Helsinn Healthcare SA
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CLINICAL STUDY REPORT

Multicenter, Phase III, Open-Label, Uncontrolled Study to Assess the Safety and Efficacy of a Single Oral Dose of Palonosetron 0.75 mg in the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients Undergoing Repeated Cycles of Moderately Emetogenic Chemotherapy

Name of Test Drug:	Palonosetron
Indication Studied:	Chemotherapy-Induced Nausea and Vomiting
Protocol Identification:	PALO-03-14
EudraCT number:	2005-001944-21
Drug Development Phase:	III
Study Initiation Date (first patient in):	June 15, 2005
Study Completion Date (last patient out):	April 27, 2006
Sponsor's responsible medical officer:	[redacted] Helsinn Healthcare SA, Pambio-Noranco, Switzerland
Author:	[redacted], Munich
Date of the Report:	September 07, 2007

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

APPROVAL/SIGNATURE PAGE

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SYNOPSIS

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Title of the study:
Multicenter, Phase III, Open-Label, Uncontrolled Study to Assess the Safety and Efficacy of a Single Oral Dose of Palonosetron 0.75 mg in the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients Undergoing Repeated Cycles of Moderately Emetogenic Chemotherapy

Investigators:
Investigators in 22 study centers in Europe, Mexico and the United States.

Study Centres:
In this study, there were 22 active study centers: 8 centers in Europe (5 in Czech Republic, 3 in Poland), 5 centers in Mexico and 9 centers in the United States.

Publication (reference):
(not applicable)

Study period (years): First patient enrolled: June 15, 2005 Last patient completed: April 27, 2006	**Phase of development:** III

Objectives:
The **main objective** of this study was to assess the safety of single oral doses of palonosetron 0.75 mg (with or without concomitant corticosteroids) used for the prevention of moderately emetogenic chemotherapy induced nausea and vomiting in repeated (up to a maximum of four) and consecutive chemotherapeutic cycles.
As a **secondary objective**, the continued efficacy of a single oral dose of palonosetron 0.75 mg (with or without corticosteroids) was assessed in up to a maximum of four consecutive moderately emetogenic chemotherapy cycles for the prevention of moderately emetogenic chemotherapy induced nausea and vomiting.

Methodology: This was a multicenter, open-label, repeated cycle, uncontrolled phase III study to assess the safety and the efficacy of single oral doses of palonosetron 0.75 mg in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting (CINV) in repeated and consecutive moderately emetogenic chemotherapy cycles.

Number	Planned:	600 cycles	
of cycles:	Performed	654 cycles	(in 217 patients)
	Analyzed	Safety Set:	654 cycles Palonosetron 0.75 mg: 171 cycles
			Palonosetron 0.75 mg +dexamethasone: 483 cycles
		Full analysis set:	654 cycles Palonosetron 0.75 mg: 171 cycles
			Palonosetron 0.75 mg +dexamethasone: 483 cycles

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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 scheduled to receive repeated and consecutive moderately emetogenic chemotherapy cycles employing the same basic moderately emetogenic regimen (single or multi-drug regimen; this could include changes in dose or discontinuation of concomitant chemotherapeutic agents as clinically appropriate, as long as the agent that defined the regimen as moderately emetogenic was still included and no highly emetogenic agents were added); naïve or non-naïve to cancer chemotherapy (if a patient was non-naïve before the first study cycle, he/she had to have experienced no more than mild nausea and no vomiting following any previous chemotherapy cycle); a Karnofsky index of ≥50%; scheduled to receive a single intravenous dose of at least one of the following moderately emetogenic 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; if a patient scheduled to receive the above mentioned chemotherapeutic agents had a known hepatic, renal or cardiovascular impairment or had a known history or predisposition to cardiac conduction interval abnormalities, including QTc, he/she could be enrolled in this study at the discretion of the Investigator; the time interval between two consecutive study drug administrations (between the two 'Day 1' days in two consecutive study cycles) had to be at least seven days (i.e. study drug could be administered at weekly intervals).

Main criteria for exclusion: Any investigational drugs within 30 days before study entry; any drug with potential anti-emetic efficacy within 24 hours of the intake of study treatment, with the exception of topical or inhaled steroids; any antacid medication within 24 hours of the intake 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 intake 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 was allowed); palonosetron 0.75 mg not administered in consecutive chemotherapy cycles, i.e. if a chemotherapy cycle was performed without oral palonosetron 0.75 mg administration after the patient had already received at least one preceding cycle in this study (including palonosetron 0.75 mg), the patient had to be excluded from further participation in the study; scheduled to receive any of the following: moderately emetogenic chemotherapy within 7 days prior to the study, on Days 2-5 of each study cycle, or on any day between two consecutive cycles; orally or intravenously: any dose of cisplatin, dacarbazine, streptozotocin, carmustine, mechlorethamine, hexamethylmelamine or procarbazine, or cyclophosphamide ≥1500 mg/m^2,

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Main criteria for exclusion (continued) : within 7 days prior to the study or during the study; radiotherapy of upper abdomen or cranium or total body irradiation within 7 days prior to the study or during the study; docetaxel, paclitaxel or pemetrexed on Day 1 in association with corticosteroids for the prevention of hypersensitivity reactions; any low-level emetogenic chemotherapeutic agent during Days 2 to 5 of each study cycle, if this chemotherapy, in the Investigators' opinion, required co-administration of antiemetics. Administration of low-level emetogenic chemotherapy without antiemetics was allowed on Days 2 to 5; known contraindication to 5-HT_3 receptor antagonists.

Test product: Oral palonosetron
Dose: 0.75 mg
Batch number: [redacted]
Mode of administration: oral (soft gelatin capsules)

Duration of treatment: single palonosetron oral dose 60 minutes before the start of administration of the first emetogenic chemotherapeutic agent; this treatment could be repeated up to a maximum of 4 consecutive moderately emetogenic chemotherapy cycles.

Reference therapy: (not applicable)

Criteria for evaluation:

Safety criteria:

- Adverse events (collected from patients during visits or from vital signs, physical examination, ECG or clinical laboratory parameters)
- Vital signs (blood pressure, heart rate)
- Physical examination (covering twelve body systems)
- 12-lead ECG
- Clinical laboratory parameters (hematology, blood chemistry, urinalysis)

Efficacy criterion of main interest:

- Complete Response (CR) (defined as no emetic episode and no rescue medication) for the 0-24 hour interval ($CR_{0\text{-}24h}$) and Complete Response for the 24-120 hour interval ($CR_{24\text{-}120h}$)

Further efficacy criteria:

- CR daily for the 24-120 hour interval, for cumulative time intervals (0-48 hours, 0-72 hours and 0-96 hours) and for the overall 0-120 hour interval (Days 1-5)
- Complete control (CC) (defined as complete response and no more than mild nausea) daily for the 0-120 hour interval, for cumulative time intervals (0-48 hours, 0-72 hours, 0-96 hours and 24-120 hours) and for the overall 0-120 hour interval (Days 1-5)
- 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

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Further efficacy criteria (continued):

- 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 on visual analogue scale (VAS) daily for the 0-120 hour interval

Statistical methods:

Safety: All safety analyses were performed for the safety set. The results were descriptive in nature. All safety analyses were performed for chemotherapy cycles with administration of oral palonosetron 0.75 mg alone, for chemotherapy cycles with administration of oral palonosetron 0.75 mg in combination with dexamethasone and overall.

The incidence of adverse events was calculated overall, by category and by preferred term and system organ class. Furthermore, the incidence of adverse events was provided by cycle (if data were available for more than 30 patients in this cycle), by country/region and by gender, based on cycles including 95% confidence intervals. In addition, 95% confidence intervals were provided for the incidence of adverse events for each treatment group (palonosetron alone and palonosetron + dexamethasone), overall and overall by patients.

Physical examination and vital signs data were listed and summarized by treatment group and overall. Physical examination data recorded at Visit 1 of each cycle (Day -7 to Day 0 for the 1st cycle; Day -2 to Day 0 for repeated cycles) were summarized. For vital signs, data were summarized for each visit. In addition, differences were calculated for Visit 3 (Day 2) and Visit 4 (Day 8-10) compared to Visit 2A (Day 1) of the relevant cycle.

Hematology, blood chemistry and urinalysis data 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 (including changes from baseline of the relevant cycle), frequency tables and “shift tables”. Laboratory data were analysed and described by treatment group and overall.

For all ECG intervals, heart rate, PR, QRS, QT, QTcB and QTcF were analysed by treatment group and overall. 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) of the relevant cycle. 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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Statistical methods (continued):

Efficacy: All analyses of efficacy variables were performed for the full analysis set (FAS) only. The results were interpreted in a descriptive manner. All tables were presented by treatment group and overall. Subgroup analyses of all efficacy parameters (all cycles combined) were provided by gender. The efficacy variables of main interest in this study were the proportion of chemotherapy cycles in which patients were considered to have achieved Complete Response (CR) during the first 24 hours (CR_{0-24h}) and during the 24-120 hour time interval ($CR_{24-120h}$) after the start of administration of chemotherapy. The proportion of complete responders (and 95% Confidence Intervals) in these time periods was described overall and for each cycle separately, if data were available for more than 30 patients in this cycle. In case of comparable treatment in the previous cycle (i.e. either administration of oral palonosetron 0.75 mg alone in both cycles or administration of oral palonosetron 0.75 mg in combination with dexamethasone in both cycles) the proportion of complete responders (and 95% confidence intervals) during the first 24 hours and during the 24-120 hour time interval was also compared to the previous cycle in order to explore the maintenance of efficacy over time. These comparisons were done for each set of 2 subsequent cycles with comparable treatment.

The proportion of chemotherapy cycles in which patients were considered to have achieved a CR during the 0-48, 0-72, 0-96 and 0-120 hour time period as well as the proportion of chemotherapy cycles in which patients were considered to have achieved a CR during the 24-48, 48-72, 72-96 and 96-120 hour time periods were examined as done for the efficacy variables of main interest. The proportion of chemotherapy cycles in which patients were considered to have achieved Complete Control (CC) was calculated daily for the 0-120 hour interval and for cumulative time intervals (0-48 hours, 0-72 hours, 0-96 hours and 24-120 hours) and for the overall 0-120 hour interval (Days 1-5). The number of emetic episodes was calculated daily for the 0-120 hour interval and for the overall 0-120 hour interval (Days 1-5). In addition, the proportion of chemotherapy cycles in which patients did / did not experience emesis was calculated daily for the 0-120 hour interval, the overall 0-120 hour interval and for the 24-120 hour interval. The severity of nausea, as assessed by a 4-point Likert scale, was summarized daily for the 0-120 hour interval, overall and for each cycle separately (if data were available for more than 30 patients in this cycle). In addition, the proportion of chemotherapy cycles in which patients did / did not experience nausea was calculated daily for the 0-120 hour interval, the overall 0-120 hour interval and for the 24-120 hour interval, overall and for each cycle separately (if data were available for more than 30 patients in this cycle). The proportion of chemotherapy cycles in which patients needed / did not need rescue medication was calculated daily for the 0-120 hour interval, the overall 0-120 hour interval and for the 24-120 hour interval, overall and for each cycle separately (if data were available for more than 30 patients in this cycle). Time to first emetic episode, time to first administration of rescue medication and time to treatment failure were evaluated by Kaplan-Meier estimates. The estimated survival functions were plotted. Patient global satisfaction with anti-emetic therapy as assessed using the VAS was summarized daily for the 0-120 hour interval.

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Summary

Safety results:

Overall, 720 treatment emergent adverse events (Palonosetron 0.75 mg + dexamethasone: 629 adverse events; Palonosetron alone: 91 adverse events) were reported in 306 out of 654 cycles (46.8%) by 148 out of 217 patients (68.2%). The incidence of cycles with adverse events was higher in the palonosetron 0.75 mg + dexamethasone group (248 out of 483 cycles; 51.3%) than in the palonosetron 0.75 mg alone group (58 out of 171 cycles; 33.9%).

The majority of adverse events were assessed as not related to study medication, overall and in each treatment group.

Related adverse events were reported for a slightly higher percentage of cycles in the palonosetron 0.75 mg + dexamethasone group (9.1% of cycles) than in the palonosetron 0.75 mg alone group (8.2% of cycles). The most common related adverse event, overall and in each treatment group, was headache. Only few of these related adverse events were reported for more than one cycle, while the majority of preferred terms were reported for one cycle only.

Considering all treatment emergent adverse events (regardless of relationship to study drug), gastrointestinal disorders were the most frequently reported adverse events in both treatment groups, followed by nervous system disorders. The incidence of cycles with gastrointestinal and nervous system adverse events was higher when palonosetron was given with dexamethasone than when palonosetron was given alone. At the preferred term level, the most common adverse event was headache (palonosetron 0.75 mg alone group: headache reported in 9.4% of cycles; palonosetron 0.75 mg + dexamethasone group: 13.9% of cycles; overall: 12.7% of cycles), followed by constipation (palonosetron 0.75 mg alone group: constipation reported in 4.7% of cycles; palonosetron 0.75 mg + dexamethasone group: 6.6 % of cycles; overall: 6.1% of cycles).

A higher incidence of cycles with adverse events in the palonosetron 0.75 mg + dexamethasone group compared to the palonosetron alone group could be expected due to the additional administration of the corticosteroid in this group. Additional explanations for the higher incidence of cycles with adverse events in the palonosetron + dexamethasone group versus the palonosetron alone group include (1) patients in the palonosetron + dexamethasone group were older than those in the palonosetron alone group and (2) the percentage of baseline pathological findings was higher in the palonosetron + dexamethasone group than in the palonosetron alone group.

The incidence of cycles with adverse events was also analysed in each cycle. In each of the 4 cycles, the incidence of cycles with adverse events was higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group. In both treatment groups, the incidence of cycles with adverse events decreased slightly from Cycle 1 to Cycle 3 and remained about the same in Cycle 4. A similar tendency was seen for cycles with related adverse events.

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Safety results (continued):

Overall and in each treatment group, the majority of adverse events were of mild intensity, followed by moderate adverse events and severe adverse events. The percentage of mild and severe adverse events was higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group, while the reverse appeared for adverse events of moderate intensity.

Regardless of relationship to study drug, the majority of adverse events were of mild intensity. The one severe adverse event in the palonosetron alone group was not related to study drug. In the palonosetron + dexamethasone group, 21 severe adverse events were not related to study drug, while 3 severe adverse events were assessed by the investigator as related to study drug.

Overall, 17 serious adverse events were reported for 14 cycles (2.1%) by 14 patients. When palonosetron was given alone, 2 serious adverse events were reported in 2 cycles (1.2% of cycles) by 2 patients and when palonosetron was given together with dexamethasone, 15 serious adverse events were reported in 12 cycles (2.5% of cycles) by 12 patients. The incidence of cycles with at least one serious adverse event was slightly higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group. Anaemia (2 out of 171 cycles, 1.2%) was the only serious adverse event reported in the palonosetron 0.75 mg alone group. It was also the only serious adverse event that occurred in more than one cycle. Of the 17 SAEs, only one (convulsion in the palonosetron 0.75 mg + dexamethasone group) was assessed as related to study drug.

One death (palonosetron 0.75 mg + dexamethasone group) was reported during this study. The adverse event which resulted in death (cardiac arrest) was assessed by the investigator as serious, severe and not related to study medication.

Only 4 adverse events in 3 out of 654 cycles (0.5%) led to the withdrawal of 3 patients from the study. One of these 4 events (preferred term: convulsion; palonosetron 0.75 mg + dexamethasone group) was serious and was assessed as possibly related to study medication. The remaining 3 adverse events that led to withdrawal (2 non-serious events in the same patient and cycle in the palonosetron alone group and 1 serious event in the palonosetron + dexamethasone group) were assessed by the investigator as not related to study medication.

In both treatment groups, the incidence of cycles with adverse events was higher in male than in female patients (palonosetron alone group: 39.5% vs 32.3% of cycles, respectively; palonosetron + dexamethasone group: 60.7% vs 48.2% of cycles, respectively).

With regards to cycles with related adverse events, their incidence was also higher in male than in female patients in the palonosetron 0.75 mg alone group (13.2% vs 6.8% of cycles, respectively), while the reverse was the case in the palonosetron 0.75 mg + dexamethasone group (4.9% vs 10.5% of cycles, respectively).

Differences were also seen between the different countries/regions of the study. Overall, the highest incidence of cycles with AEs was seen in the US (77.7%), followed by Mexico (44.0%) and Europe (30.0%).

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Safety results (continued):

For the majority of cycles in both treatment groups, the ECG was assessed as normal both by the investigator and by the study cardiologist. Compared to baseline (Visit 1), in both groups the mean QT and QTc duration increased slightly at both Visit 2 (Day 1) and Visit 3 (Day 2), such increase being generally of few milliseconds in both treatment groups.

Categorized by the magnitude of changes from baseline (Visit 1) to Visit 2 or Visit 3 (< 30 msec, 30 – 60 msec or > 60 msec), the vast majority of cycles in both treatment groups showed changes in QTc values < 30 msec, followed by the 30 - 60 msec range. Only few cycles with changes in QTc from Visit 1 (baseline) to Visit 2 or Visit 3 with a magnitude above 60 msec were reported in both groups and concerned more cycles in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group.

Cycles showing changes in QT or QTc by Bazett or Fridericia from ≤ 500 msec at Visit 1 (baseline) to > 500 msec post dose (Visit 2 or Visit 3) were rare. These changes in QTcB and QTcF concerned 1 patient in the palonosetron 0.75 mg alone group and 4 patients in the palonosetron 0.75 mg + dexamethasone group.

Concerning ECG morphology, no new abnormalities were seen for U-waves in either of the two treatment groups and for the morphology parameter in the palonosetron 0.75 mg alone group at Visit 2 (Day 1) or Visit 3 (Day 2). For the remaining parameters, new abnormalities were found in a low number of cycles. The percentage of cycles with new abnormalities (compared to baseline) was lower at Visit 3 than at Visit 2 for most parameters. No ECG adverse events were seen in the palonosetron alone group, and in the palonosetron + dexamethasone group ECG events were rare.

The great majority of reported adverse events were non-lab, non-ECG events. The changes in hematology seen were typical for patients receiving chemotherapy. No pronounced differences were observed between the palonosetron alone and the palonosetron + dexamethasone treatment groups for laboratory parameters, vital signs and 12-lead ECG. Overall, safety assessments did not raise any safety concern.

Efficacy results :

The percentage of cycles in which patients showed a complete response was higher for both the 0-24 and the >24-120 hours periods when palonosetron was given together with dexamethasone (73.9% and 63.1%, respectively) than when palonosetron was given alone (61.4% and 59.6 %, respectively). Complete response was seen in a higher percentage of cycles for the 0-24 hours period than for the >24-120 hours period. The results of both sensitivity analyses were consistent with these results.

The percentage of cycles in which patients had a complete response was higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group for cumulative time intervals and on Study Days 1 and 2, whereas for all individual study days following Day 2 the complete response rates were comparable between the two treatment groups.

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Efficacy results (continued):

Generally, the anti-emetic efficacy shown on Day 1 as well as the efficacy measured in the >24-120 hour and 0-120 hour intervals was maintained throughout at least 4 repeated and consecutive study cycles in both treatment groups. Additionally, to show the maintainance of efficacy, an analysis by cycle was performed. The percentage of cycles with complete response for the 0-24, 24-120 and 0-120 hour intervals is shown by cycle in Table 1.

Table 1: Complete response by cycle (Full analysis set, N = 654)

	Palonosetron 0.75 mg (N=171)			Palonosetron 0.75 mg + Dexamethasone (N=483)			Total (N=654)		
	CR_{0-24h}	**$CR_{24-120h}$**	**CR_{0-120h}**	**CR_{0-24h}**	**$CR_{24-120h}$**	**CR_{0-120h}**	**CR_{0-24h}**	**$CR_{24-120h}$**	**CR_{0-120h}**
Cycle 1	(N=53)			(N=164)			(N=217)		
	66.0	60.4	54.7	78.0	63.4	57.3	75.1	62.7	56.7
Cycle 2	(N=49)			(N=137)			(N=186)		
	57.1	59.2	46.9	75.2	63.5	62.0	70.4	62.4	58.1
Cycle 3	(N=40)			(N=103)			(N=143)		
	67.5	65.0	57.5	73.8	62.1	61.2	72.0	62.9	60.1
Cycle 4	(N=28)			(N=79)			(N=107)		
	50.0	50.0	46.4	63.3	63.3	58.2	59.8	59.8	55.1

N= Number of cycles in specific group, CR: percentage of cycles with complete response based on N

Similar to complete response, the proportion of cycles with complete control, the proportion of cycles in which patients did not experience any emesis and the proportion of cycles without nausea was slightly higher when palonosetron was given together with dexamethasone than when palonosetron was given alone during Days 1 and 2.

For the 0-24 h time period, the percentage of cycles with rescue medication was slightly lower in the palonosetron 0.75 mg + dexamethasone group (15.1%) than in the palonosetron 0.75 mg alone group (20.5%), while for the remaining time periods as well as for the delayed time period (>24 – 120 h) and the overall time period (0-120 h) the percentages of cycles where rescue medication was required were comparable between both groups.

For both treatment groups, the median patient global satisfaction with anti-emetic therapy was high during this study. The median patient global satisfaction was slightly higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group on Day 1 and Day 2, while it was comparable between the two treatment groups for the remaining days.

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Efficacy results (continued):

The median time to first emetic episode, the median time to first administration of rescue medication and the median time to treatment failure were longer than 120 hours in both treatment groups. Concerning the 25% quantile, however, the time to first emetic episode, the time to first administration of rescue medication and the time to treatment failure were longer in the palonosetron 0.75 mg + dexamethasone group compared to the palonosetron 0.75 mg alone group.

The subgroup analysis by gender showed a 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. Also, judging from the 25% quantile, the time to first administration of rescue medication was longer in male than in female patients. The time to first emetic episode and the time to treatment failure tended to be longer in male compared to female patients when palonosetron alone was given.

When comparing complete response for both 0-24 and 24-120 hour interval by country/region, the highest percentage of cycles with complete response was seen in Europe and the lowest in Mexico in both treatment groups. Both in Europe and Mexico, the percentage of cycles with complete response was higher in the palonosetron 0.75 mg + dexamethasone group than in the palonosetron 0.75 mg alone group.

Conclusions:

In this study, the analysis of adverse events, laboratory values, vital signs and 12-lead ECG data did not raise any safety concern for the administration of a single oral dose of palonosetron 0.75 mg (with or without dexamethasone) in repeated (up to a maximum of four) consecutive moderately emetogenic cycles of chemotherapy. Additionally, as shown by the analysis of complete response during the first 24 hours and during 24-120 hours (which were the efficacy parameters of main interest) oral palonosetron 0.75 mg (with or without dexamethasone) administered in repeated (up to a maximum of four) consecutives cycles of chemotherapy showed continued efficacy for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Continued efficacy in subsequent cycles was also shown by results of other efficacy variables.

Date of report: September 07, 2007