Single-dose, multicenter, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.50 mg compared to I.V. palonosetron 0.25 mg administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic cisplatin-based chemotherapy.

Sponsor:	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano/Pazzallo Switzerland Telephone: +41 91 985 2121 Fax: +41 91 993 2122
Sponsor's Responsible Medical Expert	[redacted]
Sponsor's Study Coordinator	[redacted]
Study/Protocol No.:	PALO-10-01
Study Drug or Product Name:	Palonosetron
Development Phase:	III
Indication:	Prevention of highly emetogenic cisplatin-based chemotherapy-induced nausea and vomiting
Study Drug Dose	Oral palonosetron (0.50 mg) and I.V. palonosetron (0.25 mg)
Duration of Treatment	Single dose
Date of First Enrollment:	21 June 2011
Date of Last Patient Completed:	14 November 2012
Date of Report:	5 June 2013, Final

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: Single-dose, multicenter, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.50 mg compared to I.V. palonosetron 0.25 mg administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic cisplatin-based chemotherapy.
Protocol Number: PALO-10-01
Study Period: **Phase of Development:** III **Date of first enrollment:** 21 June 2011 **Date of last completed:** 14 November 2012
Study Center(s): A total of 80 study sites were activated in 12 countries.
Publication(s): Not applicable.
Objectives: The primary objective of the study was: • To demonstrate the non-inferiority of single dose oral palonosetron 0.50 mg versus single dose Intravenous (I.V.) palonosetron 0.25 mg in terms of percentage of patients with Complete Response (CR) during the acute phase (0-24 hours). Secondary objectives were: • To assess the efficacy of single dose oral palonosetron 0.50 mg versus single dose I.V. palonosetron 0.25 mg by the evaluation of further secondary efficacy variables during the acute phase (0-24 hours) and to describe the efficacy during the delayed (25-120 hours) and overall (0-120 hours) phases. • To evaluate the safety and tolerability of oral palonosetron 0.50 mg versus I.V. palonosetron 0.25 mg for the prevention of Highly Emetogenic Chemotherapy (HEC) induced nausea and vomiting.
Study Design: This was a phase III, multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified study in patients receiving HEC. The stratification criteria were gender (male, female) and region (United States, Latin America, Europe, Commonwealth of Independent States [i.e., former Soviet Republics] and Asia). Patients were randomized on Day 1 of their first chemotherapy cycle before administration of HEC to one of the following treatment groups: • Oral palonosetron 0.50 mg (Aloxi®) and oral dexamethasone 20 mg both given on Day 1, followed by dexamethasone (8 mg) twice daily (bid) from Days 2 through 4. • I.V. palonosetron 0.25 mg (Aloxi®) and oral dexamethasone 20 mg both given on Day 1, followed by dexamethasone (8 mg bid) from Days 2 through 4. Patients participated in the study for a maximum of 37 days (including a screening period of up to 14 days, 6+2 days on study of which 4 days on active treatment, and a follow-up visit or a telephone call 21±2 days after Day 1).

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Number of Patients (planned and analyzed): The study was planned to randomize a total of 740 patients equally distributed (1:1 randomization ratio) in 2 treatment groups of 370 patients each.
The number of patients included in the analysis populations were:

	Oral PALO n (%)	I.V. PALO n (%)	Overall n (%)
Randomized/Intent-To-Treat (ITT)	371 (100.0)	372 (100.0)	743 (100.0)
Full Analysis Set (FAS)	369 (99.5)	369 (99.2)	738 (99.3)
Per-Protocol (PP) population	329 (88.7)	338 (90.9)	667 (89.8)
Safety population	370 (99.7)	369 (99.2)	739 (99.5)

Of the 743 patients randomized, four did not receive study medications. Thirty three (33) of the 743 randomized patients discontinued from the study prematurely, therefore a total of 710 (95.6%) patients completed the study.

Diagnosis and Main Criteria for Inclusion: The study population consisted of adult (≥18 years of age) chemotherapy naïve male or female patients scheduled to receive their first course of a cytotoxic chemotherapy regimen with cisplatin (administered as a single I.V. dose of ≥70 mg/m^2 over 1-4 hours on study Day 1, either alone or in combination with other chemotherapeutic agents) for the treatment of a solid malignant tumor. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, fulfill criteria indicating a hematologic and metabolic status adequate for receiving a HEC regimen, and to be able to read, understand and follow study procedures and complete the patient diary. Female patients of childbearing potential were required to have a negative pregnancy test within 24 hours prior to the first dose of study drug on Day 1 and to practice an acceptable method of contraception during the study. Patients could not participate in the study if they were currently using illicit drugs or abusing alcohol, were scheduled to receive any moderately emetogenic chemotherapy (MEC) or HEC from Day 2 to Day 5 following cisplatin administration, received or were scheduled to receive (within 1 week prior to Day 1 or between Days 1 to 5) radiation therapy to the abdomen or pelvis, had symptomatic primary or metastatic central nervous system malignancy, active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any uncontrolled medical condition that, in the opinion of the investigator, may have confounded the results of the study, represented another potential etiology for emesis and nausea (other than chemotherapy-induced nausea and vomiting [CINV]) or posed unwarranted risk in administering the study medications. Females could not be pregnant or lactating.

Test Product, Dose and Mode of Administration, and Lot Number(s):
Palonosetron (0.50 mg) soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted] ([redacted]), [redacted] ([redacted]).

Reference Therapy, Dose and Mode of Administration, and Lot Number(s):
Palonosetron (0.25 mg) 5 mL vial for I.V. administration; Batch No. (expiry date): [redacted] ([redacted] and [redacted]).

Additional Study Drug:
Dexamethasone (4 mg) tablets for oral administration; Batch No. (expiry date): [redacted] ([redacted]), [redacted] ([redacted]).

Placebo:
For blinding of the study medications in a double-dummy fashion, the following were used:
Placebo soft gelatin capsules matching palonosetron soft gelatin capsules for oral administration; Batch No. (expiry date): [redacted] ([redacted]), [redacted] ([redacted]).
Placebo vial matching palonosetron vial for I.V. administration; Batch No. (expiry date): [redacted] and [redacted]).

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Duration of Treatment: Oral palonosetron or placebo to oral palonosetron (a total of 1 capsule) was administered 60 minutes prior to the start of cisplatin infusion on Day 1. I.V. palonosetron or placebo to I.V. palonosetron (a total of one 5 mL vial) was administered 30 minutes prior to the start of cisplatin infusion on Day 1 and over 30 seconds. Oral dexamethasone tablets were administered 30 minutes prior to the start of cisplatin infusion on Day 1 (a total of 5 tablets), and in the morning and evening on Days 2-4 (a total of 4 tablets per day).

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was:

- The proportion of patients with CR (defined as no emesis and no rescue medications) within 24 hours after the start of the HEC administration on Day 1.

Secondary efficacy endpoints were:

- The proportion of patients with CR during the delayed and overall phase.
- The proportion of patients with no emesis during the acute, delayed and overall phase.
- The proportion of patients with no rescue medications during the acute, delayed and overall phase.
- The proportion of patients with no significant nausea (maximum Visual Analog Scale [VAS] <25 mm) during the acute, delayed and overall phase.
- The proportion of patients with no nausea (maximum VAS <5 mm) during the acute, delayed and overall phase.
- The proportion of patients with complete protection (no emetic episode, no rescue medications and no significant nausea) during the acute, delayed and overall phase.
- The proportion of patients with total control (no emetic episode, no rescue medications and no nausea) during the acute, delayed and overall phase.
- Severity of nausea, defined as the maximum nausea on the VAS in the acute, delayed and overall phase.
- Time to first emetic episode, time to first rescue medications intake and time to treatment failure (based on time to the first emetic episode or time to the first rescue medications intake, whichever occurred first).
- Impact on patients' daily life activities in the acute and delayed phase following the administration of cisplatin as assessed by the Functional Living Index-Emesis (FLIE) questionnaire.

Safety: Safety assessments included physical examination, vital signs, 12-lead electrocardiogram (ECG), laboratory tests (hematology, blood chemistry, urinalysis), and adverse events (AEs).

Statistical Methods:

Efficacy: The primary efficacy analysis was based on the 2-sided stratum adjusted Cochran-Mantel-Haenszel (CMH) method on the proportion of patients with CR in the acute phase. The model included gender and region as strata. The non-inferiority margin was set at -15%. The null hypothesis of no difference between treatments was to be rejected, and the non-inferiority of oral palonosetron 0.50 mg versus I.V. palonosetron 0.25 mg demonstrated if the lower limit of the two-sided 99% Confidence Interval (CI) for the difference in the proportions of patients with CR was greater (i.e., closer to zero) than -15%. The primary efficacy analysis was performed on the Full Analysis Set (FAS) and Per-Protocol (PP) populations; all missing data were imputed as treatment failures. To challenge the robustness of the study and to increase confidence in the non-inferiority conclusion, a number of sensitivity analyses were also performed.

The number and percentage of patients with CR in the acute phase and 95% CI for the response rate (using the Wilson score method) was presented by treatment group. The difference in response rate between the two groups and the 95% CI (using Newcombe-Wilson's method) was also provided. The risk difference and the 99% CI for the risk difference were calculated. In addition, the odds ratio (ORs), the 2-sided 95% CI for the OR and p-value from the CMH test were presented.

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Results of analyses for secondary efficacy endpoints were interpreted descriptively with nominal p-values. No test for non-inferiority was performed. The numbers and percentages of patients with no emesis, no rescue medications, no nausea and no significant nausea, complete protection and total control and the differences in response rates between the treatment groups were summarized. The 95% CIs for the response rates (using the Wilson score method) and for the difference in response rates (using Newcombe-Wilson's method) were also provided. Comparison between treatments was performed using a CMH test including gender and region as factors. Results were presented using ORs, 2-sided 95% CIs for the ORs and p-values.

Antiemetic rescue medications and severity of nausea were summarized using descriptive statistics. In addition, severity of nausea was compared between treatment groups using a stratified Wilcoxon rank sum test (with gender and region as strata). Time to first emetic episode, time to first rescue administration and time to treatment failure were analyzed by means of a life table analysis using Kaplan-Meier estimates. As an exploratory analysis, a log-rank test was used to compare the survival curves in the 2 treatment groups, with stratification by gender and region. To assess the impact of nausea and vomiting on patients' quality of life in the acute and delayed phases, the FLIE with a 24-hour recall period followed by the FLIE with a 4-day recall period were used. The number and percentage of patients (including 95% CI) with No Impact on Daily Life (NIDL) (overall, by domain and by individual item) for the 24-hour and 4-day periods and the difference between the treatment groups were descriptively summarized by treatment. A comparison between treatments for total FLIE score and domain scores (nausea and vomiting) was done using a CMH test, including gender and region as factors. ORs with 95% CIs and p-values were provided. The mean nausea and vomiting domain scores (expressed in FLIE points) and the mean total score were descriptively summarized and compared between treatments using a stratified Wilcoxon rank sum test (i.e., van Elteren test) with gender and region as strata.

Safety: All safety analyses were performed for the safety population. The incidence of Treatment Emergent Adverse Events (TEAEs), defined as AEs that begin or worsen in severity after the start of the first administration of the study drug, in each treatment group was presented overall, by system organ class and preferred term, and additionally grouped by severity and relationship to the study medications. The number of patients with serious TEAEs and the number of patients with TEAEs leading to discontinuation of study drugs were summarized. All AEs were listed.

Laboratory data were summarized as follows: descriptive statistics for observed values and change from baseline, shift tables from baseline with respect to normal ranges, and tabulation of the number of patients with at least one marked abnormality (National Cancer Institute Common Toxicology Criteria [NCI CTC] grade $\geq$3) for selected hematology and blood chemistry parameters with respect to normal ranges. All data were listed. ECG data were summarized highlighting differences from baseline for quantitative variables and frequencies of treatment emergent abnormalities. An outlier analysis was performed to show the number of patients who met pre-specified criteria. Physical examination and vital signs were summarized using descriptive statistics, in addition to being listed.

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Efficacy Results:

This study demonstrated the non-inferiority of oral palonosetron 0.50 mg compared with I.V. palonosetron 0.25 mg in terms of the primary efficacy endpoint i.e. CR in the acute phase.

Analysis of the primary endpoint showed that, in the acute phase, 89.4% of patients in the oral palonosetron group and 86.2% of patients in the I.V. palonosetron group achieved a CR. The difference in proportion between the oral and I.V. palonosetron groups was 3.21% (99% CI: -2.74% to 9.17% from stratum-adjusted CMH method for difference in proportions). Non-inferiority of oral palonosetron versus I.V. palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions was greater (i.e. closer to zero) than the pre-defined non-inferiority margin set at -15%.

Similar results were obtained in the PP population with a difference in proportions between the oral and I.V. palonosetron group of 3.77% (99% CI: -3.22% to 10.76% from stratum-adjusted CMH method for difference in proportions).

All the planned sensitivity analyses supported the results obtained on the primary efficacy endpoint.

Table 1 Complete Response Rate for the Acute Phase – FAS

	Oral PALO (N=369)	I.V. PALO (N=369)
Acute phase (0-24 hours)		
Responder, n (%)	330 (89.4)	318 (86.2)
95% CI[a]	85.9, 92.2	82.3, 89.3
Risk difference, % (99% CI)[b]	3.21 (-2.74; 9.17)	

Abbreviation: I.V.=intravenous

a 95% CI using Wilson score method.

b Stratum-adjusted Cochran-Mantel-Haenszel method for difference in proportions, stratified by gender and region according to Loch et al. and O'Gorman et al.

The non-inferiority margin is set at -15%

The two treatments showed a similar efficacy also when considering CR in the delayed and overall phases and the secondary efficacy endpoints in all phases: proportion of patients with no emesis; proportion of patients with no rescue medication; proportion of patients with no nausea or no significant nausea; complete protection rate; total control rate; severity of nausea; time to first emetic episode; time to first administration of rescue medication; time to treatment failure and quality of life questionnaire (FLIE). Thus the results of the secondary efficacy endpoints supported the demonstration of non-inferiority based on the primary efficacy endpoint.

In conclusion, this study demonstrated the non-inferiority of oral palonosetron versus I.V. palonosetron for the primary efficacy endpoint CR in the acute phase. The results of the secondary efficacy endpoints supported the conclusion of non-inferiority.

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Safety Results:

The general safety profile observed in this study was as expected in the context of cancer patients receiving treatment with cisplatin-based chemotherapy. The most commonly reported TEAEs overall were asthenia (8.0%) and neutropenia (6.6%), with similar frequencies in both treatment groups.

The percentage of patients with at least one TEAE was comparable between the treatment groups (48.6% for the oral palonosetron group and 51.8% for the I.V. palonosetron group).

The percentage of patients with TEAEs related to the study drugs was 3.2% in the oral palonosetron group and 6.5% in the I.V. palonosetron group. The most common TEAE related to study drugs was constipation reported in 1.9% of patients overall (1.4% for oral palonosetron and 2.4% for I.V. palonosetron). The percentage of patients with TEAEs related to dexamethasone was comparable between the treatment groups (5.7% for oral palonosetron and 5.4% for I.V. palonosetron). The most common TEAEs related to dexamethasone were hypokalaemia (0.7% patients overall), and dyspepsia, asthenia and hyperglycaemia (all 0.5% patients overall).

The percentage of patients with severe TEAEs was 10.3% in each treatment group. Two (0.5%) patients in the oral palonosetron group had severe TEAEs that were related to the study drugs (these were the same patients who had serious treatment related TEAEs).

Seven (1.9%) patients in the oral palonosetron group and 12 (3.3%) in the I.V. palonosetron group died due to TEAEs. None of these deaths were assessed as being related to the study drugs or dexamethasone.

The percentage of patients with at least one serious TEAE was comparable between the treatment groups (9.7% for the oral palonosetron group and 9.8% for the I.V. palonosetron group). Neutropenia was the most frequently reported serious TEAE, and was experienced by 5 (1.4%) patients in the oral palonosetron group and 9 (2.4%) patients in the I.V. palonosetron group.

Two (0.5%) patients in the oral palonosetron group had serious TEAEs assessed as being related to the study drugs: abdominal pain and constipation (one patient) and diarrhoea and asthenia (one patient). For both patients, the events were severe and recovered/resolved. No patients in the I.V palonosetron group had serious TEAEs assessed as being related to study drugs.

One (0.3%) patient in each treatment group discontinued from the study due to a TEAE: multi-organ failure in the oral palonosetron group and gastric haemorrhage in the I.V palonosetron group.

There were no safety concerns for hematology and blood chemistry parameters in this study. The spectrum of laboratory changes observed during the study is typical of the side effects of chemotherapy and/or treatment with dexamethasone: increased liver enzymes, anemia, neutropenia, leukopenia, thrombocytopenia, electrolyte imbalances and hyperglycemia.

Analysis of ECG data indicated that changes in QTc interval values were observed at a co mparable frequency in both treatment groups. No patients had an increase in QTcF to a value of >500 ms. The proportion of patients with QTcF interval increases of >60 ms from baseline was low in both treatment groups (0.3% and 1.1% for oral and I.V palonosetron, respectively). The most frequently reported treatment emergent ECG abnormalities were sinus tachycardia (10.0% and 14.9%, for oral and I.V palonosetron, respectively), followed by flat T waves (9.2% and 11.1%, respectively). No new abnormal U-waves were observed in either group.

Interpreting outlier results is difficult in a setting of cancer patients, considering the presence of any confounding effect of risk factors such as electrolyte imbalance, comorbidities and comedication in addition to chemotherapy. However, recommended assessment criteria that could indicate a potential safety signal include a change in QTcF from baseline to >500 ms in more than 5% of patients and from baseline of >60 ms in more than 15% of patients. The above results, together with the absence of patients with new abnormal U-waves indicate a satisfactory cardiac safety profile for both oral and I.V. palonosetron.

Vital signs were not adversely affected by the administration of oral or I.V. palonosetron.

Overall, the results of this study showed that oral palonosetron, given with dexamethasone to cancer patients before receiving highly emetogenic chemotherapy, is generally safe. Moreover, the safety profile of palonosetron is consistent with the information gathered so far during previous clinical experience as well as from safety information collected during ten years of post-marketing experience worldwide.

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Conclusions:

This study demonstrated the non-inferiority of oral palonosetron versus I.V. palonosetron as assessed by the primary efficacy endpoint, CR in the acute phase.

The demonstration of non-inferiority was well supported by all the planned sensitivity analyses on the primary efficacy endpoint and by the analyses of the secondary endpoints.

The safety profiles of oral and I.V palonosetron were comparable and no new safety signals were detected

Date of Report: 5 June 2013, Final