CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Ser Nr:	21372/S008 (b) (4)
DATE RECEIVED:	April 27, 2007
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DRUG NAME:	Aloxi (palonosetron HCL) Intravenous Injection
INDICATION:	Prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery
APPLICANT:	Helsinn Healthcare SA
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics 3 (HFD-725)
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STATISTICAL KEYWORDS:	Clinical studies; NDA review; Multiplicity adjustments; Baseline adaptive randomization.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Based on review of the pivotal Study Palo-04-06 and the supportive Study Palo-04-07, palonosetron 0.075 mg is supported by substantial evidence of efficacy for use in prevention of postoperative nausea and vomiting for the first 24 hour postoperative observation period following elective abdominal or gynecological laparoscopic surgery.

1.2 Brief Overview of Clinical Studies

Two phase 3 Studies PALO-04-06 and PALO-04-07 were submitted by the applicant to support Aloxi for the prevention of postoperative nausea and vomiting (PONV) (b) (4)
(b) (4)
Supplement 008 refers to the PONV indication (b) (4)
(b) (4)

(b) (4)

For the PONV indication, due to partial unblinding of treatment codes, Study PALO-04-07 is considered a supportive study, and Study PALO-04-06 is considered a single principal study and thus required to show substantial evidence of efficacy, with the uncompromized data from the PALO-04-07 trial providing supportive evidence. However, based on that data, the applicant's efficacy analysis for study PALO-04-07 failed to show effectiveness of palonosetron over placebo for either the 0-24 or 24-72 hour periods for any of the dose groups (0.025 mg, 0.05 mg, and 0.075 mg). Thus the data from Study PALO-04-07 do not provide positive support for the pivotal Study PALO-04-06. (For more detail review of Study 07, refer to Section 2.1.2.)

Study PALO-04-06 was designed as a randomized, double-blind, multi-center, parallel group, placebo-controlled phase 3 trial to evaluate the efficacy and safety of single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) versus placebo for the prevention of PONV from 0 to 24 hours and 24 to 72 hours in the post-operative period in male and female outpatients undergoing elective laparoscopic abdominal or gynecological surgery with general anesthesia. In this study, outpatients were defined as those expected to go home on the same day as surgery (no overnight stay). All laparoscopic procedures took place under general anesthesia.

The population for this study consisted of eligible male or female outpatients with age ≥ 18, undergoing elective laparoscopic abdominal or gynecological surgery, who met the inclusion and not the exclusion criteria for the study and gave their informed consent to participate in the study.

The duration of this study was 12 and one-half months: first patient enrolled on 23 May 2005 and last patient completed on 12 June 2006. A total of 43 investigators from two countries (USA and Romania) participated in the study: 36 from USA and 7 from Romania.

The study drug was administered as a single i.v. dose of palonosetron or placebo for the prevention of PONV immediately (no more than 5 minutes) prior to induction of anesthesia (Study Day 1). In addition, efficacy and safety were assessed on the day of study drug administration at Visit 2 (Study Day 1) and at a final visit (Study Days 6 to 10) following the surgical procedure. The primary endpoint for this study was Complete Response (CR) defined as the absence of nausea and vomiting during the specified period.

The study had two co-primary objectives as follows:

1. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-hour postoperative observation period.
2. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-72 hour postoperative observation period.

A total of 639 patients were screened for this study, of which 574 patients were randomized into one of the four treatment arms: single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) or placebo. A total of 547 patients were treated. The applicant used an adaptive randomization method to stratify and assign subjects to the four treatment groups in a 1:1:1:1 ratio.

1.3 Statistical Issues and Findings

1.3.1 Study PALO-04-06

For the first 24 hour observation period, superiority of palonosetron over placebo was demonstrated for the 0.05 and 0.075 mg dose groups showing efficacy evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery. However, the efficacy comparisons performed by the applicant for the 0.025 mg dose for the 0-24 hour period did not show superiority; and for the 24-72 hour postoperative observation period, all three palonosetron doses (0.025 mg, 0.05 mg, and 0.075 mg) failed to demonstrate superiority to placebo.

The following comments on the efficacy assessments are for the superiority of palonosetron 0.05 mg and 0.075 mg to placebo based upon the primary endpoint - complete response (no nausea, no vomiting) for the first 24 hour postoperative observation period.

- First, the estimated proportion of complete response using data from baseline adaptive randomization may not be an unbiased estimate of the population proportion. It follows that the estimated proportion should be used with caution in estimating the effect size of study drug versus placebo. In general, simple randomization with permuted blocks is currently the favored allocation method in clinical trials. Accordingly, based upon the number of 574 patients, the applicant should have applied simple randomization with random permuted blocks to allocate patients to different treatment groups and applied the proposed logistic regression analysis method to adjust the covariate effect on the efficacy comparisons assessed by the two co-primary endpoints (complete response in the 0-24 and 24-72 hours of postoperative periods).

- Second, based upon the efficacy comparison by investigate-site, for palonosetron 0.075mg, the proportions of complete response in most sites are much greater than that in the placebo group. No particular sites are identified to have unusually large proportions of complete response to dominate the superiority of palonosetron 0.075 mg to placebo. However, for palonosetron 0.05mg, although the proportions of complete response in most sites are greater than that of placebo, it seems unusual that the complete responses for all nine patients in Site 182 are assessed as success. The concern of 9 out of 9 (100%) patients in Site 182 of palonosetron 0.05 mg assessed as success in complete response can not be ruled out. In addition, it is also noted that the p-value of testing the superiority of palonosetron 0.05 mg to placebo is on the border-line close to the nominal significance level proposed by the applicant's multiplicity adjustment method.

- Thirdly, based upon the results of the sensitivity analyses, one learns that in the efficacy analysis of palonosetron 0.05 mg to placebo, a small Site 182 (total patients of this site only covered 5% patient of the study) has influence on the superiority testing of palonosetron 0.05 mg. It is also noted that the superiority of palonosetron 0.05 mg to placebo is no longer held when the status of the complete responses of two patients switching from success to failure. Accordingly, the superiority of palonosetron 0.05 mg to placebo is not robust. In addition, since the supportive Study PALO-04-07 did not replicate the superiority of palonosetron 0.05 mg to placebo using primary analysis data set (PFAS), palonosetron 0.05 mg is considered not supported by substantial evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery.

- Finally, for the efficacy assessment of palonosetron 0.075 mg during the first 24 hour postoperative observation period, based upon the applicant's logistic regression analysis and this reviewer's non-parametric covariate analysis, the superiority of palonosetron 0.075 mg versus placebo is demonstrated and is a robust result. In addition, the secondary endpoint analyses on the complete control, emetic episodes, severity nausea, and quality

of life indicated that Palonosetron 0.075 mg are numerically better than placebo. As a consequence, the superiority of palonosetron 0.075 mg to placebo can be considered supported by substantial evidence in use of the prevention of postoperative nausea and vomiting during the first 24 hour postoperative observation period.

1.3.2 Study PALO-04-07

- Due to the issue of unblinding the treatment codes and based upon the Agency's response to this issue, Study PALO-04-07 is treated as a supportive study. In addition, in order to respond to the Agency's concern regarding data integrity, the applicant specified the primary full analysis set (PFAS) excluding the 175 patients involved in the unblinding problem as the primary analysis data set.

- However, using this PFAS population, the applicant's efficacy analysis showed that for both periods of 0-24 hours and the 24-72 hours, comparisons of the single dose groups of palonosetron with placebo did not result in significant differences for any of the palonosetron treatment groups (0.025, 0.05, and 0.075 mgs) versus placebo after multiplicity adjustments proposed by the applicant. In this reviewer's opinion, data from Study PALO-04-07 do not support the efficacy results of the pivotal Study PALO-04-06.

2.0 INTRODUCTION

2.1 Overview

In the introduction of the clinical study report for Study PALO-04-07, the applicant made the following comments with regard to Aloxi:

> Postoperative nausea and vomiting (PONV) is a frequent complication of surgery under general anesthesia, with considerable medical and economic impact, and associated with high levels of patient discomfort and dissatisfaction. To many patients, PONV is a distressing adverse event (AE), which is reportedly feared more than postoperative pain. (b) (4)
> (b) (4)
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> Research into preventing PONV (b) (4) has been directed at blocking neurotransmitter receptors located either centrally or peripherally such as histamine Hi, dopamine D2, muscarinic acetylcholine, and 5-hydroxytryptamine sub-receptor 3 (5-HT3). The 5-HT3 antagonists such as ondansetron, dolasetron and granisetron have proven effective for the prevention and treatment of PONV, with minimal adverse effects and no dose-related sedation or extrapyramidal reactions and no effect on vital signs. Patients at substantial risk of PONV are expected to benefit from multiple anti-emetic interventions including a 5-HT3 antagonist. Palonosetron hydrochloride (Aloxi) is a potent and selective 5-HT3 receptor antagonist that blocks the binding of serotonin to 5-HT3 receptors. The compound has a higher receptor binding affinity and a longer plasma half-life (40 hours) compared to ondansetron, dolasetron, and granisetron.

Two phase 3 studies (PALO-04-06 and PALO-04-07) were submitted by the applicant to support Aloxi in the prevention of postoperative nausea and vomiting (PONV) (b) (4)

(b) (4)

[redacted]

For the PONV indication, due to the issue of partial unblinding of treatment codes, Study PALO-04-07 was to be considered as a supportive study. This would imply that a positive finding in the pivotal Study PALO-04-06, could then be supported by the remaining data in PALO-04-07 trial.

2.1.1 Overview of Study PALO-04-06

The study was designed as a randomized, double-blind, multi-center, parallel group, balanced, stratified, placebo-controlled phase III trial to evaluate the efficacy and safety of single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) versus placebo for the prevention of PONV from 0 to 24 hours and 24 to 72 hours in the post-operative period in male and female outpatients undergoing elective laparoscopic abdominal or gynecological surgery with general anesthesia. In this study, outpatients were defined as those expected to go home on the same day as surgery (no overnight stay). All laparoscopic procedures took place under general anesthesia.

The population for this study consisted of eligible male or female outpatients with age $\geq$ 18, undergoing elective laparoscopic abdominal or gynecological surgery, who met the inclusion and not the exclusion criteria for the study and gave their informed consent to participate in the study.

The duration of this study was 12.5 months: first patient enrolled on 23 May 2005 and last patient completed on 12 June 2006. A total of 43 investigators from two countries (USA and Romania) participated in the study: 36 from USA and 7 from Romania.

The study drug was administered as a single i.v. dose of palonosetron or placebo for the prevention of PONV immediately (no more than 5 minutes) prior to induction of anesthesia (Study Day 1). In addition, efficacy and safety were assessed on the day of study drug administration at Visit 2 (Study Day 1) and at a final visit (Study Days 6 to 10) following the surgical procedure. The primary endpoint for this study was Complete Response (CR) defined as the absence of nausea and vomiting during the specified period.
The study had two co-primary objectives, as follows:
1. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-hour postoperative observation period.

2. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-72 hour postoperative observation period.

A total of 639 patients were screened for this study, of which 574 patients were randomized into one of the four treatment arms: single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) versus placebo. A total of 547 patients were treated. The sponsor used an adaptive randomization method to stratify and assign subjects to the four treatment groups in a 1:1:1:1 ratio.

2.1.2 Overview of Study PALO-04-07

PALO-04-07, similar in design to Study PALO-04-06, was conducted in Europe including Germany, Poland, and the Czech Republic. This study enrolled 674 PONV patients from 28 recruiting centers, and enrollment was completed in April 2006. Two separate potential unblinding incidents occurred during this study: (1) A clinical label supply issue resulted in possible unblinding of the first 130 patients enrolled; and (2) after completion of the clinical phase of the study, a problem was found with vial labels at the Germany sites, which resulted in possible unblinding of 178 subjects. Meetings were held with the sponsor to discuss the unblinding problems and seek resolution. (Refer to Agency Meeting Minutes dated February 1, 2006 and October 24, 2006, respectively.)

In partial resolution of the first incident, the applicant enrolled an additional 130 subjects into the study, and redefined the efficacy analysis data based to exclude those subjects potentially unblinded. Regarding the second incident, the applicant indicated that in Germany, 261 patients enrolled at 13 sites participated in the study, and of these, 178 subjects were potentially affected by an unblinding of treatment codes. That is, drug accountability forms were erroneously affixed with the adhesive tear-off treatment vial label. The applicant further indicated that this active treatment label did not identify the active treatment doses being evaluated, namely, 0.025 mg, 0.05 mg or 0.075 mg, but it identified whether the treatment was palonosetron or placebo. The concern was that the clinical staff responsible for signing the drug accountability forms may have become unblinded when they signed the forms.

In order to reduce the impact of the second unblinding issue on the efficacy assessments, the Agency responded that it had significant concerns regarding the data integrity from the affected clinical sites. It was agreed that patients from the 13 sites in Germany should be excluded from the full efficacy analysis data set. The Agency then, agreed that a positive finding in the PALO-04-06 study, if robust, could then be supported by data from the remaining subjects who were not involved in the unblinding of treatment codes.

In order to explore the impact of the unblinding issue on the efficacy analysis for the supportive Study PALO-04-07, this reviewer calculated the proportions of complete responses for the four treatment groups (three palonosetron treatments plus placebo). Since none of the efficacy for the three palonosetron treatments (palonosetron 0.025 mg, 0.05 mg and 0.075 mg) in the pivotal

study PALO-04-06 showed superior to that of placebo during the 24-72 hour post-operative period, following the comments regarding the role of the supportive study stated in the meeting minutes, efficacy data from the supportive study for the 24-72 hour post-operative period can not be used to support the pivotal study. Accordingly, the proportions of complete responses for this supportive study are calculated only for the postoperative period of 0-24 hours. Table 2.1.2 presents the proportions of complete responses during 0-24 hour postoperative period using PFAS set for the supportive Study PALO-04-07.

Table 2.1.2 (Reviewer's) Proportions of complete responses during 0-24 hour postoperative period using PFAS set

175 patients involved in unblinding problem

ENDPOINT	PLACEBO n/N (%)	PAL† 0.025 MG n/N (%)	PAL 0.05 MG n/N (%)	PAL 0.075 MG n/N (%)
Complete response in first 24 hour postoperative observation period.	12/48 (26.0%)	13/48 (27.1%)	18/41 (44.0%)	23/40 (58.0%)

369 patients (PFAS) not involved in unblinding problem

ENDPOINT	PLACEBO n/N (%)	PAL† 0.025 MG n/N (%)	PAL 0.05 MG n/N (%)	PAL 0.075 MG n/N (%)
Complete response in first 24 hour postoperative observation period.	37/90 (41.0%)	50/88 (57.0%)	46/96 (48.0%)	53/95 (56.0%)

†: Palonosetron

From Table 2.1.2, it is noted that the percentage of complete responders for placebo using patients involved in the unblinding is 15% less than that of patients not involved in the unblinding. The applicant indicated that due to the unblinding of treatment codes, the clinical staff may be able to identify whether the treatment is palonosetron or placebo. It appears that the result shown by this table for placebo lends support to that assessment. In addition, this result also reinforces the Agency's concern regarding loss of data integrity due to the unblinding.

In addition, using the PFAS population (data not involved in the unblinding), the applicant's efficacy analysis showed that for study PALO-04-07, during the periods of 0-24 hours and the 24-72 hours, comparisons of the single dose groups of palonosetron with placebo resulted in no significant differences for any of the palonosetron treatment groups, after multiplicity adjustments as proposed by the applicant were applied to adjust the p-values. It follows that data from Study PALO-04-07 does not lend positive support for the pivotal Study PALO-04-06. Therefore, Study -07 is not further detailed in this review.

2.2 Data Sources

To assess the clinical efficacy of Aloxi in prevention of postoperative nausea and vomiting, I reviewed the NDA submission hard copies Volumes 211 to 332, dated April 27, 2007. In addition, I reviewed the data sets and documents submitted by the applicant and located at \\CDSESUB1\NONECTD\N21372\S_008\2007-12-06.

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy for Study PALO-04-06

3.1.1 Study Design and Endpoints

The study was designed as a randomized, double-blind, multi-center, parallel group, balanced, stratified, placebo-controlled phase 3 trial to evaluate the efficacy and safety of single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) versus placebo for the prevention of PONV from 0 to 24 hours and 24 to 72 hours in the post-operative period in male and female outpatients undergoing elective laparoscopic abdominal or gynecological surgery with general anesthesia. In this study, outpatients were defined as those expected to go home on the same day as surgery (no overnight stay). All laparoscopic procedures took place under general anesthesia.

The population for this study consisted of eligible male or female outpatients with age $\geq$ 18, undergoing elective laparoscopic abdominal or gynecological surgery, who met the inclusion and not the exclusion criteria for the study and gave their informed consent to participate in the study.

The duration of this study was 12.5 months: first patient enrolled on 23 May 2005 and last patient completed on 12 June 2006. A total of 43 investigators from two countries (USA and Romania) participated in the study: 36 from USA and 7 from Romania.

The study drug was administered as a single i.v. dose of palonosetron or placebo for the prevention of PONV immediately (no more than 5 minutes) prior to induction of anesthesia (Study Day 1). In addition, efficacy and safety were assessed on the day of study drug administration at Visit 2 (Study Day 1) and at a final visit (Study Days 6 to 10) following the surgical procedure.

Patients were contacted on three occasions by telephone (Days 2, 4 and 15) to check on any AEs. Patient diaries were used to record emetic episodes, use of rescue medication, the severity of nausea, the severity of postoperative pain experienced by patients and Quality of Life (QoL). QoL evaluations for nausea and emesis were assessed according to the Osoba questionnaire, which was partially implemented in the study to investigate the interference of nausea and vomiting on patients' daily activities. Rescue medication for the treatment of nausea and vomiting after surgery, with the exception of palonosetron and droperidol, was permitted at the discretion of the investigator.
The investigational drug and the comparator were administered in a blind fashion according to specific procedures described below (Table 3.1.1.1). The pre-filled syringes containing the study drug supplied by the unblinded research pharmacist or unblinded designated person at site were to be administered within 3 hours of preparation on Study Day 1.

Table 3.1.1.1 (Applicant's) Treatment Group

Group	Dose	Volume for IV injection
Group 1	0.025 mg	0.5 mL aliquot of palonosetron + 1.5 mL saline
Group 2	0.050 mg	1.0 mL aliquot of palonosetron + 1.0 mL saline
Group 3	0.075 mg	1.5 mL aliquot of palonosetron + 0.5 mL saline
Group 4	Placebo	2.0 mL saline

A kit randomization list (b) (4) prior to commencing the study to allow for blinding of the four treatment groups. The block size was 4. According to this randomization list, sealed cartons containing the study drugs were prepared and supplied to the unblinded research pharmacist or designated person at the investigative sites. Patients meeting the inclusion and exclusion criteria were randomized to receive a single IV dose for one of the four treatments (palonosetron: 0.025 mg, 0.050 mg, 0.075 mg, or placebo).

The applicant indicated that randomization was stratified by gender, history of PONV and/or currently prone to motion sickness, and smoking status. The stratified randomization scheme produced eight strata. Considering each stratum, patients who met the inclusion and exclusion criteria were assigned to one of four I.V. treatments, following an adaptive randomization algorithm. Randomization was performed to assign patients to the four treatment groups in the ratio of 1:1:1:1. [For full details of the adaptive randomization algorithm, see Appendix I of the protocol, Section 16.1.1.]

The time frame of the study included Visit 1 (Screening/Baseline) from Study Day -7 to 0, Visit 2 (Randomization/Treatment) at Study Day 1, Study Days 2 and 4 scheduled for Telephone Contact 1 and 2, Final Visit (Visit 3) from Study Day 6 to 10, and Study day 15 scheduled for third telephone contact.

The efficacy of I.V. palonosetron or placebo was assessed by measuring complete response (CR, defined as no emetic episode, no rescue medication), complete control (CC, defined as CR and no more than mild nausea), number of emetic episodes, patients with emetic episodes, time to first emetic episode, time of administration and need for rescue medication, time to treatment failure (TTF) (time to first emetic episode, or administration of rescue medication, whichever occurred first), time to first fluid intake, time to first solid meal intake, and severity of nausea.

For the efficacy parameters recorded up to 72 hours after T0, T0 was defined as the time when the patient woke up and was able to respond to verbal commands post operatively.

The study had two co-primary objectives, as follows:

1. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-hour postoperative observation period.

2. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-72 hour postoperative observation period.

Patients with missing or incomplete data were handled as follows (worst case scenario):

- A patient with missing date regarding emetic episodes and/or rescue medication was defined as non-responder for each time interval.
- A patient for whom the duration of retching or relaxation could not be calculated, e.g. due to incomplete onset or end time, was defined as non-responder for the affected time interval.
- If no retching and no vomiting were ticked, but date and/or time was provided, the episode was considered as a vomiting episode.
- A patient who discontinued during the first 24 hours of the 72 hours observation period was defined as a non-responder for both primary efficacy variables.
- A patient who discontinued during the 24-72 hours was defined as a non-responder for the second primary efficacy variable.

The following parameters were evaluated as secondary efficacy measures during the 72 hours postoperative observation period:

- CR at 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours
- CC (CR and no more than mild nausea) at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours
- The number of emetic episodes at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours
- Severity of nausea, measured on a 4-point Likert scale at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours
- Time to first emetic episode
- Time to first administration and need for rescue medication
- TTF (Time to Treatment Failure: time to first emetic episode or time to first administration of rescue medication, whichever occurred first)
- Time to first fluid intake
- Time to first solid meal intake

In addition to the efficacy assessments, the following endpoints for quality of life were also collected in the patient diary:

- Interference of nausea and vomiting symptoms on patients' daily life activities.
- Severity of post-operative pain.

The sample size was based on the assumption of a responder rate of 60% in the palonosetron group and a responder rate of 40% in the placebo group. Using a two-sided test of difference, with α = 0.0166 (obtained as Type I error divided by the number of comparison = 0.05/3) and ß = 0.2 for each comparison, the sample size was estimated at 131 evaluable patients per group. The number was rounded up to a planned sample size of 136 patients per group. For the multiple secondary endpoints comparisons, the sponsor did not specify a procedure to control the Type I error rate.

3.1.2 Statistical Methodologies

The applicant indicated that analysis of data in this study was based on the final protocol dated 28 February 2005 and protocol amendments 1 and 2 dated 18 October 2005 and 06 April 2006, respectively, and the final statistical analysis plan (SAP) dated 06 September 2006. A blind review meeting for the definition of analysis sets was held on 07 September 2006. The database was closed on 11 October 2006 and data were unblinded on 12 October 2006.

The co-primary efficacy hypotheses relevant to the co-primary endpoints were that at least one dose of palonosetron was superior to placebo, considering the CR rate, in the 0-24 hour period and in the 24-72 hour period. These were tested using a closed testing procedure. The 0-24 hour period was tested first; if at least one comparison result was statistically significant, the 24-72 hour interval can be tested, using the same method and the same alpha as further detailed.

For each of the two primary efficacy variables three comparisons were considered:

- To assess the superiority of a single i.v. dose of palonosetron 0.025 mg over placebo.
- To assess the superiority of a single i.v. dose of palonosetron 0.050 mg over placebo.
- To assess the superiority of a single i.v. dose of palonosetron 0.075 mg over placebo.

To control Type I error for the three primary treatment comparisons (0.025 mg vs. placebo, 0.050 mg vs. placebo and 0.075 mg vs. placebo) a multiple type-I error level was guaranteed by the Holm-Bonferroni method: in order to claim a significant difference, the smallest of the three 2-sided p-values must not exceed 0.0166 (0.05/3). If this was achieved, the second smallest p-value must not exceed 0.025 (0.05/2) in order to be significant, and if this was also achieved, the significance threshold for the third p-value was 0.05. This sequential procedure was to be stopped, if the respective threshold was exceeded. The procedure guarantees the multiple type-I error level of 0.05.

Each primary test was performed using a multiple logistic regression adjusted for covariates, where each dose of palonosetron was compared with placebo. The covariates included into the model were the stratification criteria, i.e. gender, history of PONV and/or currently prone to motion sickness, and smoking status. Odds ratio, 95% CI for the odds ratio and p-values derived from the logistic regression were summarized. The same logistic regression model was used to compare each dose of palonosetron to each other. This was done on a descriptive level, i.e. without any further adjustment for multiplicity.

It is noted that a dynamic adaptive treatment allocation procedure including a randomization component was applied in this study. The applicant indicated that to confirm the validity of the primary efficacy analysis, a sensitivity analysis was performed using re-randomization as follows: a list of uniformly distributed numbers between 0 and 1 were created at random 30,000 times. Given the actual patients assigned to the FAS with their stratification factors and their actual sequence of enrolment, the dynamic randomization treatment assignment algorithm was applied using each of these 30,000 lists to get 30,000 sets of patient treatment assignments. The logistic regression for the two co-primary efficacy parameters based on the MFAS was run for each of the 30,000 sets of patient treatment assignments calculating Wald chi -square test statistics for each of the three comparisons of interest. The p-value for each comparison was derived from the re-randomization distributions, as the proportion of the 30,000 test statistics that were larger or equal to the test statistic actually observed in the study.

In addition, statistical summaries for continuous parameters included n, mean, standard deviation (SD), minimum, median, maximum and 95% confidence interval (95% CI) for the mean. Continuous data that were expected to be skewed were presented in terms of n, minimum, 1st quartile, median, 3rd quartile, and maximum. Categorical data were summarized in terms of frequency counts and percentages. If not stated otherwise, percentages were based on the number of patients in the relevant treatment group. The 95% CI for proportions and for the difference between two proportions were calculated according to the formulas proposed by R. G. Newcombe and D. G. Altman in "Statistics with Confidence". Efficacy summaries were provided by treatment group, overall and stratified by gender, history of PONV and/or currently prone to motion sickness, and smoking status.

Within country/region and center summaries were provided by treatment group for the two co-primary efficacy variables and for the summary of adverse events table. Centers with "few" patients were pooled in order to homogenize groups. In addition, during the blind review meeting the number of patients in each site was checked in order to identify the regions for the by country/region analysis. The number of patients in each category for the analysis by age group and by narcotic analgesics was discussed.

As for the country/region analysis, five main regions were identified: US East Coast, US West Coast, US South East, US South West (Texas) and Romania. The pooling of low-enrolling centers was performed to obtain a comparable sample size to that in centers that had enrolled higher numbers of patients within the predefined regions.

The applicant emphasized that less than 2% of the enrolled patients were aged 65 years or more. Therefore an analysis for the subgroups $\leq$ 65 years, >65 years, $\leq$ 75 years and >75 years would have been meaningless. As a consequence an analysis was only performed for patients $\leq$ 40 years and > 40.
For the analysis population, the following three types of populations were proposed by the applicant:

Full Analysis (FAS) Set: The FAS was defined as patients who received study drug, anesthetic procedures and surgical operation. Following the intent-to-treat principle, patients were assigned to the study drug group according to the treatment to which they were randomized.

Per-Protocol (PP) Set: PP set was defined as all patients who completed Day 3 (i.e., the first 72 hours after T0) and who were compliant with the study protocol. The PP set is a subset of the FAS. As there were two co-primary endpoints in the study, and since major protocol deviations occurred in the 24-72 hours period could not influence the results for the primary endpoint in the 0-24 hours period, a PP (0-24) set was defined in addition to the PP set. Patients without major protocol deviation in the 0-24 hours period were part of the PP (0-24) analysis even if they were excluded from the PP set.

Safety Set: The safety set was defined as all patients who received study drug and had at least one safety assessment after treatment. Patients were assigned to the study drug group according to the actual treatment received.

The primary analysis population for efficacy analyses was the FAS. A secondary analysis of the primary efficacy parameters was performed based on the PP (0-24) set for the interval 0-24 hours and based on the PP set for the interval 24-72 hours. In the event of major discrepancies in the results of the analysis using the different populations, e.g., significant results in only one of the two populations, an appropriate sensitivity analysis was to be performed.

During the blind review meeting, the adherence of protocol for each patient was investigated. Deviations were coded as "major" or "minor" depending on the impact they could have in the results. A patient with one or more major protocol deviations was not included into the PP set. A patient listing containing all identified major protocol deviations was provided and agreed with HELSINN Healthcare SA. HELSINN Healthcare SA confirmed the analysis populations on 11 October 2006, prior to unblinding the database.

Patients with partial or completely missing data for the primary efficacy variable were classified as not having a CR. For the "time to event" analyses (time to first emetic episode, time to first administration of rescue medication and time to treatment failure), survival times that were not known exactly were considered as censored data.

If there was no event in the period of observation, survival time was censored at the end of observation at 72 hours. Premature study termination was censored at the day of termination. In this case the time of the last entry documented in the diary (if present) was used to censor survival time.

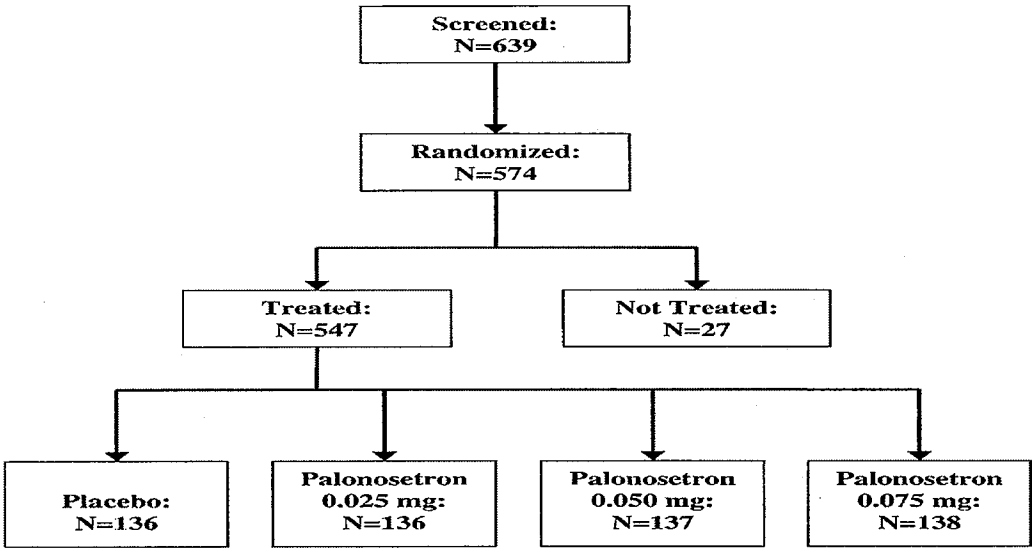
Missing or incomplete data for other secondary efficacy variables were replaced by the last value available (last observation carried forward, LOCF) or, in case no data at all for LOCF were available, would be replaced with the worst value obtained in the same analysis set for the same parameter. These principles were used for severity of nausea, intake of rescue medication, and the number of emetic episodes. Based on these data CR and CC were calculated.

For the Osoba total score, missing values in up to two items were ignored and the total score was obtained from the other non-missing items. If more than two items were missing the total score was regarded as missing. Thus, the LOCF principle was not used for missing items of the Osoba questionnaire.
Patients with missing informed consent were excluded from all the populations. The planned subpopulations to be used for statistical analyses were also investigated during the blind review meeting. The disposition of patients is summarized below:

Patient Disposition

A total of 639 patients were screened for this study, of which 574 patients were randomized into one of the four treatment arms. A total of 547 patients were treated. The disposition of patients is shown in Figure 3.1.2.1

Figure 3.1.2.1 (Applicant's) Disposition Flow Chart: All Patients



Forty-eight (8.4%) out of 574 randomized patients did not complete the study. The reasons for premature study termination were patient lost to follow-up (16 patients, 2.8%), violation of inclusion and/or exclusion criteria (7 patients, 1.2%), decision of patient (4 patients, 0.7%), decision of investigator (3 patients, 0.5%), non-serious AE (1 patient, 0.2%), and other reasons (17 patients, 3.0%).

A total of 489 patients were randomized at 36 centers in the USA, while seven centers in Romania randomized 85 patients. All 85 patients randomized in Romania received treatment and 462 out of 489 randomized patients were treated in the US.

Patient randomization was stratified by the following PONV risk factors: gender, history of PONV and/or currently prone to motion sickness, and smoking status (i.e. producing eight strata,

four of which were filed). The number of patients with these risk factors is shown in Table 3.1.2.1.

Table 3.1.2.1 (Applicant's) PONV Risk Factors: Randomized Patients

Gender (N=574)		History of PONV or prone to motion sickness (N=573*)		Smoking status (N=574)	
Male	Female	Yes	No	Non-smoker	Smoker
25	549	375	198	489	85

Source: Section 16.5, Table 1.1
N=number of patients in each category
** Information was missing in CRF for 1 patient*

From Table 3.1.2.1, the applicant asserted that the majority of patients were females; about two third of patients had a positive history of PONV or motion sickness; whereas non smoking status was strongly predominant.

Demographics and Baseline Characteristics

Demographic data and stratification criteria for patients within each treatment group are presented for the FAS in Table 3.1.2.3.

Table 3.1.2.3 (Applicant's) Demographic Characteristics and Stratification Criteria (FAS, N = 546)

	Placebo (N=135)	Palonosetron 0.025 mg (N=136)	Palonosetron 0.050 mg (N=137)	Palonosetron 0.075 mg (N=138)	Overall (N=546)
Gender, n (%)					
Male	5 (3.7)	6 (4.4)	6 (4.4)	6 (4.3)	23 (4.2)
Female	130 (96.3)	130 (95.6)	131 (95.6)	132 (95.7)	523 (95.8)
Age (years)					
Mean (SD)	36.5 (9.77)	38.5 (10.91)	36.9 (10.14)	37.9 (10.74)	37.4 (10.40)
Min	18	18	20	21	18
Median	35.0	36.0	35.0	36.0	36.0
Max	76	77	71	74	77
Age group, n (%)					
≤40 years	95 (70.4)	84 (61.8)	94 (68.6)	96 (69.6)	369 (67.6)
>40 years	40 (29.6)	52 (38.2)	43 (31.4)	42 (30.4)	177 (32.4)
≤65 years	134 (99.3)	133 (97.8)	135 (98.5)	135 (97.8)	537 (98.4)
>65 years	1 (0.7)	3 (2.2)	2 (1.5)	3 (2.2)	9 (1.6)
≤75 years	134 (99.3)	135 (99.3)	137 (100.0)	138 (100.0)	544 (99.6)
>75 years	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)
Race, n (%)					
Caucasian	92 (68.1)	91 (66.9)	100 (73.0)	87 (63.0)	370 (67.8)
Black	16 (11.9)	20 (14.7)	14 (10.2)	27 (19.6)	77 (14.1)
Hispanic	22 (16.3)	20 (14.7)	21 (15.3)	21 (15.2)	84 (15.4)
Asian	4 (3.0)	4 (2.9)	1 (0.7)	2 (1.4)	11 (2.0)
Other	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	4 (0.7)
History of PONV, n (%)					
Yes	86 (63.7)	86 (63.2)	90 (65.7)	91 (65.9)	353 (64.7)
No	49 (36.3)	49 (36.0)	47 (34.3)	47 (34.1)	192 (35.2)
Missing	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Smoking status, n (%)					
Non-smoker	116 (85.9)	116 (85.3)	117 (85.4)	117 (84.8)	466 (85.3)
Smoker	19 (14.1)	20 (14.7)	20 (14.6)	21 (15.2)	80 (14.7)
Alcohol consumption*, n (%)					
Not done	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
No	67 (49.6)	74 (54.4)	80 (58.4)	79 (57.2)	300 (54.9)
Rarely	25 (18.5)	29 (21.3)	24 (17.5)	20 (14.5)	98 (17.9)
Occasionally	41 (30.4)	30 (22.1)	32 (23.4)	36 (26.1)	139 (25.5)
Daily	1 (0.7)	3 (2.2)	1 (0.7)	3 (2.2)	8 (1.5)
Height (cm)*					
Mean (SD)	164.8 (7.11)	164.3 (7.10)	164.6 (7.79)	163.6 (7.25)	164.3 (7.31)
Min	148	150	140	144	140
Median	165.0	165.0	165.0	163.0	165.0
Max	183	185	185	180	185
Weight (kg)*					
Mean (SD)	71.0 (15.19)	72.4 (16.53)	70.8 (16.06)	73.8 (15.38)	72.0 (15.80)
Min	47	42	40	45	40
Median	68.0	69.3	68.0	70.8	69.5
Max	125	111	126	117	126
BMI (kg/m²)*					
Mean (SD)	26.1 (5.33)	26.8 (5.72)	26.1 (5.33)	27.6 (5.49)	26.6 (5.49)
Minimum	18	17	15	18	15
Median	25.5	25.5	25.4	26.6	25.8
Maximum	40	40	40	40	40

Source: Section 16.5, Tables 1.5, 2.1.1 and 2.2.1
N=number of patients in each treatment group; n=number of patients in relevant category;
*SD=standard deviation; BMI=Body Mass Index; *=N was 134 for the placebo group and 545 for the overall FAS.*

Overall, 23 out of the 546 patients (4.2%) in the FAS were male and 523 (95.8%) were female. The mean (±SD) age of patients overall was 37.4 years (10.40). Age was also grouped in categories: ≤ or > 40 years, ≤ or > 65 years and ≤ or > 75 years. Nine patients were aged over 65 years, of these two were aged over 75 years. Analysis by age was only performed for the categories ≤ or > 40 years old as a result of the sample size for elderly patients being too small.

Patients from Romania were slightly younger than US patients. The mean (±SD) age for Romanian patients was 32.2 (± 6.54) years, while for patients across the US regions the mean ranged from 35.8 (± 8.19) years to 40.8 (± 11.09) years.

The majority of patients were Caucasian (370 patients, 67.8%), 84 patients were Hispanic (15.4%) and 77 were Black (14.1 %). Eleven patients were Asian (2.0%) and the remaining 4 patients (0.7%) were of other races. Treatment groups were homogeneous. The majority of black patients were recruited in Texas, while in Romania all patients were Caucasian.

Eighty of the 546 (14.7%) patients in the FAS were smokers. All of these patients (100%) were female and had a history of PONV or were currently prone to motion sickness (due to the inclusion criterion that all recruited patients had to have at least two out of three PONV risk factors). The percentage of patients that were smokers was similar across the treatment groups. Alcohol consumption was similar across the treatment groups, with 300 patients (54.9%) overall that did not drink alcohol, 98 patients (17.9%) drank rarely, 139 patients (25.5%) drank occasionally and 8 patients (1.5%) drank daily in the FAS.

Age, height, weight and BMI were similar across the treatment groups; therefore the 4 treatment groups were well-balanced according to these demographic characteristics. Overall, patient height ranged from 140 to 185 cm, weight ranged from 40 kg to 126 kg, and BMI from 15 to 40 kg/m^2. The lowest mean weight was observed in Romania (62.8 kg) and the highest in the US West Coast (76.8 kg). The mean BMI was 22.9 (± 3.81) kg/m^2 in Romania, while in US regions the mean ranged from 26.1 (±5.00) kg/m^2 (East Coast) to 28.4 (±5.45) kg/m^2 (South East). The demography and anamnesis of the safety and PP cohort were similar to those of FAS cohort.

3.1.3 Applicant's Efficacy Analysis Results and Conclusions

Efficacy comparison analysis

3.1.3.1 Co-primary Endpoint Analysis

There were two co-primary endpoints: complete response during the first 24-hour (0-24 hours) postoperative observation period and during the 24-72-hour (24-72 hours) postoperative observation period. For the two co-primary endpoints, the applicant basically performed two pre-specified efficacy analyses to compare the efficacy of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo: 1) a simple analysis of proportions and 2) a logistic regression analysis. The applicant declared that the logistic analysis is the primary efficacy analysis. In addition, patients with partially or completely missing data for the primary efficacy variable were classified as not having a complete response.

1) Simple proportions analysis

Table 3.1.3.1.1 presented the applicant's summary of the efficacy analysis results based on the proportions for the complete responses at 0-24 hours and 24-72 hours using full analysis set (FAS).

Table 3.1.3.1.1 (Applicant's) Primary Efficacy Results for Complete Response (FAS, N = 546)

	Placebo (N=135)	Palonosetron 0.025 mg (N=136)	Palonosetron 0.050 mg (N=137)	Palonosetron 0.075 mg (N=138)
0-24 hours, n (%)	**35 (25.9)**	**45 (33.1)**	**54 (39.4)**	**59 (42.8)**
95% CI for CR rate	[19.3;33.9]	[25.7;41.4]	[31.6;47.8]	[34.8;51.1]
Palo-Placebo: Difference in CR rate and 95% CI		7.2% [-3.7;17.8]	13.5% [2.3;24.2]	16.8% [5.6;27.5]
24-72 hours, n (%)	**55 (40.7)**	**60 (44.1)**	**65 (47.4)**	**67 (48.6)**
95% CI for CR rate	[32.8;49.2]	[36.0;52.5]	[39.3;55.8]	[40.4;56.8]
Palo-Placebo: Difference in CR rate and 95% CI		3.4% [-8.3; 14.9]	6.7% [-5.0;18.2]	7.8% [-3.9;19.3]

N=number of patients in each treatment group; n=number of patients with CR; CR=Complete Response; CI = Confidence Interval.

Based upon Table 3.1.3.1.1, the applicant indicated that the proportion of patients with CR during the first 24 hours in the postoperative observation period was highest in the palonosetron 0.050 mg and 0.075 mg groups (39.4% and 42.8%, respectively) and lowest in the placebo group (25.9%). Differences in CR between palonosetron and placebo were 7.2%, 13.5% and 16.8% for the 0.025 mg, 0.050 mg and 0.075 mg groups, respectively.

In the 24-72 hour interval, the proportion of patients with complete response was numerically higher in the palonosetron groups as compared to placebo. In general, the proportion of patients with CR in the 24-72 hour period was higher than the proportion of patients with CR in the first 0-24 hours. This was more evident in the placebo group; the applicant then, indicated that the difference between the palonosetron treatment groups and placebo at 24-72 hours is less than in the initial 24 hour period.

2) Logistic regression analysis

The applicant indicated that to account for multiple comparisons of treatments (0.025 mg vs. placebo, 0.050 mg vs. placebo and 0.075 mg vs. placebo), a logistic regression adjusted by covariates (stratification criteria) was performed to compare the efficacy of each dose of palonosetron versus placebo for each of the two main time intervals (i.e. 0-24 and 24-72 hours) using the Holm-Bonferroni method to keep overall type-I error level of 0.05. To claim a significant difference by the Holm-Bonferroni method, the smallest of the three 2-sided p-values must not exceed 0.0166 (0.05/3). If this was achieved, the second smallest p-value must not exceed 0.025 (0.0512) to be significant, and if this was also achieved, the significance threshold for the third p-value was 0.05. This sequential procedure was stopped if the respective threshold was exceeded.

For the logistic regression analysis, the results using two data sets (FAS and PP) were reported and FAS was defined as the primary data set. Summary results of the logistic regression are presented in Table 3.1.3.1.2 using full analysis set.

Table 3.1.3.1.2 (Applicant's) Efficacy comparison by logistic regression analysis† (FAS; N=546)

		Adjusted Significance Level	Superiority Over Placebo
0-24 hours			
Palonosetron 0.075 mg vs placebo			
Difference in CR Rate and 95% CI	16.8% [5.6; 27.5]		
p-Value	0.0035	0.0166	YES
Palonosetron 0.050 mg vs placebo			
Difference in CR Rate and 95% CI	13.5% [2.3; 24.2]		
p-Value	0.0171	0.025	YES
Palonosetron 0.025 mg vs placebo			
Difference in CR Rate and 95% CI	7.2% [-3.7; 17.8]		
p-Value	0.1868	0.05	NO
24-72 hours			
Palonosetron 0.075 mg vs placebo			
Difference in CR Rate and 95% CI	7.8% [-3.9; 19.3]		
p-Value	0.1877	0.0166	NO
Palonosetron 0.050 mg vs placebo			
Difference in CR Rate and 95% CI	6.7% [-5.0; 18.2]		
p-Value	0.2490	0.025	NO
Palonosetron 0.025 mg vs placebo			
Difference in CR Rate and 95% CI	3.4% [-8.3; 14.9]		
p-Value	0.6380	0.05	NO

CR: Complete Response; CI: Confidence Interval.

For the 0-24 hour time period, comparisons of the single dose groups of palonosetron with placebo resulted in significant p-values for palonosetron 0.075 mg (p=0.0035) and palonosetron 0.050 mg (p=0.0171), whereas no significant p-values were observed for the lowest dose versus placebo. Then, based on the results, the applicant indicated that as the smaller of the p-values was 0.0035 (less than 0.0166) and the second smallest was 0.0171 (less than 0.025), the superiority for both palonosetron 0.075 mg and palonosetron 0.050 mg over placebo in the 0-24 hours time period were demonstrated.

Regarding the time interval 24-72 hours, as all p-values exceeded the pre-set adjusted significance levels, the superiority of palonosetron for the three doses (0.025, 0.05, and 0.075 mgs) versus placebo in this interval were not statistically demonstrated.

For the result using PP set, the applicant indicated that since some patients were administered prohibited anti-emetic medications, these patients were considered in the FAS data set as failures. Being also assessed as protocol violators, they were excluded from the PP sets and therefore the proportion of patients with complete response was greater in all treatment groups compared to the FAS. However, in the PP set, unlike FAS set, there were not significant differences during the 0-24 hour period between the placebo group and the palonosetron 0.050 mg group and between the placebo group and the palonosetron 0.075 mg group, after using Holm-Bonferroni method to adjust the Type I error rate. Thus, the findings in the PP set were not consistent with that in the FAS.

Verification of treatment allocation procedure

As a dynamic randomization was used for this study, a sensitivity analysis was performed based upon the re-randomization data to verify the validity of the primary efficacy analysis. The applicant indicated that the results of this check are similar to those obtained with the real patient

assignment using logistic regression analysis: for CR 0-24 hours, significant p-values were observed for the comparison of palonosetron 0.075 mg versus placebo (p=0.0027) and for the comparison of palonosetron 0.050 mg versus placebo (p=0.0190), whereas no significance was seen for palonosetron 0.025 mg versus placebo. No comparison resulted in statistical significance in the 24-72 hour period as shown for the FAS.

3.1.3.2 Secondary Endpoint Analysis

The sponsor did not pre-specify any method to control Type I error for the testing of secondary endpoints. In the sponsor submission, section 9.8.1.5.2, it is stated that the analyses of secondary endpoints are considered descriptive. Consequently, the results below should not be considered as confirmatory comparisons.

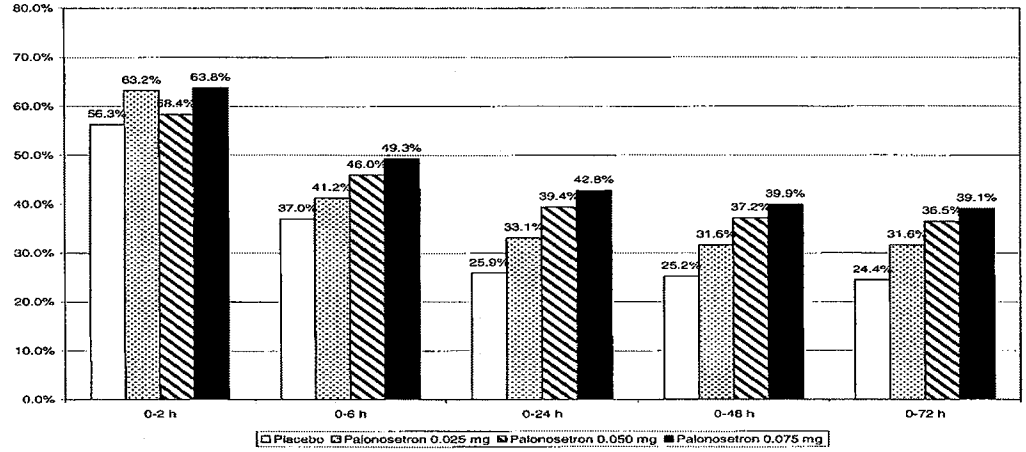
1) Complete response at further time periods

The proportion of patients considered to have achieved complete response (CR) during the 0-2, 0-6, 2-6, 6-24, 24-48, 48-72 hours as well as during the overall 0-48 and 0-72 hours postoperative observation periods, was evaluated as additional parameter for the characterization of the anti-emetic effect of the study drug.

In the 0-2 hour postoperative period, the applicant indicated that the proportions of patients with CR in the 3 palonosetron groups (0.025 mg: 63.2%; 0.050 mg: 58.4%; and 0.075 mg: 63.8%) were numerically higher than that in the placebo group (56.3%). Similarly, for the rest of the intervals assessed also showed that the proportions of patients with CR in the 3 palonosetron groups were numerically higher than that in the placebo group.

The proportions of patients with CR over time for the cumulative time intervals are described in Figure 3.1.3.2.1.

Figure 3.1.3.2.1 (Applicant's) Complete Response: Analysis over Time using FAS set



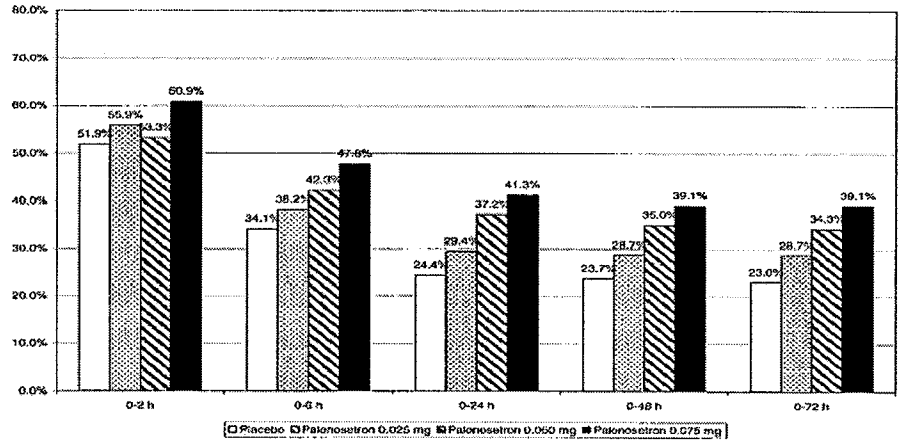
2) Complete Control

The proportion of patients considered to have achieved a Complete Control (CC defined as CR, and no more than mild nausea) in the postoperative observation period, i.e. during the 0-24,24-72,0-2,0-6,2-6,6-24,24-48,48-72,0-48 and 0-72 hours was analyzed to further investigate the efficacy of the study drugs in the trial.

Over the 0-2 hour postoperative period, the applicant indicated that the proportions of patients with CC in the three palonosetron groups (0.025 mg: 55.9%; 0.050 mg: 53.3%; and 0.075 mg: 60.9%) were numerically higher than in the placebo group (51.9%). Similarly, for the rest of the intervals assessed (except for the interval 6-24 hours), also showed that the proportions of patients with CR in the 3 palonosetron groups were numerically higher than that in the placebo group.

The proportions of patients with CC over time for the cumulative time intervals are described in Figure 3.1.3.2.2

Figure 3.1.3.2.2 (Applicant's) Complete Control: Analysis over Time using the FAS



3) Emetic episodes and time to first emetic episode

Emetic episodes

The number of patients with emetic episodes and the number of emetic episodes were recorded as secondary efficacy parameters. Evaluations were carried out at 0-24, 24-72, 0-2,0-6, 2-6, 6-24, 24-48,48-72,0-48 and 0-72 hours postoperatively. The mean number of emetic episodes was small in each time interval and in each treatment group. Over the whole duration of the study, i.e. 0-72 hours, the mean (±SD) number of emetic episodes was highest in the palonosetron 0.025 mg group (1.5±2.76), which was higher than the placebo group (1.1±1.79) and both the palonosetron 0.050 mg group (0.9±1.56) and the palonosetron 0.075 mg group (0.8±1.43). Most of the episodes occurred during the first 0-24 hours: the mean number of emetic episodes was the greatest in the palonosetron 0.025 mg group (1.1±1.93), compared with the placebo group (1.0±1.58) and both the palonosetron 0.050 mg group (0.7±1.18) and the palonosetron 0.075 mg group (0.7±1.16).

For the cumulative periods 0-24, 0-48 and 0-72 hours, a greater proportion of patients in the placebo group and palonosetron 0.025 mg group experienced an emetic episode when compared with the palonosetron 0.050 mg and 0.075 mg groups. A similar trend was observed for most of the time intervals, i.e., there was a greater proportion of placebo and palonosetron 0.025 mg patients with emetic episodes in any given time interval compared to palonosetron 0.050 mg and 0.075 mg patients. The exceptions were the 24-48 hour interval where a slightly greater proportion of palonosetron 0.075 mg patients (7.2%) experienced an emetic episode than in the placebo group (6.7%) and the 0-2 hour interval where the proportion of patients with emetic episodes was 13.0% for palonosetron 0.075 mg and 10.3% for the palonosetron 0.025 mg group.

Table 3.1.3.2.1 shows the number of patients with emetic episodes in the FAS.

Table 3.1.3.2.1 (Applicant's) Number of Patients with Emetic Episodes using FAS set (N = 546)

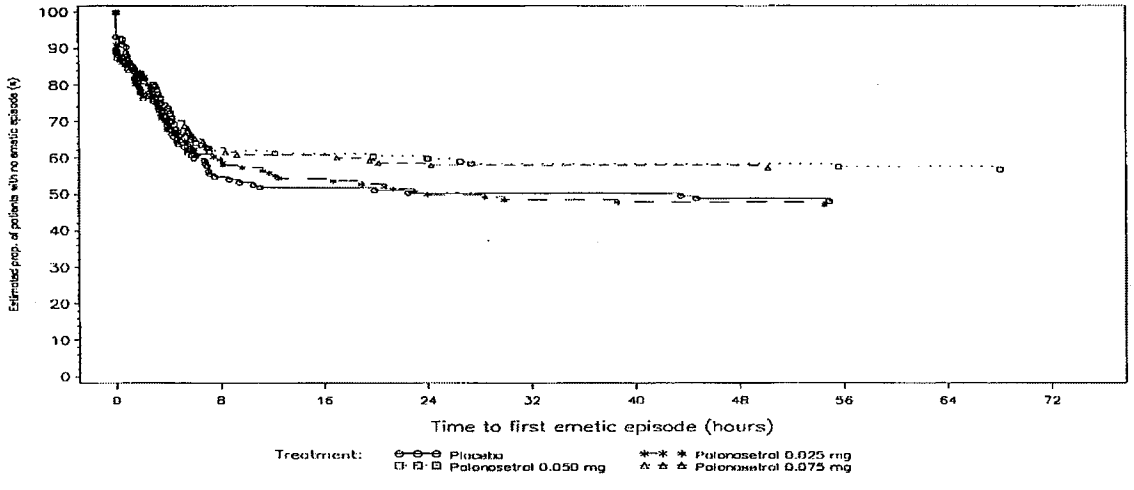
Time Interval, n (%)	Placebo (N=135)	Palonosetron 0.025 mg (N=136)	Palonosetron 0.050 mg (N=137)	Palonosetron 0.075 mg (N=138)
0-24 hours	60 (44.4)	58 (42.6)	42 (30.7)	46 (33.3)
24-72 hours	12 (8.9)	19 (14.0)	7 (5.1)	12 (8.7)
0-2 hours	22 (16.3)	14 (10.3)	11 (8.0)	18 (13.0)
0-6 hours	46 (34.1)	43 (31.6)	35 (25.5)	36 (26.1)
2-6 hours	37 (27.4)	38 (27.9)	29 (21.2)	24 (17.4)
6-24 hours	28 (20.7)	38 (27.9)	19 (13.9)	22 (15.9)
24-48 hours	9 (6.7)	17 (12.5)	4 (2.9)	10 (7.2)
48-72 hours	7 (5.2)	8 (5.9)	3 (2.2)	5 (3.6)
0-48 hours	61 (45.2)	61 (44.9)	44 (32.1)	48 (34.8)
0-72 hours	62 (45.9)	62 (45.6)	46 (33.6)	49 (35.5)

Time to first emetic episode

Using the Kaplan-Meier estimate, the 25% quantiles for the time to first emetic episode were similar in all treatment groups, ranging from 3.2 hours (placebo and palonosetron 0.025 mg) to 3.8 hours (palonosetron 0.050 mg). The Kaplan-Meier estimate for the median time to first emetic episode was 43.5 hours in the placebo group, and 26.2 hours in the palonosetron 0.025 mg group. The applicant indicated that since more than 50% of patients were considered censored at the end of the 72-hour observation period in the palonosetron 0.050 mg and 0.075 mg treatment groups (i.e. patients with no vomiting through 72 hours), median time to first emetic episode cannot be calculated. The log-rank test for overall comparison did not show any significant differences between the groups (p=0.0965).

The results of the analysis of time to first emetic episode for the FAS are shown in Figure 3.1.3.2.3.

Figure 3.1.3.2.3 (Applicant's) Time to first emetic episode: Kaplan-Meier Curves



Note: Patients who did not have emetic episodes were censored at 72 hours

4) Severity of nausea

The severity of nausea was assessed on a 4-point scale (none, mild, moderate, and severe) at the following time points to 72 hours; i.e. at 2, 6, 24, 48 and 72 hours.

The applicant indicated that overall, the severity of nausea increased during the 2-6 hour time period, especially in the placebo and palonosetron 0.025 mg groups and thereafter decreased with time.

During the first two hours of observation approximately half of the patients had no nausea in all treatment groups. Considering the 0-72 hour observation period most of the patients had no or mild nausea. At each time interval up to the first 24 hours, the greatest percentage of patients with severe nausea received placebo, whereas the greatest percentage of patients with no nausea received palonosetron 0.075 mg.

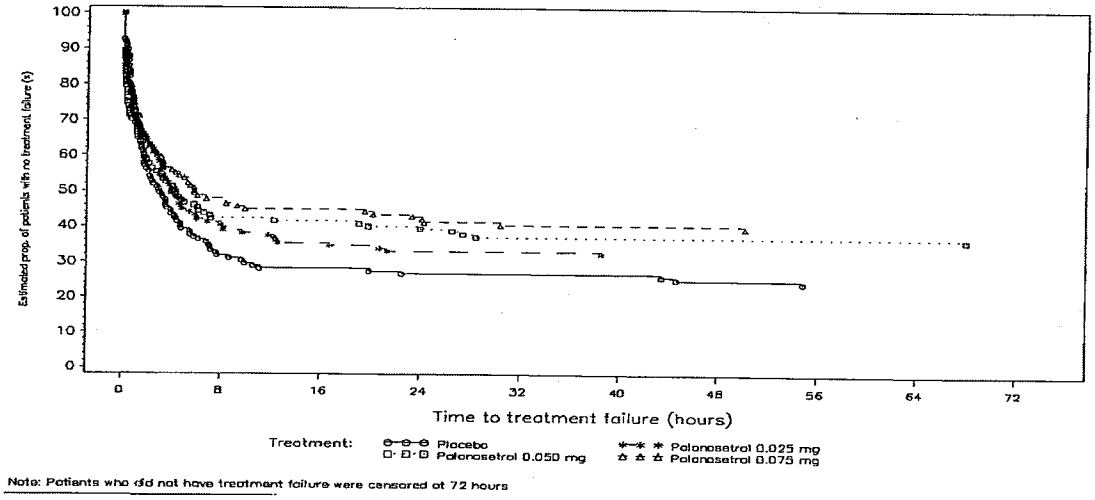
5) Time to Treatment Failure

The time to treatment failure (time to first emetic episode or time to first administration of rescue medication, whichever occurred first) was evaluated as a secondary efficacy parameter.

Using the Kaplan-Meier estimate, the 25% quantile for the time to treatment failure was numerically shortest in the palonosetron 0.050 mg group (0.3 hours) and longest in the palonosetron 0.075 mg group (0.9 hours).

The median time to treatment failure showed a dose-related response: 5.8 hours in the palonosetron 0.075 mg group; 4.3 hours in the palonosetron 0.050 mg group; and 3.9 hours in the palonosetron 0.025 mg group, compared to 3.0 hours in the placebo group. The result of the analysis of time to treatment failure for the FAS was shown in Figure 3.1.3.2.4.

Figure 3.1.3.2.4 (Applicant's) Time to treatment failure: Kaplan-Meier Curves



6) Quality of life

The interference of quality of life (QoL) based upon nausea and vomiting in patients' functioning was assessed daily using the modified Osoba nausea and emesis questionnaire. This instrument has not been validated for the intended indication, and these results will not be considered for labeling. The results described below are considered exploratory.

The questionnaire consisted of 5 questions related to the interference of nausea and vomiting with appetite, sleep, physical activities, social life and enjoyment of life. These were answered by patients using a 4-point scale at 24 hours, 48 hours and 72 hours. Lower values corresponded with better function and QoL. The total score ranges from 0 to 100, with 0 representing no interference.

For the 0-24 hour observation period, there was less overall interference of nausea and vomiting in the palonosetron 0.075 mg group (mean±SD:13.8±24.07) compared to the other groups: placebo, 19.7±24.55; palonosetron 0.025 mg, 20.2±28.09; and palonosetron 0.050 mg, 19.2±25.94. An overall statistical comparison showed significant differences between the groups (p=0.0265), with palonosetron 0.075 mg showing statistical significant differences in pair-wise comparisons with placebo (p=0.0038) and palonosetron 0.025 mg (p=0.0170). At 48 and 72 hours the total scores were similar between treatment groups.

For the 0-24 hour observation period, there was less interference of nausea and vomiting on social life in the palonosetron 0.075 mg group (mean±SD: 1.3±0.78) than any of the other groups: placebo, 1.5±0.89; palonosetron 0.025 mg, 1.5±0.95; and palonosetron 0.050 mg, 1.5±0.91. An overall statistical comparison showed no significant differences between the groups but pair-wise comparisons showed palonosetron 0.075 mg to be statistically significant different compared to placebo (p=0.0128), palonosetron 0.025 mg (p=0.0356) and palonosetron 0.050 mg (p=0.0342). At 48 and 72 hours the scores for this domain were similar between

treatment groups, although pair-wise comparisons showed palonosetron 0.075 mg to be statistically significant different compared to palonosetron 0.050 mg (p=0.0345) at 72 hours.

For the 0-24-hour observation period, there was less interference of nausea and vomiting on enjoyment of life in the palonosetron 0.075 mg group (mean±SD: 1.4±0.84) than any of the other groups: placebo, 1.6±0.93; palonosetron 0.025 mg, 1.6±0.98; and palonosetron 0.050 mg, 1.6±0.99. An overall statistical comparison showed no significant differences between the groups but pair-wise comparisons showed palonosetron 0.075 mg to be statistically significant different compared to placebo (p=0.0296), and palonosetron 0.025 mg (p=0.0474). At 48 and 72 hours the scores were similar between treatment groups.

For all intervals of the observation period, scores were similar for all groups for both the interference of nausea and vomiting on sleep and the interference of nausea and vomiting on physical activities. There were no statistically significant differences between any of the treatment groups at any time point for either of these individual domains.

3.1.4 Statistical Reviewer's Analysis and Comments

In this section, this reviewer first would like to perform the following three analyses based upon complete response: 1) efficacy comparison by site, 2) sensitivity analysis, and 3) non-parametric analysis of covariance. Then, this reviewer makes comments on the following two issues: 1) impact of baseline adaptive randomization on efficacy analysis and 2) single pivotal study.

Since the three palonosetron doses (0.0025, 0.05, 0.075 mgs) failed to demonstrate superiority to placebo during the first 24-72 hour postoperative observation period, the three analyses performed by this reviewer based upon complete response are for the first 24 hour postoperative observation period. Data used by this reviewer was submitted by the applicant dated April 27, 2007.

Reviewer's Analysis

1) Efficacy comparison by site

In order to explore whether the effects of the palonosetron 0.05 mg and 0.075 mg compared to placebo were dominated by certain investigator-sites, this reviewer calculated the proportions on the complete response for the first 24 hour postoperative observation period (primary endpoint) by investigator-site using the FAS population. The investigator-sitesused in this analysis were provided in the data set submitted by the applicant on April 27, 2007.

Since a small site has no capability to dominate the superiority of the study drug palonosetron to placebo, the proportions of complete responses for sites with more than ten patients are explored and presented in Table 3.1.4.1.

Table 3.1.4.1 (Reviewer's) proportions of complete response by site using FAS population

SITE NUMBER	PLACEBO % (n/N)	PAL. 0.025MG % (n/N)	PAL. 0.05MG % (n/N	PAL. 0.075MG % (n/N
Site 102	0.0 (0/5)	50.0 (2/4)	0.0 (0/5)	0.0 (0/3)
Site 103	20.0 (2/10)	25.0 (3/12)	30.8 (4/13)	14.3 (2/14)
Site 105	0.0 (0/1)	25.0 (1/4)	50.0 (2/4)	66.7 (2/3)
Site 108	0.0 (0/4)	50.0 (2/4)	33.3 (1/3)	0.0 (0/1)
Site 109	0.0 (0/3)	20.0 (1/5)	0.0 (0/2)	16.7 (1/6)
Site 116	0.0 (0/4)	60.0 (3/5)	50.0 (2/4)	25.0 (1/4)
Site 118	25.0 (1/4)	16.7 (1/6)	25.0 (1/4)	33.3 (2/6)
Site 121	40.0 (6/15)	36.4 (4/11)	38.5 (5/13)	38.5 (5/13)
Site 123	0.0 (0/4)	0.0 (0/2)	33.3 (1/3)	50.0 (1/2)
Site 124	33.3 (2/6)	50.0 (2/4)	16.7 (1/6)	40.0 (2/5)
Site 127	33.3 (1/3)	33.3 (1/3)	50.0 (2/4)	66.7 (2/3)
Site 132	25.0 (3/12)	35.7 (5/14)	33.3 (4/12)	53.8 (7/13)
Site 134	0.0 (0/5)	0.0 (0/2)	0.0 (0/2)	60.0 (3/5)
Site 137	25.0 (1/4)	25.0 (1/4)	20.0 (1/5)	25.0 (1/4)
Site 138	25.0 (1/4)	50.0 (1/5)	0.0 (0/1)	66.7 (2/3)
Site 139	33.3 (1/3)	66.7 (2/3)	75.0 (3/4)	100.0 (1/1)
Site 152	25.0 (1/4)	50.0 (2/4)	66.7 (2/3)	75.0 (3/4)
Site 182	*60.0 (3/5)*	*55.6 (5/9)*	*100.0 (9/9)*	*83.3 (5/6)*
Site 183	0.0 (0/3)	0.0 (0/1)	100.0 (1/1)	75.0 (3/4)
Site 184	25.0 (1/4)	40.0 (2/5)	25.0 (1/4)	25.0 (1/4)
Site 185	33.3 (1/3)	25.0 (1/4)	75.0 (3/4)	50.0 (2/4)

Based upon the results from Table 3.1.4.1, for palonosetron 0.075mg, the proportions of complete response in most sites are much greater than that in the placebo group. No particular sites are identified to have unusually large proportions of complete response to dominate the superiority of palonosetron 0.075 mg to placebo.

However, for palonosetron 0.05mg, although the proportions of complete response in most sites are greater than that of Placebo, it seems unusual that the complete responses for all nine patients in Site 182 are assessed as success. In addition, only 5 out of 9 patients (56%) in palonosetron 0.025 mg and 5 out of 6 patients (83%) in palonosetron 0.075 mg assessed as success, the concern of 9 out of 9 (100%) patients in Palonosetron 0.05 mg assessed as success in complete response can not be ruled out. It is also noted that the superiority of Palonosetron 0.05 mg to placebo is close to border line (p=0.0171 versus significance level of 0.025). Accordingly, this reviewer will perform sensitivity analysis to further explore the impact of this site on the superiority of palonosetron 0.05 mg to placebo.

2) Sensitivity analysis

Since the complete responses for all nine patients treated with Palonosetron 0.05 mg in Site 182 were assessed as success, in order to explore the robustness of the superiority of palonosetron 0.05 mg to placebo, this reviewer employs the applicant's logistic regression analysis method to perform the following two efficacy analyses: i) efficacy analysis without site 182 and ii) efficacy analysis by switching status of complete response. Then, based upon the analysis result, the overall comments are given with regard to the strength of palonosetron 0.05 mg to placebo.

i) Efficacy analysis without site 182

It is noted that the superiority of palonosetron 0.05 mg to placebo is close to border line (p=0.0171 versus significance level of 0.025) and all 9 patients in this arm were assessed as success in complete response. In order to explore the influence of site 182 on the superiority of palonosetron 0.05 mg versus placebo, this reviewer follows the applicant's logistic regression analysis without using Site 182 data to compare the efficacy of the two treatments.

Table 3.1.4.2 presents the efficacy comparison between palonosetron 0.05 mg versus placebo without data from Site 182 using FAS population.

Table 3.1.4.2 (Reviewer's) Efficacy comparison without data from Site 182 using FAS population

ENDPOINT	PLACEBO n/N (%)	PALONOSETRON 0.05 MG n/N (%)	p-value for testing superiority vs. Adjusted significance level
Complete response in first 24 hour postoperative observation period.	32/130 (25%)	45/128 (35%)	0.060 vs. 0.025

Table 3.1.4.2 shows that without using data from Site 182, palonosetron 0.05 mg is no longer superior to placebo (p=0.060 much higher than the adjusted significance level of 0.025). However, it is noted that only 5% (14/272) of patients (5 from placebo and 9 from palonosetron 0.05 mg in Site 182) excluded from the original efficacy comparison analysis, the superiority of Palonosetron 0.05 mg to placebo is no longer held. This result indicates that Site 182 has influence on the superiority finding of palonosetron 0.05 mg to placebo.

ii) Efficacy analysis by switching status of complete response

As indicated in the section of "Efficacy comparison by site", it is unusual that all nine patients treated with Palonosetron 0.05 mg in site 182 were assessed as success. Therefore, in order to explore the robustness of the superiority of Palonosetron 0.05 mg to Placebo, in this efficacy comparison analysis, the complete responses of one patient and then, two patients from palonosetron 0.05 mg are switched to failure.

Table 3.1.4.3 presents the efficacy comparison between palonosetron 0.05 mg versus placebo by switching the complete responses of patients in palonosetron 0.05 mg from success to failure using FAS population.

Table 3.1.4.3 (Reviewer's) Efficacy comparison by switching status of complete response using FAS Population

Complete response of one patient in Palonosetron 0.05 mg switched failure

ENDPOINT	PLACEBO n/N (%)	PALONOSETRON 0.05 MG n/N (%)	p-value for testing superiority vs. Adjusted significance level
Complete response in first 24 hour postoperative observation period.	35/135 (26%)	53/137 (39.0%)	0.024 vs. 0.025

Complete responses of two patients in Palonosetron 0.05 mg switched failure

ENDPOINT	PLACEBO n/N (%)	PALONOSETRON 0.05 MG n/N (%)	p-value for testing superiority vs. Adjusted significance level
Complete response in first 24 hour postoperative observation period.	35/135 (26%)	52/137 (38.0%)	0.032 vs. 0.025

Table 3.1.4.3 indicated that based upon the applicant's multiplicity adjustment technique, although the superiority of palonosetron 0.05 mg over Placebo is still held when the status of the complete responses of one patient switching from success to failure, the corresponding p-value of 0.024 is just on the border line, very close to the adjusted significance level of 0.025.

Based upon the result of switching the complete response of one patient from success to failure, it is not surprising that the superiority of palonosetron 0.05 mg to placebo is failed (p-value of 0.032 greater than the adjusted significance level of 0.025) when the status of the complete responses of two patients switching from success to failure.

Overall comments on the strength of Palonosetron 0.05 mg

Based upon the results of the sensitivity analyses, one learns that in the efficacy analysis of palonosetron 0.05 mg to placebo, Site 182 (total patients of this site only covered 5% patient of the study) seems to influence the superiority of palonosetron 0.05 mg. In fact, the superiority of palonosetron 0.05 mg to placebo is no longer held when the status of the complete responses of two patients switching from success to failure. Accordingly, I do not consider the superiority of palonosetron 0.05 mg to placebo a robust finding.

3) Non-parametric covariate analysis

In order to validate the superiority of palonosetron versus placebo, this reviewer applied a non-parametric method to compare treatment efficacy: Koch, G., "Issues for Covariance Analysis of Dichotomous and Ordered Categorical Data from Randomized Clinical Trials and Non-parametric Strategies for Addressing Them" Statistics in Medicine, 17, 1863-1892 (1998). Since in the applicant's co-primary endpoint analysis for the first 24 hour postoperative observation period, palonosetron 0.025 mg failed to show superiority to placebo and the superiority of palonosetron 0.05 mg to placebo is not deemed a robust finding, the non-parametric covariate analysis of the efficacy comparison between palonosetron 0.075 mg versus placebo is the focus.

Table 3.1.4.4 presents the efficacy comparison between palonosetron 0.05 mg versus placebo assessed by the non-parametric covariate analysis.

Table 3.1.4.4 (Reviewer's) Efficacy comparison assessed by non-parametric method using FAS population

ENDPOINT	PLACEBO n/N (%)	PALONOSETRON 0.075 MG n/N (%)	p-value for testing superiority vs. adjusted significance level†
Complete response in first 24 hour postoperative observation period.	35/135 (26.0%)	59/138 (43.0%)	0.0032 vs. 0.0166

†: Holm-Bonferroni multiplicity adjustment method proposed by the applicant.

Table 3.1.4.4 shows that based upon the non-parametric analysis method, palonosetron 0.075 mg versus placebo is still superior to placebo (p=0.0032 smaller than the adjusted significance level of 0.0166) and the p-value of 0.0032 from the non-parametric analysis method is close to the p-value of 0.0035 generated by the applicant's logistic regression analysis method. Accordingly, the superiority of palonosetron 0.075 mg versus placebo assessed by complete response during the first 24 hour postoperative observation period is supported by the non-parametric covariate analysis method.

Reviewer's Comments

1) Validity of the applicant's baseline adaptive randomization

It is well known that the goal of randomization is to achieve balance in all known and unknown, observed and unobserved covariates (e.g., prognostic factors) at baseline. In theory, the baseline balance is "expected" to be achieved in the long run (in average). However, in stead of using randomization technique to allocate patients to different treatment groups, the applicant applied a dynamic adaptive stratification type of randomization (i.e., baseline adaptive randomization) method to balance the four treatment groups across the criteria of gender, history of PONV and/or currently prone to motion sickness, and smoking status. The treatments were balanced across the entire study, not within each individual site.

In order to explore the impact of a dynamic randomization on the p-value or Type I error rate of standard test, the applicant performed a sensitivity analysis based upon the re-randomization data for the primary efficacy analysis. The applicant indicated that the results of the re-randomization tests are similar to those obtained with the covariate adjusted logistic regression analysis. For CR in the period of 0-24 hours, p-value of 0.0027 from re-randomization test versus p-value of 0.0035 from logistic regression was observed for the comparison of palonosetron 0.075 mg versus placebo. Similarly, p-value of 0.019 from re-randomization test versus p-value of 0.017 from logistic regression was observed for the comparison of palonosetron 0.050 mg versus placebo. As the logistic regression analysis result, no significance was seen for palonosetron 0.025 mg versus placebo from re-randomization test. Finally, no comparisons for the three doses of palonosdetron versus placebo from the re-randomization tests resulted in statistical

significance in the 24-72 hour period as shown from the logistic regression analysis using FAS population.

Although the results from re-randomization tests are similar to those obtained from logistic regression analyses, the superiority of palonosetron 0.05 mg to placebo may be dominated by Site 182. Since the re-randomization test for the superiority of palonosetron 0.05 mg to placebo also uses data from Site 182, the result from the re-randomization test can not be considered adding more supportive evidence for the efficacy of palonosetron 0.05 mg. Thus, only the superiority of palonosetron 0.075 mg to placebo is considered positively upheld by the re-randomization test.

In general, studies using minimization method usually contain selection bias. It is difficult to rely on the p-value report from such study since the effect of baseline adaptive randomization on Chi-square test has not been studied. The applicant should investigate the properties of Chi-square test when baseline adaptive randomization, simple randomization, and stratification are used as allocation strategies. More specifically, the following questions need to be addressed:

1. Does baseline adaptive randomization provide an unbiased estimate of treatment effect?
2. What is the actual size of rejection regions of selected nominal size?
3. What was the actual power to reject the alternative hypotheses?

Since the estimated proportion of complete response using data from baseline adaptive randomization may not be an unbiased estimate of the population proportion, the estimated proportion can not be used to explore the effect size of study drug versus placebo. In general, simple randomization with permuted blocks is currently the favored allocation method in clinical trials. Accordingly, based upon the number of 574 patients, the applicant should have applied simple randomization with random permuted blocks to allocate patients to different treatment groups and applied the proposed logistic regression analysis method to adjust the covariate effects on the efficacy comparisons assessed by the two co-primary endpoints (complete response in the 0-24 and 24-72 hours of postoperative periods).

2) Issue on the single pivotal study

Although two phase-III Studies PALO-04-06 and PALO-04-07 were submitted by the applicant to support Aloxi in the prevention of postoperative nausea and vomiting (PONV). However, due to the issue of potential partial unblinding for Study PALO-04-07, the meeting minutes for the meeting conducted on October 13, 2006 indicated that Study PALO-04-07 was considered as a supportive study, indicating that Study PALO-04-06 was considered as the pivotal study.

In addition, for Study PALO-04-07, based upon the meeting minutes, patients involved in the unblinding problem should be excluded from the efficacy analysis. Accordingly, the primary full analysis set (PFAS) excluded 175 patients involved in the unblinding issue were considered as the primary analysis data set by the applicant. However, the efficacy result from PFAS for Study PALO-04-07 during the first 24 and 24-72 hours in the postoperative observation period (i.e.,

two co-primary endpoints) showed that none of the proportions of patients with CR in the palonosetron 0.075 mg, 0.05 mg, and 0.025 mg dose groups was significantly better than that in the placebo group after applying the multiplicity adjustment method proposed by the applicant. Consequently, the efficacy assessments on the three doses of Palonosetron are mainly relied on the single pivotal Study PALO-04-06.

For Study PALO-04-06, it is noted that the applicant proposed a closed testing procedure and the Holm-Bonferroni method to account for multiple comparisons for co-primary endpoints and for treatment comparisons (0.025 mg vs. placebo, 0.050 mg vs. placebo and 0.075 mg vs. placebo). However, no multiplicity adjustments were proposed by the applicant for the secondary endpoints. Since for the secondary endpoints, many comparisons were made and the associated overall Type I error rate was not controlled, the secondary endpoint comparisons should be deemed as exploratory analyses, and any statistical significance claims would not appropriate for labeling.

First, for the efficacy assessments regarding Study PALO-04-06 during the 24-72 hour postoperative observation period, none of the three doses (0.025, 0.05, and 0.075 mgs) of palonosetron demonstrated superiority to placebo by the applicant's proposed logistic regression analysis.

Then, for the efficacy assessments during the first 24 hour postoperative observation period, although palonosetron 0.05 mg showed superiority to placebo, the corresponding p-value of 0.0171 is close to the adjusted significance level of 0.025. In addition, this reviewer's sensitivity analysis with regard to the effect of Site 182 indicates that the superiority of palonosetron 0.05 mg to placebo is influenced by Site 182, and the finding is not robust. Since no other study replicates superiority of palonosetron 0.05 mg to placebo, palonosetron 0.05 mg is not supported by substantial evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery.

Finally, for the efficacy assessment of palonosetron 0.075 mg during the first 24 hour postoperative observation period, based upon the applicant's logistic regression analysis and this reviewer's non-parametric covariate analysis, the superiority of palonosetron 0.075 mg versus placebo is demonstrated and robust. In addition, the secondary endpoint analyses on the complete control, emetic episodes, severity nausea, and quality of life indicated that palonosetron 0.075 mg are numerically better than placebo. Accordingly, palonosetron 0.075 mg is considered supported by substantial evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery during the first 24 hour postoperative observation period.

3.2 Evaluation of Safety for Study PALO-04-06

The reader is referred to the Medical Officer's review for a fuller evaluation of safety for all studies submitted. Below, this reviewer highlights safety results for Study PALO-04-06.

In total, 266 out of 547 patients (48.6%) experienced at least one treatment emergent adverse event (TEAE). The applicant indicated that the number of patients with TEAEs was higher in the palonosetron 0.025 mg (71/136 patients, 52.2%) and 0.050 mg (69/138 patients, 50.0%) groups, and in the placebo group (67/137 patients, 48.9%) compared to the palonosetron 0.075 mg group (59/136, 43.4%).

The applicant indicated that there were no deaths in the study and no patients were withdrawn due to significant adverse events (SAEs). Seventeen out of 547 patients (3.1 %) developed a total of 20 SAEs. The proportion of patients with SAEs was slightly higher in the palonosetron 0.025 mg dose group: 8 events were reported by 7 patients (5.1 %) compared to the palonosetron 0.050 mg dose group in which 2 events occurred in 2 patients (1.4%), and to the palonosetron 0.075 mg dose group with 5 events in 4 patients (2.9%). The rate of patients reporting SAEs in the placebo group was similar to the highest palonosetron dose (5 events in 4 patients; 2.9%). The most common system organ classes (SOCs) in which SAEs occurred were gastrointestinal disorders (5 events in 5 patients), injury, poisoning and procedural complications (5 events in 5 patients), and renal and urinary disorders (2 events in 2 patients). In all other system organ classes, only 1 patient reported one event. The only SAEs that occurred in more than 1 patient were post procedural pain (1 patient each in the placebo, palonosetron 0.025 mg and 0.050 mg dose groups) and abdominal pain (1 patient each in the palonosetron 0.025 mg and 0.075 mg dose groups).

Five SAEs were mild in intensity, 7 were moderate and 8 severe. All patients recovered from the SAEs, with the exception of one patient in the placebo group who recovered with sequelae. Only one SAE, a prolonged QTc interval in a patient receiving placebo, was possibly related to the study medication.

Finally, the applicant indicated that overall, fewer patients in the palonosetron 0.075 mg treatment group had TEAEs when compared with the other treatment groups. Of all patients who had TEAEs, a lower proportion of patients in the 0.075 mg dose group had related TEAEs, when compared to the other treatment groups. There were, however, no notable differences between placebo and palonosetron groups, or among the palonosetron groups, in any of the other safety parameters assessed.

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

In order to assess the consistency of the treatment effect of the palonosetron versus placebo across subgroups, this reviewer performs the subgroup analysis by the applicant's logistic

regression method to compare treatment efficacy using FAS population. However, since for Study PALO-04-07, the efficacy of the three palonosetron treatments are not superior to that of placebo for both 0-24 and 24-72 hour post-operative periods, the subgroup analysis is only performed for Study PALO-04-06.

It is also noted that for Study PALO-04-06, none of the efficacy for the three palonosteron treatments is superior to that of placebo during the period of 24-72 hour post-operation. The subgroup analysis is performed for the 0-24 hour post-operative period. In addition, for this study, more than 95% of patients were with ages less than 65 and were females. Accordingly, the subgroup analyzed is only for Race group (Caucasian vs. Non-Caucasian).

Race group (Caucasian versus Non-Caucasian)

Table 4.1.1 presents the results of treatment efficacy comparisons by Race group (Caucasian versus Non-Caucasian).

Table 4.1.1 (Reviewer's) Proportions of complete response for the 0-24 hour post-operative period (FAS)

Caucasian

Treatment	With Complete Response		P-value for testing† Palonosetron versus Placebo
	n/m	%	
Palonosetron 0.075 mg	41/87	47.0	0.006*
Palonosetron 0.05 mg	42/100	42.0	0.039
Palonosetron 0.025 mg	33/91	36.0	0.20
Placebo	26/92	28.0	

N0n-Caucasian

Treatment	With Complete Response		P-value for testing Palonosetron versus Placebo
	n/m	%	
Palonosetron 0.075 mg	18/51	35.0	0.15
Palonosetron 0.05 mg	12/37	32.0	0.24
Palonosetron 0.025 mg	12/45	27.0	0.56
Placebo	9/43	21.0	

*: significant after multiplicity adjustment; Complete Response = No vomiting and no use of rescue;

†: Model included terms for treatment, type of surgery, smoking status, and history of PONV or prone to motion sickness;

n/m= Number of patients with desired response/number of patients included in analysis.

Table 4.1.1 shows that for Caucasian group, the proportions of the complete response for palonosetron 0.075 mg is significantly greater than that of placebo at the multiplicity adjustment level of 0.016. However, for other two dose levels (0.05 mg and 0.025 mg), the proportions of the complete responses are not significantly but numerically higher than that of placebo.

For Non-Caucasian group, the proportions of the complete responses for the three palonosetron treatments are not significantly but numerically higher than that of placebo.

4.2 Other Special/Subgroup Populations (Not applicable)

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Study PALO-04-06

Since the efficacy comparisons performed by the applicant for palonosetron three doses (0.025, 0.05, 0.075 mgs) during the 24-72 hour postoperative observation period failed to demonstrate superiority to placebo, the three doses of palonosetron are not supported by substantial evidence in prevention of postoperative nausea and vomiting for the 24-72 hour postoperative observation period following elective abdominal or gynecological laparoscopic surgery. In addition, superiority to placebo was not demonstrated for palonosetron 0.025 mg during the first 24 hour postoperative observation period. Thus the 0.025 mg dose is not supported by substantial evidence in prevention of postoperative nausea and vomiting for the first 24 hour postoperative observation period following elective abdominal or gynecological laparoscopic surgery.

The following comments on the efficacy assessments are for the superiority of palonosetron 0.05 mg and 0.075 mg to placebo based upon the primary endpoint - the complete response for the first 24 hour postoperative observation period.

- First, the estimated proportion of complete response using data from baseline adaptive randomization may not be an unbiased estimate of the population proportion. It follows that the estimated proportion should be used with caution in estimating the effect size of study drug versus placebo. In general, simple randomization with permuted blocks is currently the favored allocation method in clinical trials. Accordingly, based upon the number of 574 patients, the applicant should have applied simple randomization with random permuted blocks to allocate patients to different treatment groups and applied the proposed logistic regression analysis method to adjust the covariate effect on the efficacy comparisons assessed by the two co-primary endpoints (complete response in the 0-24 and 24-72 hours of postoperative periods).

- Second, based upon the efficacy comparison by investigate-site, for palonosetron 0.075mg, the proportions of complete response in most sites are much greater than that in the placebo group. No particular sites are identified to have unusually large proportions of complete response to dominate the superiority of palonosetron 0.075 mg to placebo. However, for palonosetron 0.05mg, although the proportions of complete response in most sites are greater than that of placebo, it seems unusual that the complete responses for all nine patients in Site 182 are assessed as success. In addition, it is also noted that the p-value resulting from testing the superiority of palonosetron 0.05 mg to placebo is close to the nominal significance level proposed by the applicant's multiplicity adjustment method.

- Third, based upon the results of the sensitivity analyses, one learns that in the efficacy analysis of palonosetron 0.05 mg to placebo, a small Site 182 (total patients of this site only covered 5% patient of the study) may unduly influence the superiority of palonosetron 0.05 mg. It is also noted that the superiority of palonosetron 0.05 mg to placebo is no longer held when the status of the complete responses of two patients switching from success to failure. Accordingly, the superiority of palonosetron 0.05 mg to placebo is not a robust finding. In addition, the supportive Study PALO-04-07 did not replicate the superiority of palonosetron 0.05 mg to placebo using primary analysis data set (PFAS), palonosetron 0.05 mg is considered not supported by substantial evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery.

- Finally, for the efficacy assessment of palonosetron 0.075 mg during the first 24 hour postoperative observation period, based upon the applicant's logistic regression analysis and this reviewer's non-parametric covariate analysis, the superiority of palonosetron 0.075 mg versus placebo is demonstrated and robust. In addition, the secondary endpoint analyses on the complete control, emetic episodes, severity nausea, and quality of life indicated that Palonosetron 0.075 mg are numerically better than Placebo. As a consequence, the superiority of palonosetron 0.075 mg to placebo can be considered supported by substantial evidence in use of the prevention of postoperative nausea and vomiting during the first 24 hour postoperative observation period.

5.1.2 Study PALO-04-07

- Due to the issue of unblinding the treatment codes and based upon the Agency's response to this issue, Study PALO-04-07 is treated as a supportive study. In addition, in order to respond to the Agency's concern regarding data integrity, the applicant specified the primary full analysis set (PFAS) excluding 175 patients involved in the unblinding problem as the primary analysis data set.

- However, using PFAS population (data not involved in the unblinding problem), the applicant's efficacy analysis showed that for both periods of 0-24 hours and the 24-72 hours, comparisons of the single dose groups of palonosetron with placebo resulted in no significant differences for any of the palonosetron treatment groups (0.025, 0.05, and 0.075 mgs) versus placebo after multiplicity adjustments proposed by the applicant. It follows that data from Study PALO-04-07 does not provide positive support for the pivotal Study PALO-04-06.

5.2 Conclusions and Recommendations

Following the efficacy assessments for the pivotal Study Palo-04-06 and the supportive Study Palo-04-07, palonosetron 0.075 mg is supported by substantial evidence in use of prevention of postoperative nausea and vomiting for the first 24 hour postoperative observation period following elective abdominal or gynecological laparoscopic surgery.

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/s/

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