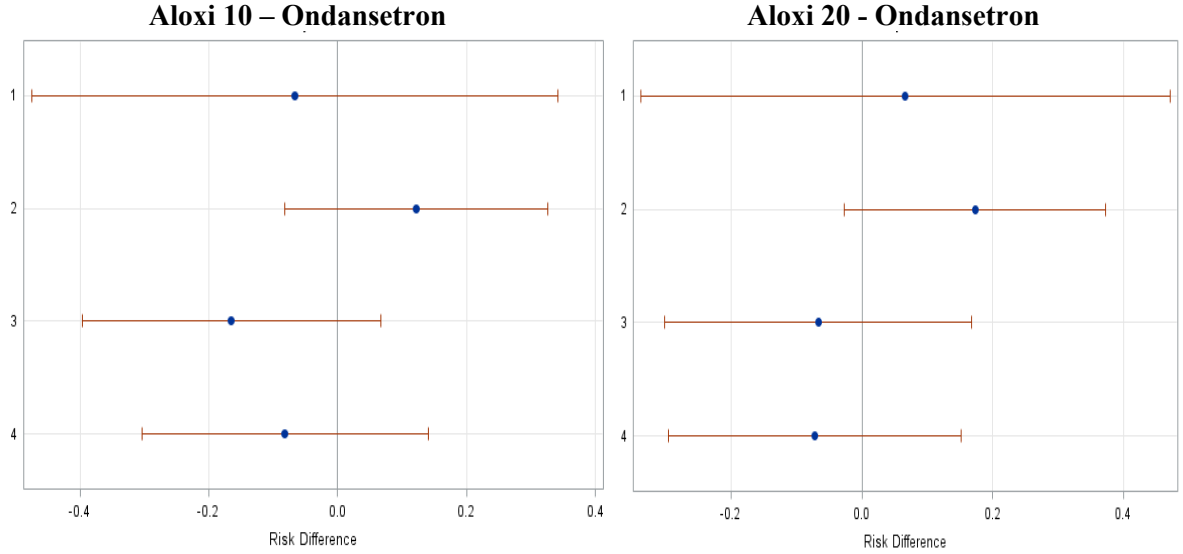
The below table and the graph show complete response by age. Better Aloxi performance can be seen in the 2 to 6 year age category. The sample sizes however are small and these subgroup results are exploratory.

**Table 17: Complete Response by Age Category (Study PALO 10-20)**

| | Aloxi 10 n/N (%) | Aloxi 20 n/N (%) | Ondansetron n/N (%) |
|---|---|---|---|
| <2 years | 7/15 (46.7) | 9/15 (60.0) | 8/15 (53.3) |
| 2 to <6 years | 38/54 (70.4) | 40/53 (75.5) | 32/55 (58.2) |
| 6 to <12 years | 19/46 (41.3) | 23/45 (51.1) | 26/45 (57.8) |
| 12 to <17 | 26/51 (51.0) | 26/50 (52.0) | 29/49 (59.2) |
| Comparisons | Difference (97.5% CI) | | |
| | Aloxi 10 - Ondansetron | Aloxi 20 - Ondansetron | |
| <2 years | -7% (-48%, 34%) | 7% (-34%, 47%) | |
| 2 to <6 years | 12% (-1%, 33%) | 17% (-3%, 37%) | |
| 6 to <12 years | -16% (-40%, 7%) | -7% (-30%, 17%) | |
| 12 to <17 | -8% (-30%, 14%) | -7% (-30%, 15%) | |

Source: Reviewer

**Figure 5: 97.5% Confidence Intervals of Treatment Differences in Complete Response by Age (Study PALO 10-20)**




Source: Reviewer

**1 = <2 years**
**2 = 2 to <6 years**
**3 = 6 to <12 years**
**4 = 12 to <17 years**

**Analysis by Country**

A total of 71 centers in 17 countries participated in this study. The reviewer conducted an analysis by site, and results did not show any trend reflecting site differences.

The table below show complete response by country. Argentina and Germany had only 4 subjects each, hence I eliminated these two countries from the analysis by country. However, no apparent

differences between dose groups are indicated, consistent with the overall analysis. However, the small sample sizes of the subgroups preclude any clear interpretation.

**Table 18: Complete Response by Country (Study PALO 10-20)**

| | Aloxi 10<br>n/N (%) | Aloxi 20<br>n/N (%) | Ondansetron<br>n/N (%) |
|---|---|---|---|
| Austria | 2/6 (33) | 2/4 (50) | 1/10 (10) |
| Bulgaria | 5/10 (50) | 3/7 (43) | 2/3 (67) |
| Chile | 5/9 (56) | 6/12 (50) | 4/8 (50) |
| Czech Republic | 6/14 (43) | 13/20 (65) | 20/29 (69) |
| Estonia | 1/3 (33) | 1/3 (33) | 2/4 (50) |
| France | 2/3 (67) | 0/1 (0) | 2/3 (67) |
| Hungary | 15/23 (65) | 18/24 (75) | 11/18 (61) |
| Peru | 3/5 (60) | 6/11 (55) | 3/3 (100) |
| Poland | 14/20 (70) | 15/24 (63) | 14/21 (67) |
| Romania | 13/21 (62) | 9/19 (47) | 12/18 (67) |
| Russia | 6/18 (33) | 11/16 (69) | 8/16 (50) |
| Serbia | 10/11 (91) | 4/5 (80) | 5/11 (45) |
| Ukraine | 5/7 (71) | 7/10 (70) | 7/10 (70) |
| USA | 1/11 (9) | 2/8 (25) | 3/8 (38) |

Source: Reviewer

# 5 SUMMARY AND CONCLUSIONS

**Study PALO-10-14 (PONV)**
Study PALO-10-14 did not show Aloxi to be non-inferior to ondansetron for treatment of PONV based on the primary efficacy endpoint of complete response (CR) using a non-inferiority margin of 10%. The treatment difference (palonosetron minus ondansetron) was -4%, and the 95% CI of the difference was (-10.5%, 1.6%).

The sponsor acknowledged that the non-inferiority margin of 10% was not considered valid for secondary endpoint comparisons, and that those results were to be based on descriptive statistics. Moreover, type I error control was not pre-specified, and failure of the primary comparison would have precluded any subsequent hypothesis testing regardless.

**Study PALO-10-20 (CINV)**
In Study PALO-10-20, two doses of Aloxi were tested against ondansetron; Aloxi 10 and Aloxi 20. Aloxi 20, using a primary endpoint of complete response during the acute phase (0-24 hours) of the first treatment cycle. Only Aloxi 20 was found to be non-inferior to ondansetron based on a 97.5% CI (as a consequence of the two comparisons) and a margin of 15%. The treatment difference (Aloxi 20 minus ondansetron was 1% and the 95% CI of the difference was (-11%, 13%).

Important secondary endpoints were CR in the Delayed Phase (24-120 hours) and in the Overall Phase (0-120 hours). Aloxi 20 showed results numerically similar to ondansetron for these endpoints, however, the non-inferiority margin for all secondary endpoint comparisons was not justified or based on historical data and cannot be deemed valid. Thus these results cannot support a clinical benefit claim in the labeling package.

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/s/

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SHAHLA S FARR
05/14/2014

MICHAEL E WELCH
05/14/2014