Helsinn Healthcare SA

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CLINICAL STUDY REPORT

Single Dose, Randomized, Double-Blind, Parallel Group, Multicenter Study of Palonosetron 0.25 mg, 0.50 mg and 0.75 mg Administered by the Oral Route versus Palonosetron 0.25 mg IV for the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting in Patients with Cancer

A multicenter, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, Phase III Study

Name of Test Drug:	Palonosetron
Indication Studied:	Chemotherapy-Induced Nausea and Vomiting
Protocol Identification:	PALO-03-13
EudraCT number:	2005-000137-37
Drug Development Phase:	III
Study Initiation Date (first patient in):	June 21, 2005
Study Completion Date (last patient out):	August 07, 2006
Sponsor's responsible medical officer	[redacted] Helsinn Healthcare SA, Pambio-Noranco, Switzerland
Author:	[redacted] [redacted], Munich
Date of the Report:	September 06, 2007

The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

SYNOPSIS

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<tr><td colspan="3">Title of the study:
Single Dose, Randomized, Double-Blind, Parallel Group, Multicenter Study of Palonosetron 0.25 mg, 0.50 mg and 0.75 mg Administered by the Oral Route versus Palonosetron 0.25 mg IV for the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting in Patients with Cancer
A multicenter, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, Phase III Study</td></tr>
<tr><td colspan="3">Investigators:
Investigators in 46 centers in Europe, Mexico and the United States.</td></tr>
<tr><td colspan="3">Study Centers:
In this study, there were 46 active study centers: 24 centers in Europe (11 in the Czech Republic, 7 in Poland and 6 in Romania), 7 centers in Mexico and 15 centers in North America.</td></tr>
<tr><td colspan="3">Publication (reference):
(not applicable)</td></tr>
<tr><td colspan="2">Study period (years):
First patient enrolled: June 21, 2005
Last patient completed: August 07, 2006</td><td>Phase of development: III</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to compare the effect of single doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg administered orally versus a single IV dose of palonosetron 0.25 mg on complete response (defined as no emetic episode and no rescue medication) during 0-24 hours and 24-120 hours after the start of moderately emetogenic chemotherapy administration.

Secondary objectives of this study were to investigate the effect of study treatments on the efficacy by the evaluation of further secondary efficacy variables, and on safety by the evaluation of the safety variables.

To avoid any possible misunderstanding or confusion between the primary objective of the study and the primary efficacy variable, the following more general wording was preferred for describing the study objectives in the Statistical Analysis Plan:

• To compare the effect of single doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg administered orally versus a single IV dose of palonosetron 0.25 mg on efficacy in preventing acute and delayed moderately emetogenic chemotherapy induced nausea and vomiting (CINV) in patients with cancer.
• To assess the safety and tolerability of single doses of palonosetron 0.25 mg, 0.50 mg and 0.75 mg administered orally and their relative safety in comparison with a single IV dose of palonosetron 0.25 mg in cancer patients receiving moderately emetogenic chemotherapy.</td></tr>
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Efficacy and safety variables

Primary Efficacy variable:

- Proportion of patients considered to have achieved complete response (CR) for the 0-24 hour interval after the administration of the first (most) emetogenic chemotherapeutic agent

Key secondary Efficacy variable:

- Proportion of patients considered to have achieved complete response for the 24-120 hour interval after the administration of the first (most) emetogenic chemotherapeutic agent

Other secondary Efficacy variables:

- Proportion of patients considered to have achieved complete response daily for the 24-120 hour interval, for cumulative time periods (except for 24-120 hours) and for the overall 0-120 hour interval (Days 1-5)
- Proportion of patients considered to have achieved complete control (CC) (defined as complete response and no more than mild nausea) daily and cumulative for the 0-120 hour interval, for the overall 0-120 hour interval (Days 1-5) and for the 24-120 hour period
- Number of emetic episodes daily for the 0-120 hour interval and for the overall 0-120 hour interval (Days 1-5)
- Time to first emetic episode
- Time to first administration of rescue therapy
- Time to treatment failure (time to first emetic episode or to administration of rescue therapy, whichever occurred first)
- Severity of nausea (4-point Likert scale) daily for the 0-120 hour interval
- Percentage of patients with/without nausea, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval
- Percentage of patients with/without rescue medication, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval
- Percentage of patients with/without emesis, daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval
- Patient global satisfaction with anti-emetic therapy (VAS) daily for the 0-120 hour interval

In addition, the efficacy of palonosetron was to be investigated by gender, by chemotherapeutic history and by use of dexamethasone.

Safety variables

- Adverse events (collected by questioning of patients during visits)
- Vital signs (blood pressure, heart rate)
- Physical examination (covering twelve body systems)
- 12-lead ECG
- Clinical laboratory parameters (hematology, blood chemistry, urinalysis)

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Methodology:
This was a multicenter, randomized, balanced, stratified, double-blind, double-dummy, active control, non-inferiority phase III study with four parallel groups.

Number of patients:	Planned:	The number of patients to be included in the study was estimated to be 640, equally distributed in four groups (i.e. 160 patients/ group).		
	Enrolled:	651 patients		
	Analyzed	Safety set:	639 patients	
			Oral Palonosetron 0.25 mg:	157
			Oral Palonosetron 0.50 mg:	161
			Oral Palonosetron 0.75 mg:	158
			IV Palonosetron 0.25 mg:	163
		FAS:	635 patients	
			Oral Palonosetron 0.25 mg:	155
			Oral Palonosetron 0.50 mg:	160
			Oral Palonosetron 0.75 mg:	158
			IV Palonosetron 0.25 mg:	162
		PP set:	591 patients	
			Oral Palonosetron 0.25 mg:	143
			Oral Palonosetron 0.50 mg:	152
			Oral Palonosetron 0.75 mg:	149
			IV Palonosetron 0.25 mg:	147

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Diagnosis and main criteria for inclusion: Male or female patients; ≥ 18 years of age; with histologically or cytologically confirmed malignant disease; who were naïve or non-naïve to cancer chemotherapy (if a patient was non-naïve, he/she had to have experienced no more than mild nausea and no vomiting following any previous chemotherapy cycle); had a Karnofsky index of ≥50%; were scheduled to receive a single IV dose of at least one of the following agents administered on Day 1: any dose of oxaliplatin, carboplatin, epirubicin, idarubicin, doxorubicin, ifosfamide, irinotecan or daunorubicin or cyclophosphamide <1500 mg/m^2 or cytarabine >1g/m^2; scheduled to receive the most emetogenic chemotherapeutic agent during a maximum of 4 hours; with given written informed consent (with additional legal representative's or parent's consent if required). If a patient had known hepatic, renal or cardiovascular impairment and was scheduled to receive the above mentioned chemotherapeutic agents or if a patient had a known history or predisposition to cardiac conduction interval abnormalities, including QTc, he/she could be enrolled in the study at the discretion of the Investigator; if a patient was female of childbearing potential, she had to be using reliable contraceptive measures with a negative pregnancy test at the pretreatment (screening) visit.
Main criteria for exclusion: Patients administered any drug with potential anti-emetic efficacy within 24 hours of the start of study treatment; patients administered any antacid medication within 24 hours of the start of study treatment; any vomiting, retching, or NCI Common Toxicity Criteria grade 2 or 3 nausea in the 24 hours preceding chemotherapy; treatment with US, EU or Mexican commercially available IV palonosetron 0.25 mg (Aloxi®; Onicit®) within two weeks prior to the start of study treatment; enrollment in a previous study with palonosetron; ongoing vomiting from any organic etiology; presence of a clinically unstable seizure disorder with seizure activity requiring anticonvulsant medication (prophylactic anticonvulsant medication for patients free of seizure activity is allowed); any moderately or highly emetogenic chemotherapy or radiotherapy received within 1 week prior to the start of the study treatment; scheduled to receive any oral or intravenous dose of cisplatin, dacarbazine, streptozotocin, carmustine, mechlorethamine, hexamethylmelamine or procarbazine or cyclophosphamide ≥1500 mg/m^2 during Days 1 to 5 of the study, or radiotherapy of upper abdomen or cranium or total body irradiation during Days 1 to 5 of the study, or Docetaxel, Paclitaxel or Pemetrexed on Days 1 to 5 of the study, or any low-level emetogenic chemotherapeutic agent during Days 2 to 5, if this chemotherapy, in the Investigators' opinion, required co-administration of antiemetics; a known contraindication to 5-HT$_3$ receptor antagonists.

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Test product: Oral Palonosetron
Dose: 0.25 mg, 0.50 mg or 0.75 mg
Batch numbers:
Oral Palonosetron 0.25 mg: [redacted]
Oral Palonosetron 0.5 mg: [redacted]
Oral Palonosetron 0.75 mg: [redacted]
Mode of administration: oral (soft gelatin capsules)

Duration of treatment: single dose, administered 60 minutes before the start of the first (most) emetogenic chemotherapeutic agent

Reference therapy: IV Palonosetron
Dose: 0.25 mg
Batch number: [redacted]
Mode of administration: Intravenous (30 seconds bolus)

Duration of treatment: single dose, administered 30 minutes before the start of the first (most) emetogenic chemotherapeutic agent

Criteria for evaluation:

Efficacy evaluation (primary):
CR for the 0-24 hour interval after the start of the administration of the first (most) emetogenic chemotherapeutic agent.

Efficacy evaluation (secondary):
Complete Response (CR) for the 24-120 hour interval was the key secondary efficacy variable. Other secondary efficacy variables included: CR daily for the 24-120 hour interval, for cumulative time intervals and for the overall 0-120 hour interval; CC daily and cumulative for the 0-120 hour interval, for the overall 0-120 hour interval and for the 24-120 hour period; number of emetic episodes daily for the 0-120 hour interval and for the overall 0-120 hour interval; time to first emetic episode; time to first administration of rescue therapy; time to treatment failure (time to first emetic episode or to administration of rescue therapy, whichever occurred first); severity of nausea (4-point Likert scale) daily for the 0-120 hour interval; percentage of patients with/without nausea, percentage of patients with/without rescue medication, percentage of patients with/without emesis (daily for the 0-120 hour interval, the overall 0-120 hour interval, and for the 24-120 hour interval) and patient global satisfaction with anti-emetic therapy (VAS), daily for the 0-120 hour interval.

Safety:
Safety was assessed by documentation of adverse events, measurement of vital signs, ECGs, clinical laboratory tests, and physical examination findings.

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Statistical methods:

The primary efficacy variable in this study was the proportion of patients considered to have achieved a CR during the first 24 hours after the start of the first (most) emetogenic chemotherapeutic agent administration. The analysis of the primary efficacy variable was performed for the FAS and PP sets. Only the results of the FAS were interpreted in a confirmatory manner. To demonstrate non-inferiority of at least one dose of oral palonosetron to the IV dose of palonosetron (0.25 mg), the lower bound of the two-sided 98.3% confidence interval of the difference between the proportions of CR in each oral and IV dose of palonosetron was compared to the pre-set threshold (-15% difference). A sensitivity analysis of the primary endpoint was done using the FAS excluding diary card records with incomplete or discrepant information which where considered as emetic episodes following the worst case principle. Moreover, for the FAS, subgroup analyses by chemotherapeutic treatments were performed only for the most frequently used chemotherapeutic agents / combinations in order to investigate their influence on the primary variable. In addition, to identify factors potentially influencing CR rates, logistic regression analysis was performed, adjusted by confounders, e.g. gender, age, chemotherapeutic history, use of dexamethasone, chemotherapeutic treatment, country and study treatment. An exploratory analysis of equivalence of the three oral doses of palonosetron concerning the primary efficacy variable was performed using pairwise comparisons. The bounds of the two-sided 98.3% confidence intervals for the pairwise differences were compared to the pre-set threshold (±15% difference).

The validity of the study was assessed by comparing the CR rate of the active comparator (palonosetron 0.25 mg IV) at 24 hours to the historical placebo response rate (at 24 hours) and by comparing the CR rate of the active comparator (palonosetron 0.25 mg IV) at 24 hours without dexamethasone to the historical IV palonosetron (0.25 mg) response rate (at 24 hours).

For secondary efficacy variables, all analyses were performed for the FAS only, with the exception of the key secondary efficacy variable ($CR_{24\text{-}120\ hours}$) which was also analyzed for the PP set. The results were interpreted in a descriptive manner. For all secondary efficacy variables except CR, the differences between the three oral doses of palonosetron were tested two-sidedly with $\alpha = 0.05$.

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Statistical methods (continued): In addition, comparisons between any of the oral doses and the IV administration were tested two-sidedly with $\alpha = 0.0167$ (i.e. alpha is adjusted for the three comparisons within each time interval). The key secondary efficacy variable, the proportion of patients considered to have achieved a CR during the 24-120 hour time period, and the other secondary efficacy variables, the proportion of patients considered to have achieved a CR on a daily basis (24-48, 48-72, 72-96 and 96-120 hour time period) and during the cumulative 0-48, 0-72, 0-96, and overall 0-120 hour time periods were examined using the same statistical methods as for the primary efficacy variable (two-sided 98.3% confidence intervals). A sensitivity analysis similar to the primary endpoint was done for the key secondary efficacy variable only. The proportion of patients who achieved CC, the proportion of patients who did / did not experience emesis, the proportion of patients who did / did not experience nausea and the proportion of patients who needed/did not need rescue medication were analyzed using the Chi-square test. The number of emetic episodes, the severity of nausea and the patient global satisfaction with anti-emetic therapy were compared between the treatment groups using Kruskal-Wallis and Mann-Whitney tests. Time to first emetic episode, time to first administration of rescue therapy and time to treatment failure were evaluated by Kaplan-Meier estimates and log-rank test. The estimated time to event function was plotted.

All safety analyses were performed for the safety set. The results were descriptive in nature. The incidence of adverse events was calculated overall, by category, by system organ class and by preferred term. Furthermore, the incidence of all, non-related and related adverse events was provided for each treatment group overall, by country, by gender, by chemotherapy history (naïve/non-naïve) and by use of dexamethasone (yes/no) including 95% confidence intervals. Physical examination and vital signs data were listed and summarized by treatment group. Hematology, blood chemistry or urine values were listed with values marked which were out of the normal range. Marked abnormalities and assessments concerning clinical relevance for abnormal values were included. Data were summarized using mean tables, frequency tables, shift tables and shift plots. Frequency tables were generated to summarize clinical relevant abnormalities.

For all ECGs, PR, QRS, QT, QTcB and QTcF intervals and heart rate were analyzed. Summary statistics including mean, median, standard deviation, range and 95% confidence interval for the mean were presented for each visit as well as the change from baseline (Visit 1). In addition to this central tendency analysis, an outlier analysis was performed. The morphological changes of interest included changes in rhythm, conduction, hypertrophy, myocardial patterns, ST segment depression or elevation, change in T-waves and presence or absence of abnormal U-waves.

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Summary

Efficacy results:

The proportion of patients considered to have achieved complete response (CR) during the first 24 hours after the administration of the first (most) emetogenic chemotherapeutic agent was the primary efficacy variable in this study. Table 1 depicts the respective results, whereas Table 2 gives the confidence intervals for differences between the oral and IV palonosetron treatment groups.

Table 1: Patients with complete response (n) during the first 24 hours after start of chemotherapy (Full analysis set, N = 635)

Oral Palonosetron 0.25 mg (N = 155)			Oral Palonosetron 0.50 mg (N = 160)			Oral Palonosetron 0.75 mg (N = 158)			IV Palonosetron 0.25 mg (N = 162)		
n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)	n	%	95% CI (%)
114	73.5	[65.8, 80.2]	122	76.3	[68.8, 82.5]	117	74.1	[66.4, 80.5]	114	70.4	[62.6, 77.1]

Table 2: Complete response during the first 24 hours: confidence intervals (CI) for differences between oral and IV treatment groups (Full analysis set, N = 635)

Oral Palonosetron 0.25 mg - IV Palonosetron 0.25 mg 98.3% CI (%)	Oral Palonosetron 0.50 mg - IV Palonosetron 0.25 mg 98.3% CI (%)	Oral Palonosetron 0.75 mg - IV Palonosetron 0.25 mg 98.3% CI (%)
[-9.5, 15.8]	[-6.5, 18.2]	[-8.9, 16.2]

Considering the FAS, the proportion of patients with complete response during the first 24 hours after start of chemotherapy was comparable in the three oral palonosetron treatment groups. The highest percentage of patients with complete response was found in the oral palonosetron 0.50 mg group (76.3%), followed by the oral palonosetron 0.75 mg group (74.1%) and the oral palonosetron 0.25 mg group (73.5%). The smallest proportion of patients with complete response was seen in the IV palonosetron group (70.4%). Non-inferiority of all three oral palonosetron doses to IV palonosetron was demonstrated in a confirmatory manner. The results of the sensitivity and the PP analysis for the CR during the 0-24h interval and for the non-inferiority analysis were consistent with these results. Regarding the comparison of the three oral doses in the FAS, both the oral palonosetron 0.25 mg and 0.50 mg doses were equivalent to oral palonosetron 0.75 mg, indicating the lack of a clear dose dependence regarding the complete response rate during the 0-24 hour interval.

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Efficacy results (continued): The key secondary efficacy variable was the complete response during the 24-120 hour time interval. The highest complete response rate for the 24-120 hour time period for the FAS was found in the IV palonosetron treatment group (65.4%), followed by the 0.50 mg (62.5%) and the 0.75 mg (60.1%) oral palonosetron dose groups; the lowest percentage of patients with complete response during the delayed phase of emesis was reported in the 0.25 mg oral palonosetron dose group (59.4%). The differences in CR rate between the IV and oral doses were small, particularly for the 0.50 mg dose where the CR rate was 62.5% compared to the IV palonosetron CR rate of 65.4%. This difference was only 2.9%, which is not considered clinically significant by experts in the field. Despite these small, clinically insignificant differences, statistical non-inferiority to IV palonosetron could not be shown (i.e. the lower bound of the confidence interval was not above -15%) for any of the three oral palonosetron doses during the 24-120 hour interval. Both the sensitivity and PP analysis showed similar results. Regarding the comparison of the three oral palonosetron doses in the FAS for the key secondary efficacy variable, equivalence was shown for the oral 0.25 mg to the oral 0.75 mg dose.

Daily complete response rates at Day 2 to Day 5 tended to be highest in the IV palonosetron group and increased from Day 2 to Day 5 in all four treatment groups. Regarding the cumulative time periods, a slight trend to a lower complete response rate in longer time periods was shown in all four treatment groups, being less marked in the oral palonosetron 0.50 mg and the IV palonosetron groups. Comparing the three oral dose groups, the highest complete response rates tended to occur in the oral palonosetron 0.50 mg group in the cumulative time intervals, while no trend was identified for the daily complete response rates. Non-inferiority to the IV palonosetron was shown for oral palonosetron 0.25 mg on Days 4 and 5, for oral palonosetron 0.50 mg during the 0-48, 0-72 and 0-120 hour intervals and on Day 5, and for oral palonosetron 0.75 mg during the 0-48 hour time period and on Days 2 and 5. The oral 0.50 mg palonosetron dose was therefore the only oral dose showing non-inferiority to IV palonosetron for the CR during the overall 0-120 hour time period. Equivalence of oral doses was shown for oral palonosetron 0.25 mg and 0.50 mg on Day 2, Day 3, Day 4 and Day 5, for oral palonosetron 0.25 mg and 0.75 mg on Day 3, Day 5 and during the 0-72 hour, 0-96 hour and 0-120 hour time intervals as well as for oral palonosetron 0.50 mg and 0.75 mg on Day 3, Day 4, Day 5 and during the 0-48 hour time interval.

Similar to complete response, during the first time interval (0-24 hours) the percentage of patients with complete control (CC) was highest in the oral palonosetron 0.50 mg treatment group (74.4%), followed by the oral palonosetron 0.75 mg group (72.8%). Again, similar to complete response, in the delayed time period (>24-120 hours) the highest CC rate was found in the IV palonosetron group (62.3%). The response rate for CC was lowest in the oral palonosetron 0.25 mg group during all cumulative time periods and on Days 2 and 5. Again, similar to complete response, no clear dose dependence was

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Efficacy results (continued): observed when comparing the three oral treatment groups for the daily CC. On Days 2, 3, 4 and 5, however, the percentage of patients with CC was higher in the oral palonosetron 0.75 mg group than in the remaining two oral dose groups.

The percentages of patients who did not experience any emesis, any nausea or did not require rescue medication were highest in the oral palonosetron 0.50 mg or 0.75 mg treatment groups during the first 24 hours, whereas the lowest percentages were always found in the IV treatment group. For the 24-120 hour time period the highest percentage of patients without emetic episodes or without rescue medication was found in the IV palonosetron treatment group, while the highest percentage of patients without nausea was recorded in the oral palonosetron 0.50 mg treatment group. In general, for the percentage of patients without emesis, without nausea or without rescue medication, no trend in favor of any one treatment group was evident throughout the study.

For all four treatment groups, the median time to the first emetic episode, the median time to first administration of rescue medication and the median time to treatment failure were not calculable, as more than 50% of patients had no events within the first 120 hours. Concerning the 25% quantile, the time to first emetic episode and the time to treatment failure were longest in the oral palonosetron 0.50 mg group, whereas time to first administration of rescue medication was longest in the IV palonosetron treatment group.

For all four treatment groups, the median patient global satisfaction with the anti-emetic therapy was high during this study, i.e. ≥ 90.0 mm on a 100 mm VAS during all time periods.

For the early time interval after the start of chemotherapy (0-24 hours), the overall anti-emetic efficacy of the orally administered palonosetron tended to be better than that of the intravenously administered palonosetron: in fact, the lowest percentage of patients with complete response, of patients without emetic episodes, of patients without nausea and of patients not requiring rescue medication was seen in the IV palonosetron treatment group in this time interval. For the early time interval (0-24 hours), the highest efficacy was either observed in the oral palonosetron 0.50 mg (highest percentage of patients with complete response, with complete control and without emesis) or in the oral palonosetron 0.75 mg group (highest percentage of patients without nausea and not requiring rescue medication), but was never observed in the oral palonosetron 0.25 mg group. For the 24-120 hour time interval, a tendency for slightly better anti-emetic efficacy was noted in the IV treatment group (highest percentage of patients with complete response, complete control, without emesis, without rescue medication) compared to the oral dose groups. The lowest efficacy tended to be found in the oral palonosetron 0.25 mg group.

Neither the comparison between any of the three oral doses of palonosetron and IV palonosetron treatment nor the overall comparison between the three oral doses of palonosetron revealed a statistically significant difference regarding any of the secondary variables.

For the subgroup analysis by country, in all four treatment groups and during all study time periods the highest complete response rates tended to be found in Romania, whereas in the USA the percentage of patients with complete response was lowest. Considering those secondary efficacy variables which

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Efficacy results (continued): did not refer to complete response, the highest percentage of patients with complete control, of patients without emesis, of patients without nausea, of patients without rescue medication, as well as the longest time to treatment failure and the highest patient global satisfaction were seen in Romania. In general, no trends in favor of one particular treatment group were seen in the individual countries.

The subgroup analysis by gender showed better efficacy for male patients compared to female patients for complete response, complete control, number of emetic episodes, severity of nausea, use of rescue medication and patient global satisfaction with anti-emetic therapy, confirming data from the literature and from earlier palonosetron studies (25). Additionally, judging from the 25% quantile, time to first emetic episode, time to first administration of rescue medication and time to treatment failure tended to be longer in male than in female patients. Generally, differences between the four treatment groups were often rather small and no clear and consistent trend for better efficacy in one treatment group was evident.

Subgroup analyses by chemotherapy history showed that non-naïve patients tended to have higher complete response rates, higher complete control rates, fewer emetic episodes, less nausea (by intensity), longer time to first emetic episode (25% quantile), less requirement for rescue medication and longer time to first administration of rescue medication (25% quantile) and longer time to treatment failure (25% quantile – all treatment groups, and median – 0.25 mg and 0.75 mg oral palonosetron groups) than chemotherapy naïve patients. Generally, no consistent difference was seen between the four treatment groups in naïve and non-naïve patients.

Subgroup analyses by dexamethasone use showed that in patients using dexamethasone there was a trend towards higher complete response rates, higher complete control rates, fewer emetic episodes, a lower frequency of nausea, longer time to first emetic episode (25% quantile), longer time to first administration of rescue medication (25% quantile) and longer time to treatment failure (25% quantile – all treatment groups, and median – 0.75 mg oral palonosetron group), compared to patients not using dexamethasone. Regarding the differences between the treatment groups, no consistent trends were identified, with the exception of a general trend to lower complete response rates in the 0.25 mg oral palonosetron treatment group in patients using dexamethasone.

The subgroup analysis by most frequently used chemotherapeutic agents/combinations revealed a higher percentage of patients with complete response in patients receiving a platinum based regimen with respect to patients receiving an AC/EC regimen during all recorded time periods.

A logistic regression analysis of complete response rates for various time periods showed differences between male and female patients in favor of male patients during all time intervals. None of these differences, however, was statistically significant. Chemotherapy non-naïve patients were more likely to have complete response than naïve patients. In general, use of dexamethasone had a positive effect on complete response, as well as receiving a platinum based chemotherapeutic regimen compared to receiving an AC/EC regimen. The logistic regression also showed an influence of country in all time periods, with the lowest complete response rates found in the USA.

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Efficacy results (continued):

Age had a clear effect on the complete response rates, with older patients being more likely to experience complete response than younger patients. The logistic regression did not show any statistically significant effect of treatment in any time period.

The validity of the study was shown by better complete response rates of the active comparator (IV palonosetron 0.25 mg in this study) compared to modeled historical placebo. In the comparison of the active comparator (without dexamethasone) to a modeled historical palonosetron (without dexamethasone), validity of the study was not shown. Some shortcomings of the applied model need to be mentioned. First, the originally planned validation model was based on relatively low patient numbers (636 patients) as the underlying meta-analysis was performed with data derived from only two previous historical palonosetron studies. The small sample size resulted in a validation model that was not truly representative. Second, the complete response rates of the historical IV palonosetron included in the model were partly derived from one study with high response rates, leading to an optimistic assumption and model. Third, factors contributing to a higher response rate (e.g. percentage of male patients, percentage of patients ≥60 years of age and percentage of patients administered chemotherapies other than the AC/EC regimen) were overrepresented in the current study, thus further supporting the optimistic estimation of the complete response rate. Additionally, the modeled historical palonosetron had to be compared to complete response for the active comparator of this study in the subgroup of patients without dexamethasone since the historical studies did not include use of dexamethasone. This restriction to the subgroup without dexamethasone resulted in a small sample size. For these reasons, a second, more representative study validation model was used which was based on data derived from a meta-analysis (31) with historical setrons (the same model used to obtain the modeled historical placebo response rate) that was based on a higher number of patients. When the second validation model was applied to the whole current study population, the validation of the study was successful.

Safety results:

Overall, 754 treatment emergent adverse events were reported by 307 out of 639 patients (48.0% of patients). The overall percentage of patients with adverse events was comparable for the four treatment groups with no dose dependence in the oral palonosetron treatment groups and no relevant difference between the oral and IV administration (oral palonosetron 0.25 mg: 78 out of 157 patients, 49.7%; oral palonosetron 0.50 mg: 76 out of 161 patients, 47.2%; oral palonosetron 0.75 mg: 75 out of 158 patients, 47.5%; IV palonosetron 0.25 mg: 78 out of 163 patients, 47.9%).

Gastrointestinal disorders were the most frequently reported adverse events in all four treatment groups, followed by nervous system disorders, with the exception of the oral palonosetron 0.25 mg group: in this treatment group, nervous system disorders were most common, followed by gastrointestinal disorders. At the preferred term (PT) level, the most common adverse event was headache in all treatment groups. Constipation was either the second or third most common adverse event in all four groups. Headache and constipation had their highest incidences in the oral

Synopsis continued

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Safety results (continued): palonosetron 0.50 mg group. Only the incidences of headache and constipation were in the range of ≥5% overall (all four treatment groups together) as described in the Palonosetron Investigator's Brochure (25); additionally, fatigue had an overall incidence ≥5% in this study. Considering headache and constipation, only headache occurred with an incidence ≥5% in each of the four treatment groups.

The majority of adverse events were assessed as not related to study medication, overall and in each treatment group. No adverse event was reported as having a definite relationship to the study medication in any of the four study treatment groups. Patients with related adverse events were reported with similar frequencies in the three oral palonosetron groups (oral palonosetron 0.25 mg: 7.0% of patients; oral palonosetron 0.50 mg: 8.1% of patients; oral palonosetron 0.75 mg: 7.6% of patients), while the percentage of patients with related adverse events in the IV palonosetron group was about twice as high (16.0% of patients). In all four treatment groups, the SOC with the highest number and frequency of patients with related adverse events was the nervous system disorder SOC. About half of all related adverse events in this study (40 out of 82 related adverse events) were reported in this SOC. The most common related adverse event, overall and in each treatment group, was headache with the percentage of patients suffering from this event being comparable in the three oral treatment groups (oral palonosetron 0.25 mg: 3.8%; oral palonosetron 0.50 mg: 3.7%; oral palonosetron 0.75 mg: 3.8%) and being more than twice as high in the IV palonosetron group (8.6%). Regardless of relationship to study drug, the majority of the adverse events reported in this study were of mild intensity, overall and in each treatment group. Less than 8% of adverse events overall and in each treatment group were assessed as severe. Considering the intensity of treatment emergent adverse events, no dose relationship was shown within the three oral palonosetron dose groups. Only one related adverse event each in the oral palonosetron 0.75 mg and IV treatment groups were assessed as severe.

Overall, 32 serious adverse events were reported by 17 out of 639 patients (2.7%). The highest percentage of patients with serious adverse events was reported in the oral palonosetron 0.50 mg group (9 out of 161 patients, 5.6%), followed by the oral palonosetron 0.75 mg group (4 out of 158 patients, 2.5%), the oral palonosetron 0.25 mg group (3 out of 157 patients, 1.9%) and the IV palonosetron group (1 out of 163 patients, 0.6%). Anemia, chest pain and dyspnoea (each occurring in 2 patients - 1.2% of patients for each SAE, all in the palonosetron 0.50 mg group) were the only serious adverse events reported for more than 1 patient in one particular treatment group.

There was only one serious adverse event that was assessed by the Investigator as related to study drug. One patient in the oral palonosetron 0.50 mg group (patient no. [redacted]) experienced a serious atrioventricular block second degree on Day 2 of the study. The relationship to study medication was assessed by the Investigator as possible, the event was of moderate intensity and the patient recovered with sequelae (pacemaker implantation).

Three deaths (patient no. [redacted] in the oral palonosetron 0.50 mg treatment group and 2 patients in the oral palonosetron 0.75 mg group – patient nos. [redacted] and [redacted]) were reported during this study.

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Safety results (continued): The adverse event which resulted in death in the oral palonosetron 0.50 mg group, subileus (Investigator's term: "subocclusive syndrome [peritoneal carcinomatosis]"), was assessed by the Investigator as serious, moderate in intensity and not related to study medication. The adverse events leading to both deaths in the oral palonosetron 0.75 mg group (cardio-respiratory arrest in patient no. [redacted] and febrile neutropenia and septic shock in patient no. [redacted]) were considered serious, severe in intensity and unrelated to study medication. Three adverse events led to the withdrawal of 2 patients from the study. One adverse event (thrombocytopenia, oral palonosetron 0.25 mg group, patient no. [redacted]) was of mild intensity and was reported by the Investigator as not related to the study drug. The remaining 2 adverse events leading to withdrawal (febrile neutropenia and septic shock, oral palonosetron 0.75 mg group, patient no. [redacted]) occurred in the same patient, were serious, severe in intensity and led to the death of the patient, but were assessed by the Investigator as unrelated to the study medication.

In all four treatment groups, the percentage of patients with adverse events was higher in female than in male patients. In all four treatment groups, the percentage of patients with adverse events was higher in chemotherapy naïve than in non-naïve patients. To a lesser extent, the percentage of patients with adverse events was higher in patients not using dexamethasone than in patients using dexamethasone: this was true for all groups except the oral 0.75 mg palonosetron, where the opposite was seen. Differences were also seen between the different countries participating in the study. In all treatment groups, the highest percentage of patients with adverse events was reported in the USA. The treatment groups showing the highest percentage of patients with adverse events were different in the different countries.

For the majority of patients in all four treatment groups, the ECG was assessed as normal both by the Investigator and by the study cardiologist. In all four treatment groups, the mean QT and QTc duration increased from Visit 1 (Screening) to Visit 2 (Day 1) and decreased again from Visit 2 to Visit 3 (Day 2) and 4 (Days 6-8). The only exception to this trend was a very slight increase of the mean QTcB duration from Visit 3 to Visit 4 in the oral 0.25 mg palonosetron group. In general, no relevant differences between treatment groups were seen for the mean duration of QT and QTc intervals during the study. Categorized by the magnitude of changes from baseline (<30 msec, 30 – 60 msec or >60 msec), the vast majority of patients in all treatment groups showed changes in QTc values from baseline to any post dose visit of <30 msec.

Changes in QT or QTc by Bazett or Fridericia from ≤500 msec at Visit 1 (baseline) to >500 msec post dose (Visit 2, 3 or 4) were very rare. Overall, these changes in QT, QTcB or QTcF concerned 2 patients in the oral palonosetron 0.50 mg (1.2%), 3 patients in the oral palonosetron 0.75 mg (1.9%) and 1 patient in the IV palonosetron group (0.6%).

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Safety results (continued): Concerning ECG morphology, no abnormalities were seen compared to baseline at any of the post-dose visits for U-waves in any of the four treatment groups, for the ST segment in the oral palonosetron 0.75 mg treatment group and for the morphology variable in the oral palonosetron 0.25 mg. Concerning the remaining variables, new abnormalities were generally found in a low percentage of patients with a trend for T-waves and rhythm abnormalities to occur slightly more frequently in all treatment groups than ST segment, conduction and morphology abnormalities.
ECG adverse events were reported in ≤3.2% of patients in all four treatment groups and thus rare.
The great majority of reported adverse events were non-laboratory, non-ECG events. The changes in hematology seen were typical for patients receiving chemotherapy. No pronounced differences were observed between the three oral palonosetron dose groups and the IV palonosetron treatment group for laboratory parameters, vital signs and 12-lead ECG.
Overall, the safety assessments did not raise any safety concern.

Conclusions: The three oral palonosetron doses 0.25 mg, 0.50 mg and 0.75 mg were demonstrated to be non-inferior to intravenously administered palonosetron 0.25 mg in preventing nausea and vomiting induced by moderately emetogenic chemotherapy for the analysis of the proportion of patients with complete response during the first 24 hours after the administration of the first [most] emetogenic chemotherapeutic agent, which was the primary efficacy variable in this study.
During the 24-120 hour time period, differences between CR rates for oral and IV palonosetron were small and clinically insignificant, particularly for the 0.50 mg oral dose where the difference was only 2.9% versus the IV formulation. Despite this, none of the three oral palonosetron doses were shown to be statistically non-inferior to the 0.25 mg intravenous dose of palonosetron.
The remaining secondary efficacy variables measured in this study did not reveal any clear differences between the three oral doses and the IV palonosetron dose, despite the fact that when comparing the three oral dose groups, the oral palonosetron 0.50 mg and 0.75 mg doses tended to show higher anti-emetic efficacy than the oral palonosetron 0.25 mg dose. Moreover, during the overall 0-120 hour time period, the oral palonosetron 0.50 mg dose was the only oral dose showing non-inferiority to IV palonosetron in complete response.
Subgroup analyses by dexamethasone use showed that in patients using dexamethasone there was a trend towards higher complete response rates and higher complete control rates compared to patients not using dexamethasone. This trend was also confirmed by the remaining secondary efficacy variables of this study.
The analysis of adverse events, laboratory values, vital signs and 12-lead ECGs did not raise any safety concerns for the administration of palonosetron as a single oral dose of 0.25 mg, 0.50 mg or 0.75 mg or a single IV dose of 0.25 mg.

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Conclusions (continued): The overall efficacy and safety results obtained in the present study indicate that the oral palonosetron 0.50 mg dose is the lowest effective oral palonosetron dose in the prevention of chemotherapy induced nausea and vomiting following moderately emetogenic cancer chemotherapy.		
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