CLINICAL STUDY REPORT

A Randomized, Double-blind, Multicenter, Parallel Group, Balanced, Stratified Phase 3 Study to Evaluate the Efficacy and the Safety of Single IV Doses of Palonosetron 0.025 mg, 0.050 mg, and 0.075 mg versus Placebo to Prevent Postoperative Nausea and Vomiting Following Elective Gynecologic or Breast Surgery

Sponsor:	HELSINN Healthcare SA Via Pian Scairolo, 9 6915 Pambio-Noranco Switzerland
Study/Protocol No.:	PALO-04-07
EudraCT No.:	2005-000298-23
Study drug Name:	Palonosetron hydrochloride
Development Phase:	3
Indication:	Prevention of Postoperative Nausea and Vomiting
First Patient Enrolled:	31 August 2005
Last Patient Completed:	05 May 2006
Author:	[redacted] PAREXEL International 190 rue Championnet 75018, Paris, France
Date of Report:	26 March 2007

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

2. CLINICAL STUDY SYNOPSIS

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Title of Study: A Randomized, Double-blind, Multicenter, Parallel Group, Balanced, Stratified Phase 3 Study to Evaluate the Efficacy and the Safety of Single IV Doses of Palonosetron 0.025 mg, 0.050 mg, and 0.075 mg versus Placebo to Prevent Postoperative Nausea and Vomiting Following Elective Gynecologic or Breast Surgery

Protocol Number: PALO-04-07

Study Period: 8 months **Phase of Development:** 3
First patient enrolled: 31 August 2005
Last patient completed: 05 May 2006

Investigator(s): A total of 28 investigators from 3 countries (Germany, Poland and Czech Republic) participated in this study. Principal co-ordinating investigator for Germany: [redacted], MD; principal co-ordinating Investigator for Poland: Prof. [redacted].

Study Center(s): The study was performed in 28 investigative centers in Europe: Germany (13), Poland (10) and Czech Republic (5).

Publication(s): Not applicable

Objectives: The objectives of this study were to investigate the efficacy and safety of a single intravenous (IV) dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus placebo for the prevention of postoperative nausea and vomiting (PONV) from 0 to 24 hours and 24 to 72 hours in female inpatients undergoing elective gynecological or breast surgery with general anesthesia.

Study Design: This was a randomized, double-blind, multicenter, parallel group, balanced, stratified, placebo-controlled phase 3 study.

Number of Patients (planned and analyzed): The sample size was estimated to be 544 patients, randomized to 1 of the 3 palonosetron groups or to the placebo group (i.e. 136 patients/group). An additional 130 patients were enrolled since the first 130 patients could not be used for the efficacy analyses due to a potential unblinding problem identified a few months after the start of the study. The patients originally planned plus the additional 130 patients (i.e. 674 patients) were then planned to be included in the safety analyses. Due to a separate potential unblinding problem identified at German centers, after enrollment in the study concluded, patients from German sites were deemed not eligible for inclusion in the primary confirmatory full analysis set which excludes all potentially unblinded patients and is the set used for primary efficacy analysis. The Full Analysis Set (FAS), Modified Full Analysis Set (MFAS), Primary Full Analysis Set (PFAS) and the Per-Protocol Set (PP) comprised of 673, 544, 369 and 288 patients, respectively.

Due to the above events, the number of patients in the study were as follows:

Planned: 674
Enrolled: 684
Analyzed for Safety: 673

	Safety Cohort (673 patients)	Primary Full Analysis Set (369 patients)	Modified Full Analysis Set (544 patients)	Per Protocol Set (288 patients)
Placebo:	168 patients	90 patients	136 patients	66 patients
Palonosetron 0.025 mg	168 patients	88 patients	136 patients	69 patients
Palonosetron 0.050 mg	169 patients	96 patients	137 patients	79 patients
Palonosetron 0.075 mg	168 patients	95 patients	135 patients	74 patients

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Diagnosis and Main Criteria for Inclusion: Female inpatients ≥18 years of age, at a high risk of PONV undergoing elective gynecological or breast surgery under general anesthesia.

Main Inclusion Criteria: Female, ≥18 years of age, American Society of Anesthesiologists (ASA) physical status 1 to 3, undergoing elective gynecological or breast surgery under general anesthesia that was expected to last a minimum of 1 hour and requires hospitalization of at least 72 hours. Patients must provide written informed consent and have at least one of the two following PONV risk factors: 1) history of PONV and/or currently prone to motion sickness; 2) non-smoking status. Scheduled to receive nitrous oxide as part of the maintenance phase of the anesthesia.

Main exclusion criteria: Any drug with potential anti-emetic efficacy within 24 hours prior to the anesthetic procedures, any vomiting, retching, or nausea in the 24 hours preceding anesthesia, patients scheduled to receive nasogastric suctioning postoperatively, body mass index (BMI) >40, known hypersensitivity/contraindication to 5-HT_3 antagonists or study drug excipients.

Test Product, Dose and Mode of Administration, and Batch Number(s): A single IV dose of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) given as 0.5 mL, 1 mL, or 1.5 mL with the appropriate volume of saline solution added to bring the total injectable volume to 2 mL. This was administered as a bolus by a 10-second IV push immediately before start of induction of anesthesia.

Batch number: [redacted]

Reference Therapy, Dose and Mode of Administration, and Batch Number(s): A single IV dose of placebo (saline solution) given as a 2 mL bolus by a 10-second IV push immediately before start of induction of anesthesia.

Batch number: [redacted]

Duration of Treatment: The estimated study duration for each patient was approximately 22 days including screening and follow-up visits. Patients were hospitalized for at least 3 days (72 hours).

Criteria for Evaluation:

Efficacy: The primary efficacy variable was Complete Response (CR), defined as no emetic episode and no rescue medication. The study had two co-primary endpoints, which were (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 at 0-24 hours, i.e., during the first 24-hour postoperative observation period, and (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 at 24-72 hours, i.e., during the first 24-72 hour postoperative observation period.

Secondary efficacy endpoints were as follows:

- 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.
- Complete Control (defined as 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.
- Number of patients with 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.
- 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 (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.
- 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.

Safety: Safety was evaluated in all patients who received study treatment and had at least 1 safety assessment, by the incidence of adverse events (AEs) and by assessment of physical examination, vital signs, laboratory parameters (hematology, clinical chemistry and urinalysis) and electrocardiograms

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(ECGs).
Other: The severity of postoperative pain was measured by the Numeric Rating Scale (from 0=no pain to 10=pain as bad as it can be) at 2 hours, 6 hours, 24 hours, 48 hours, and 72 hours.

Comments Regarding the Clinical Phase of the Study:
Two circumstances occurred with clinical supplies related documents (the test article syringe label and the drug accountability form) which required mitigation and resulted in revision of the analysis sets. These two matters occurred separately and are described below.
Test article syringe label. During the first few months of enrollment, at one site the per protocol unblinded monitor noted that when the adhesive cover on the back of the label for the blinded test article syringe was removed, the mirror image of the test article name became visible through the back of the label in the few moments before the label was affixed to the patients case report form. This label problem was not identified by any investigator or investigator's staff. However, due to the faulty label, it was recognized by the Sponsor that there was a possibility that the first 130 patients enrolled to that date may have potentially become unintentionally unblinded to the study treatment. To correct this matter, the clinical supplies with faulty labels were immediately replaced, and an additional 130 patients were enrolled. The first 130 patients enrolled, who were potentially unblinded, were included in the FAS and Safety Set, and were excluded from the MFAS, PFAS and PP set, as defined in the Statistical Methods section below.
Drug accountability form. After enrollment in the study was completed, but before analysis was performed, an error was discovered by two designated unblinded staff, during an end-of-study review by PAREXEL, the CRO that managed the study. The completed drug accountability forms prepared by the per protocol unblinded pharmacist at sites in Germany (but at none of the study sites in Poland and Czech Republic) had been erroneously affixed with the adhesive tear-off treatment vial label for each patient treated; this small vial label identified the treatment in very small font. This was an error since the treatment randomization number should have been hand entered on the drug accountability log by each site's unblinded pharmacist, and the vial label which identified the treatment should not have been affixed. The vial label identified the treatment as either placebo or palonosetron; the palonosetron dose was not identified. When blinded clinical staff signed the drug accountability form to document receipt of the test article syringe (for administration to the patient), it is possible they may have seen the small font syringe label which identified the treatment and may have become unblinded to the study treatment (but not the dose). To address whether investigators/staff at these sites actually became unblinded, each of the potentially affected investigators/staff at the German sites were asked to review and sign, as appropriate, statements of blinding (similar to the investigator's financial disclosure statement). The statements of blinding were obtained in an unbiased fashion from the investigators/staff by an agency that was independent of the Sponsor and PAREXEL. Eleven investigators certified in writing that they did not become unblinded; 1 investigator stated that he became aware of the treatment for the first 3 patients. All patients associated with this drug accountability form error, i.e., those that were potentially unblinded, were included in the FAS, MFAS, and Safety Set, and were excluded from the PFAS, PP set.

Statistical Methods:
Four populations were defined:
Full analysis set (FAS): patients who received study drug, anesthetic procedures and surgical operation (i.e. the originally planned 544 patients + 130 patients added due to the clinical supplies label problem). Patients in the FAS were assigned to the study drug group according to the treatment to which they were randomized.
Modified full analysis set (MFAS): subset of the FAS - patients enrolled after the clinical supplies label problem was resolved and who received study drug, anesthetic procedures and surgical operation (i.e. planned 544 patients). Patients in the MFAS were assigned to the study drug group according to the treatment to which they were randomized.
Primary Full Analysis Set (PFAS): subset of the MFAS - patients who received study drug, anesthetic procedures and surgical operation and for whom no potential unblinding due to investigator signature in the study drug accountability form was evident (i.e. the originally planned 544 patients minus about

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178 patients potentially unblinded). Patients were assigned to the study drug group according to the treatment to which they were randomized. The primary efficacy analysis was performed using the PFAS.

Per-protocol (PP) set: subset of the MFAS - patients enrolled after the clinical supplies label problem was resolved, who received study drug, anesthetic procedures and surgical operation, and who completed Day 3 (i.e., up to 72 hours) and were compliant with the study protocol. Additionally a subset of the PP set, designated PP (0-24), was used for the 0-24 hour period analysis. Major protocol deviations that occurred in the 24-72 hours period did not influence the results for the primary endpoint in the 0-24 hours period.

Safety set: all patients who received study drug and had at least one safety assessment. Patients in the Safety set were assigned to the study drug group according to the treatment received.

Analysis:

Efficacy: The primary analysis population for efficacy analyses was the PFAS. This population was used for the analysis of all parameters except safey parameters. A secondary analysis based on the MFAS was performed for all the efficacy parameters. For the two co-primary efficacy variables a secondary analysis was performed based on the PP set and a sensitivity analysis was performed on the FAS. Each of the primary and secondary efficacy variable analyses were performed by treatment group, overall and stratified for type of surgery, history of PONV and/or currently prone to motion sickness, smoking status (i.e., stratification criteria), by age group and by use of narcotic analgesics both for the MFAS and PFAS, provided that a sufficient number of patients was present in each relevant subgroup.

The co-primary efficacy hypotheses 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 to be tested first, followed by the test in the 24-72 hour interval (provided that at least one comparison in the 0-24 hour period was statistically significant), using the same method and the same alpha. For each of the two primary efficacy variables the superiority of a single IV dose of palonosetron over placebo was assessed for each dose of palonosetron. To account for multiple comparisons of treatments the multiple type-I error level of 0.05 was guaranteed by the Holm-Bonferroni method. For a significant difference, for each of the co-primary endpoint analyses, the smallest of the three 2-sided p-values was not to exceed 0.0166 (0.05/3), the second smallest p-value was not to exceed 0.025 (0.05/2), and the third p-value was not to exceed 0.05. This sequential procedure was to be stopped if the respective threshold was exceeded. Each primary and confirmatory test was performed using a multiple logistic regression adjusted for covariates, where each dose of palonosetron was compared with placebo. The covariates in the model were the stratification criteria, i.e., type of surgery, history of PONV and/or currently prone to motion sickness, and smoking status. Odd ratios, 95% CI for the odds ratio and p-values derived from the logistic regression were summarized. The same logistic regression was used to compare each dose of palonosetron to each other on a descriptive level, i.e., without any further adjustment for multiplicity.

To assess interactions between treatment and each of the covariates an additional logistic regression model was calculated, including a “treatment-by-covariate” interaction term for each covariate. Interaction was considered if the corresponding p-value was <0.05. The number and proportion of patients with CR at 0-24 hours and 24-72 hours was summarized in a frequency table and 95% CIs were provided for the response rate and difference in response rate between each dose group and placebo.

Complete response at the other time intervals (24-48, 48-72, 0-48, 0-72, 0-2, 0-6, 2-6, 6-24 hours) as well as CC evaluated at the same time intervals, as well as 0-24 and 24-72 hours, were analyzed as secondary efficacy variables as described for the two co-primary efficacy variables. All comparisons were interpreted on a descriptive level and no adjustment for multiplicity was done.

The number of emetic episodes was analyzed using Kruskal-Wallis test for the overall comparison of treatment groups and Mann-Whitney test for pair-wise comparisons. The number of patients with emetic episodes was analyzed using the Chi-square test for overall and pair-wise comparisons.

The severity of nausea was summarized in a frequency table and analyzed by means of the Cochran-Mantel-Haenszel test with adjustment for stratification criteria. The time to first emetic episode, time to first administration and need for rescue medication, time to treatment failure, and time to first fluid

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and first solid food intake were analyzed by means of a life table analysis using Kaplan-Meier estimates. Overall and, if significant, pair-wise comparisons were performed using a log rank test with adjustment for stratification criteria. Kaplan-Meier survival curves were displayed.

Postoperative pain was summarized for patients in the PFAS and MFAS by treatment group, overall and stratified for each time interval. Within each time interval post operative pain was correlated with the number of emetic episodes and the severity of nausea. Spearman's rank correlation coefficients and corresponding p-values were provided.

Safety: All safety summaries were based on the safety set and provided within treatment groups. In addition, the summary of AEs table, was provided stratified for type of surgery, history of PONV and/or currently prone to motion sickness, smoking status, age group and country. AEs were coded using MedDRA (version 8.0). Laboratory parameters and vital signs were tabulated by visit and within treatment groups by means of summary statistics for measured values and for changes from baseline. Shift tables and scatter plots were provided for laboratory parameters. ECG parameters were summarized by visit and time point of measurement within treatment groups by descriptive statistics. Frequency tables were provided for the overall interpretation. Subgroups with regard to abnormal ECG values were defined and the number and proportion of patients within each group were provided.

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Efficacy Results:

Efficacy analyses were performed on the PFAS, MFAS, FAS and PP data sets. In the table below, the proportion of patients with CR and CC for the PFAS, MFAS and FAS datasets are shown. Statistically significant p-values in the table are in bold.

In the PFAS, at all dose levels of palonosetron there was a greater proportion of patients with CR compared with placebo during the 0-24 hour postoperative period. The percentage of patients with CR was highest in the palonosetron 0.025 mg and 0.075 mg treatment groups (56.8%, and 55.8%, respectively), intermediate for the 0.050 mg treatment group (47.9%), and lowest in the placebo group (41.1%). At 24-72 hours, the proportion of patients with CR was higher in the palonosetron treatment groups compared with placebo. However in the PFAS, which had a substantially reduced sample size due to excluding all potentially unblinded patients, statistical superiority of palonosetron over placebo for the prevention of PONV was not shown. To claim superiority over placebo, using the Holm-Bonferroni method which accounts for multiple comparisons, the smallest of the three 2-sided p-values should not have exceed 0.0166 (0.05/3), which was not the case for the PFAS. The results were similar during the 24-72 hour period, with a greater proportion of patients with CR in the palonosetron groups, however none of the differences were statistically significant.

Efficacy Results: Complete Response and Complete Control through 72 hours postoperatively

	Time Period	Placebo	Palonosetron 0.025mg	Palonosetron 0.050 mg	Palonosetron 0.075 mg
PFAS		**N=90**	**N=88**	**N=96**	**N=95**
CR%	0-24	41.1	56.8 [p=0.0299]	47.9 [p=0.3303]	55.8 [p=0.0364]
	24-72	60.0	68.2 [p=0.2000]	66.7 [p=0.3011]	70.5 [p=0.0991]
	0-72	41.1	**55.7 [p=0.0433]**	47.9 [p=0.3312]	51.6 [p=0.1272]
CC%	0-24	40.0	51.1 [p=0.1121]	44.8 [p=0.4766]	50.5 [p=0.1268]
	24-72	60.0	67.0 [p=0.2541]	64.6 [p=0.4400]	70.5 [p=0.0834]
	0-72	40.0	48.9 [p=0.1923]	44.8 [p=0.4698]	47.4 [p=0.2637]
MFAS		**N=136**	**N=136**	**N=137**	**N=135**
CR%	0-24	36.0	46.3 [p=0.0731]	46.7 [p=0.0690]	**56.3 [p=0.0010]**
	24-72	52.2	55.9 [p=0.5113]	60.6 [p=0.1511]	**70.4 [p=0.0024]**
	0-72	36.0	44.1 [p=0.1565]	44.5 [p=0.1449]	**51.9 [p=0.0097]**
CC%	0-24	35.3	42.6 [p=0.1979]	43.8 [p=0.1441]	**51.9 [p=0.0065]**
	24-72	52.2	55.1 [p=0.5963]	59.1 [p=0.2344]	**70.4 [p=0.0024]**
	0-72	35.3	39.7 [p=0.4323]	41.6 [p=0.2718]	**48.1 [p=0.0343]**
FAS		**N=168**	**N=168**	**N=169**	**N=168**
CR%	0-24	32.1	**45.2 [p=0.0129]**	**46.2 [p=0.0091]**	**51.8 [p=0.0002]**
	24-72	48.8	54.8 [p=0.2621]	59.2 [p=0.0607]	**66.7 [p=0.0008]**

p-values refer to the comparison of each palonosetron dose versus placebo. Statistical significance is in bold and in accordance with the relevant threshold.

The same analysis was also performed using the MFAS which had a sample size consistent with the intended study sample size of about 136 patients per group. The results obtained in the MFAS were reasonably consistent with the PFAS analysis, particularly for the palonosetron 0.075 mg dose group. In the MFAS, palonosetron 0.075 mg was statistically superior over placebo for both co-primary efficacy endpoints, CR for 0-24 (p=0.0010) and 24-72 hours (p=0.0024). Both p-values were below the adjusted significance level calculated using the Holm-Bonferroni method, meaning that the proportion of patients with CR in the palonosetron 0.075 mg was significantly higher than in the placebo group during both periods.

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Sensitivity analyses based on the FAS showed, as indicated in the table above, the same efficacy results for palonosetron 0.075 mg observed in the MFAS and support efficacy results observed in the MFAS.

For the PP (0-24) and PP (24-72) sets, like the analyses in the PFAS and MFAS, there was a greater proportion of patients with CR in the palonosetron groups compared with placebo. This difference was greater in the 0-24 hour period than in the 24-72 hour period and may be partially attributable to the greater placebo effect observed beyond 24 hours postoperatively. Pairwise comparisons were also made between the palonosetron dose groups in the PFAS, MFAS and the PP set. In the MFAS, there were significant differences between the palonosetron 0.025 mg and 0.075 mg treatment groups for intervals assessed for CR and CC during the 24-72 hour postoperative period, i.e. 24-48, 24-72, 48-72 hours, all favoring the 0.075 mg dose. At 24-72 hours, CR for palonosetron 0.075 mg and palonosetron 0.025 mg groups were 70.4% and 55.9%, respectively (p=0.0163). This observation was confirmed in the FAS analysis. In the smaller PFAS and PP sets, significant differences in CR between palonosetron doses were not shown.

Results of logistic regression analysis in the MFAS showed that there were statistically significant differences between the palonosetron 0.075 mg group and placebo for the 0-2 hours (p=0.0138), 0-6 hours (p=0.0032), 2-6 hours (p=0.0012), 6-24 hours (p<0.0001), 24-48 hours (p=0.0016), 48-72 hours (p=0.0009), 0-48 hours (p=0.0068) and 0-72 hours (p=0.0097) time intervals. Palonosetron 0.050 mg had significantly different CR rates compared to placebo at the 0-6 hours (p=0.0122) and 2-6 hours (p=0.0037) time intervals. Palonosetron 0.025 mg had significantly different CR rates compared to placebo at 6-24 hours (p=0.0407).

Results for CC were similar to those for CR. Overall in the PFAS at all of the time-points, there was a lower proportion of patients with CC in the placebo group, compared with the palonosetron treatment groups. The difference in the proportion of patients with CC between placebo and palonosetron treatment was greatest in all palonosetron groups during the 6-24 hour postoperative period, with a difference of 15.9%, 9.4% and 22.6% of patients in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg treatment groups, respectively, again favoring the 0.075 mg dose. Results from logistic regression analysis showed that the palonosetron 0.025 mg and 0.075 mg treatment groups had statistically significantly higher CC rates compared to placebo in the 6-24 hour interval (p=0.0200 and 0.0008, respectively). The results for CC in the MFAS were similar to those seen in the PFAS. At 6-24 hours in the MFAS the difference in the proportion of patients with CC versus placebo was 11.0%, 9.9% and 27.7% in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg groups, respectively.

In the PFAS analysis, during the 0-24 hour period of observation there was a statistically significant difference in the proportion of patients with emetic episodes receiving palonosetron 0.025 mg and 0.075 mg, compared with placebo (p=0.0158 and p=0.0229, respectively). During the 6-24 hour period, the difference compared with placebo was statistically significant for the palonosetron 0.075 mg dose group (p=0.0302). At 0-48 hour and 0-72 hour observation periods, palonosetron 0.025 mg was statistically different, compared to placebo (p=0.0237 for each time point).

Overall, the mean number of emetic episodes was small in each time interval and in each treatment group, both in the PFAS and the MFAS. In the PFAS the number of emetic episodes during the 0-24 hour and 6-24 hour periods was statistically significantly different for the palonosetron 0.075 mg group versus placebo (p=0.0061 and p=0.0183, respectively) and for palonosetron 0.025 mg versus placebo at 0-24 hours only (p=0.0209). At the 0-48 and 0-72 hour intervals, comparison of palonosetron 0.075 mg versus placebo favored palonosetron 0.075 mg (p=0.0164 at both time points). A similar result was observed for palonosetron 0.025 mg versus placebo (p=0.0325 and p=0.0357, for 0-48 and 0-72 hours, respectively). As for the time to first emetic episode in the MFAS, the log rank test for the overall comparison showed a significant difference between the groups (p=0.0010). In the palonosetron 0.050 mg and 0.075 mg groups, there were statistically significant differences compared with placebo (p=0.0143 and p=0.0018, respectively).

Regarding assessment of nausea, overall more patients in the placebo group experienced nausea, compared to patients who received palonosetron at any dose. The severity of nausea decreased with time in all four treatment groups. During the 0-24 hour period in the PFAS, at least 40% of palonosetron-treated patients (across all doses) were free from nausea compared with placebo (30.0%) and the highest percentage was

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observed in the palonosetron 0.075 mg treatment group (50.5%). This difference was also evident in the 6-24 hour interval where 78.9% of patients in the palonosetron 0.075 mg treatment group had no nausea compared to 65.6% in the placebo group. The frequencies of severity of nausea were similar in the MFAS. In the MFAS, statistical testing revealed a significant difference between the results in the placebo group and the palonosetron 0.075 mg group at 0-2 hours (p=0.0002), 0-6 hours (p=0.0007), 2-6 hours (p=0.0024), 6-24 hours (p=0.0028), 0-24 hours (p=0.0002), 0-48 hours (p=0.0008) and 0-72 hours (p=0.0008).

Overall, in the PFAS, rescue medications were administered most frequently to patients treated with placebo (36.7%), compared to 27.3%, 29.2% and 26.3% for the palonosetron 0.025 mg, 0.050 mg and 0.075 mg groups, respectively. Also in the MFAS, approximately 50% of patients in the placebo group received rescue medication compared with 39.7%, 35.8% and 26.7% in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg treatment groups, respectively, again favoring the 0.075 mg dose. The log rank test for the time to rescue medication for overall comparison showed no significant differences between the groups (p=0.0801) in the PFAS, while in the MFAS a significant difference between the groups (p=0.0003) was found. Moreover in the MFAS, there was a statistically significant difference between the palonosetron 0.050 mg and 0.075 mg groups compared with placebo (p=0.0403 and p=0.0006, respectively).

In the PFAS, the log rank test for the time to treatment failure for the overall comparison showed no significant differences between the groups (p=0.2106). In the MFAS, a statistically significant difference was found for the overall comparison (p=0.0023) and in the palonosetron 0.0075 mg group versus placebo (p=0.0035).

Both in the PFAS and the MFAS, the intensity of postoperative pain was similar across all treatment groups and decreased over time. Little or no correlation was found between postoperative pain and the number of emetic episodes, and postoperative pain and severity of nausea, for any treatment group at any of the time points.

An examination of the efficacy results was also performed, stratified by subgroups: type of surgery (breast or gynecological); history of PONV or currently prone to motion sickness; smoking status; age groups (≤ 40 years or > 40 years old); use of narcotic analgesics; and country. There were very few notable differences between these groups and the main PFAS or MFAS analyses.

Overall, both in the MFAS and the PFAS in the palonosetron treatment groups there were higher percentages of patients with CR and CC in the subgroup without a history of PONV, compared to patients with a history of PONV.

In the MFAS and the PFAS the proportion of smokers was small (about 15% in each population), therefore the trends seen in the subgroups of non-smokers were the same as those observed in the respective MFAS and PFAS populations as a whole.

Safety Results:

In total, 527 out of 673 patients (78.3%) experienced at least one TEAE. A similar percentage of patients in each treatment group had TEAEs, although the percentage was slightly higher in the placebo and palonosetron 0.025 mg groups (81.0% and 79.2%, respectively), compared with the palonosetron 0.050 mg and 0.075 mg treatment groups (76.3% and 76.8%, respectively). Highest absolute numbers of TEAEs were found in the palonosetron 0.050 mg treatment group, in which 129 patients (76.3%) experienced 412 TEAEs.

TEAEs of the system organ classes (SOCs) gastrointestinal disorders, injury, poisoning and procedural complications and psychiatric disorders were most frequently reported, with an incidence of > 20% in all treatment groups. Gastrointestinal disorders were reported with the greatest frequency in the palonosetron 0.050 mg group (36.7%), compared with the placebo group (27.4%) and the palonosetron 0.025 mg and 0.075 mg groups (27.4% and 28.0%, respectively). In the gastrointestinal disorders SOC, constipation was the most common TEAE, and occurred at a higher frequency in the palonosetron 0.050 mg group (21.9%) compared with placebo group (14.9%), the palonosetron 0.025 mg group (16.1%) and the palonosetron 0.075 mg group (18.5%).

In the psychiatric disorders SOC, insomnia was the most common TEAE, reported by 19.6% of patients in the placebo group, and 23.2%, 23.7% and 19.6% of patients in the palonosetron 0.025 mg, 0.050 mg and

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0.075 mg groups, respectively. The other most frequent TEAEs were: post procedural pain (palonosetron range: 18.5 to 20.7%, placebo: 17.3%), bradycardia (palonosetron range: 10.1% to 13.7%, placebo: 12.5%) and flatulence (palonosetron range: 7.7% to 13.6%, placebo: 8.9%).

Most of the TEAEs were of mild or moderate intensity in each of the treatment groups and < 5% in each treatment group were of severe intensity. Overall, TEAEs of severe intensity were reported by 37 patients (5.5%), with a greater proportion of patients in the palonosetron 0.025 mg and 0.050 mg treatment groups (6.5% in each), than in the placebo group (5.4% of patients) and the palonosetron 0.075 mg group (3.6% of patients). The majority of TEAEs were assessed by the investigator to be not related or have an unlikely relationship with the study drug in all treatment groups.

A total of 190 patients (28.2%) experienced TEAEs considered to be treatment-related. The proportion of patients with treatment-related TEAEs was comparable among treatment groups: 26.8% in placebo and 28.6%, 29.0% and 28.6% in the palonosetron 0.025 mg, 0.050 mg, and 0.075 mg groups, respectively. The most common treatment-related TEAEs were bradycardia, and electrocardiogram QT prolonged. The highest proportion of patients with bradycardia occurred in the palonosetron 0.025 mg group (9.5%) and the lowest proportion occurred in the palonosetron 0.075 mg group (7.7%). The highest proportion of patients with electrocardiogram QT prolonged occurred in the palonosetron 0.075 mg group (8.9%) and the lowest proportion occurred in the palonosetron 0.025 mg group (6.0%).

A total of 45 serious TEAEs occurred in 27 patients: 8 patients (4.8%) in the placebo group, and 10 patients (6.0%), 5 patients (3.0%), and 4 patients (2.4%) in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg groups, respectively. Seven of the 45 SAEs were considered to be possibly treatment-related. SAEs occurred most frequently in the cardiac disorders (6 SAEs) and infections and infestations (7 SAEs) SOCs. The most frequently occurring SAEs were breast cancer (4 SAEs), and atrial fibrillation, bradycardia, post procedural haematoma, urinary retention and wound infection (2 SAEs each). In the placebo group, 9 SAEs of severe intensity were reported, 5 SAEs in the palonosetron 0.025 mg group, 2 SAEs in the palonosetron 0.050 mg group, whereas no severe SAEs occurred in the palonosetron 0.075 mg group. Four patients, who experienced a total of 9 SAEs recovered with sequelae, and 3 patients with 3 SAEs (1 each) were recovering at the time of their last assessment.

In each group, the majority of patients had hematological values within the normal range at both Visit 1 (baseline) and Visit 5 (final visit). In general, across the groups, a slightly higher percentage of patients had clinically significant abnormal values at Visit 5 (final visit) compared with Visit 1 (baseline). There were no notable differences between the groups in any individual patient shifts in hematology parameters.

In each treatment group, the majority of patients had normal serum levels of clinical chemistry parameters at both Visit 1 (baseline) and Visit 5 (final visit). There were no notable differences between the groups in any individual patient shifts in clinical chemistry parameters.

Most patients had clinical chemistry values that were within the normal range during the study, or if outside the normal reference range, they were assessed by the investigator as not clinically significant. In general, across the groups, a higher percentage of patients had clinically significant abnormal values at final visit compared with baseline visit.

There were no notable changes in urinalysis throughout the study and no clinically significant urinalysis results for any of the treatment groups were observed.

There were no remarkable changes in vital signs and physical examination findings over time. There were no clinically relevant differences between placebo-treated and palonosetron-treated patients, and there were no relevant differences among the palonosetron groups.

Although the 15 minutes postdosing ECG was to be performed if feasible and on a patient by patient basis, almost all patients in the operating room underwent ECG recordings and therefore the number of strippings was similar to baseline in all groups. The percentage of patients with normal ECG, according to the blinded cardiologist's interpretation, decreased, while the occurrence of CS and NCS ECG abnormalities increased in each group. The proportion of NCS ECG abnormalities was slightly higher in the palonosetron 0.050 mg and 0.075 mg groups (36.1% and 39.9%, respectively) than the palonosetron 0.025 mg and placebo groups (35.1% and 33.3%, respectively). CS ECG abnormalities were nearly equally distributed in all treatment

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groups: 6.0% (10 patients) in the placebo group, 6.5% (11 patients) in the palonosetron 0.025 mg group, 7.1% (12 patients) in the palonosetron 0.050 mg group, and 5.4% (9 patients) in the palonosetron 0.075 mg group.

The 15-minute timepoint corresponded to the time of administration of general anesthesia for the open elective surgery, and was associated with administration of intravenous and inhalation anesthetic medication. The increase of NCS ECG abnormalities, and the appearance of clinically significant ECG abnormalities not present at baseline, in all of the groups may possibly be explained by the cardiac effects associated with the administration of anesthesia for these procedures.

At approximately 6 hours post study drug administration, the proportion of patients with NCS ECG abnormalities remained fairly similar to the rate observed at 15 minutes postdosing in all groups. In the palonosetron 0.050 mg and 0.075 mg groups and in the placebo group the percentage decreased, while a slight increase was observed in the palonosetron 0.025 mg group compared to the results at 15 minutes. There were CS abnormal ECG findings at 6 hours in the palonosetron 0.050 mg and 0.075 mg groups, with 6 patients (3.6%) in each, while 7 patients (4.2%) experienced ECG abnormalities in the palonosetron 0.025 mg group and 8 patients (4.8%) in the placebo group.

The mean QT and QTc intervals at 15 minutes post study drug administration showed a marked increase compared to baseline. This QT prolongation was consistent throughout all treatment groups, with the highest increase in QTcB (18.7 msec) in the palonosetron 0.025 mg group. The uncorrected QT- and QTcF showed similar results.

At approximately 6 hours post drug administration the mean QT and QTc intervals were still slightly increased compared to the baseline values, but had markedly normalized compared to the mean values at 15 minutes.

Overall, 46 patients had a clinically significant QTcB prolongation at 15 minutes post drug administration, defined as increase in QTcB >60 msec to baseline. Patients with clinically significant QTcB prolongation were similarly distributed in all treatment groups, with the lowest proportion in palonosetron 0.025 and 0.075 mg groups with 10 patients (6.0%) in each. Comparable results were observed for QTcF. At approximately 6 hours post drug administration the overall numbers of patients with QTcB prolongation decreased. There were no marked differences in the proportion of patients with QTcB prolongation of 30 to 60 msec and >60 msec between placebo and palonosetron groups and within the palonosetron groups.

Overall, at 15 minutes there were 17 patients with a QTcB interval of >500 msec, and 5 patients with QTcF >500 msec. There was no notable difference between the treatment groups for patients with clinically relevant QTcB prolongation >500 msec. In particular, the number of patients in the palonosetron 0.075 mg group was the same as placebo, with 2 patients each. At approximately 6 hours, the total number of patients with QTcB >500 msec decreased to 8, with no marked differences between the groups.

No patients died during the study, and no patients were withdrew due to AEs.

The safety results indicate no notable differences between placebo and the palonosetron groups, or among the palonosetron groups. The 0.075 mg palonosetron dose was generally associated with the fewest AEs versus placebo and versus all other active groups. All doses of IV palonosetron, including the 0.075 mg dose, were well tolerated.

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Conclusions:

In the MFAS, statistical superiority of palonosetron 0.075 mg versus placebo was shown for CR and CC during the first 24 hours, and from 24-72 hours, after surgery. The palonosetron 0.075 mg group showed statistically superior percentages of CR and CC compared with placebo at subsequent cumulative time intervals (6-24, 0-48, and 0-72 hours) for up to 3 days postoperatively. In addition, statistical superiority for control of severity of nausea was shown for palonosetron 0.075 mg versus placebo over the 3-day observation period. Results obtained at 6-24 hours, in association with those obtained during later intervals of observations (up to 72 hours), indicate that a single dose of palonosetron 0.075 mg has a potential benefit to prevent episodes of emesis and protect against nausea symptoms that occur when patients are discharged to the ward.

No safety concerns were associated with TEAEs, or the results of laboratory evaluations, vital signs and ECG recordings, measured during the study. A single IV dose of palonosetron 0.075 mg was safe and well tolerated by patients undergoing elective gynecological or breast surgery

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