2 SYNOPSIS

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Title of Study: Double-blind study to compare the efficacy of palonosetron with or without the use of dexamethasone on Days 2 and 3, in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy (MEC) given to female patients with breast cancer.

Investigator(s) and Study Centers: A total of 20 sites were activated and received study medication; 3 sites in Austria, 8 sites in Germany, 6 sites in Italy, and 3 sites in Spain. Among them, 17 sites enrolled patients. One site in Spain and 2 sites in Germany did not recruit patients.

Publication(s): None to date

Study Period: 03 February 2006 to 29 November 2007 **Clinical Phase:** IV

Objective(s): To show that the efficacy of intravenous (IV) palonosetron/dexamethasone on Day 1 is not inferior to the efficacy of the same regimen on Day 1, followed by oral (p.o.) dexamethasone twice daily (BID) on Days 2 and 3, in preventing acute and delayed nausea and vomiting induced by MEC. To evaluate the safety of a single IV dose of palonosetron 0.25 mg and dexamethasone 8 mg on Day 1 followed by p.o. administration of dexamethasone 4 mg or placebo BID on Days 2 and 3.

Methodology: This was a Phase IV, double-blind, randomized, parallel group, 2-arm non-inferiority study in chemotherapy-naïve female patients with breast cancer, scheduled to receive MEC. The following treatments were administered:

Treatment Day	**Arm A**	**Arm B**
DAY 1:	Palonosetron 0.25 mg IV Dexamethasone 8 mg IV	Palonosetron 0.25 mg IV Dexamethasone 8 mg IV
DAYS 2 - 3:	Dexamethasone placebo p.o. BID	Dexamethasone 4 mg p.o. BID

Patients in **Arm A** received on Day 1 dexamethasone (8 mg IV) administered 1 hour prior to chemotherapy and palonosetron (0.25 mg given as a single IV bolus over 30 seconds) 30 minutes prior to receiving chemotherapy. On Days 2 and 3 the patients received dexamethasone-matched placebo administered BID.

Patients in **Arm B** received on Day 1 dexamethasone (8 mg IV) administered 1 hour prior to chemotherapy and palonosetron (0.25 mg given as a single IV bolus over 30 seconds) 30 minutes prior to receiving chemotherapy. On Days 2 and 3, the patients received dexamethasone at a dose of 4 mg p.o. BID.

On Days 2 and 3, patients randomized to **Arm A** and **Arm B** received multi-folded blister cards coded with the unique identification number. The patient took her dose of dexamethasone (4 mg p.o. BID) or matching placebo on Days 2 and 3 once in the morning and once in the evening.

Number of Patients: 300 patients were planned for enrollment in the study (150 per treatment arm). A total of 305 patients were enrolled and 300 randomized. Five were screening failures.

- **Diagnosis and Main Criteria for Inclusion:** Female patients age 18 and older, with histologically or cytologically confirmed breast cancer requiring chemotherapy, who were naïve to chemotherapy, had a Karnofsky Performance Status grade of ≥60 and a life-expectancy >3 months, with values of alanine transaminase (ALT) and aspartate transaminase (AST) ≤2 times the upper limit of normal (ULN) and creatinine ≤1.5 times the ULN, and who were scheduled for receipt of a single dose of MEC on Day 1.
- **Main exclusion criteria:** Patients scheduled receipt of MEC on Days 2 to 6 or scheduled receipt of highly emetogenic chemotherapy (HEC) on Days 2 to 6 or scheduled receipt of radiotherapy on Days 1 to 6; use of antiemetic therapy (within 24 hours of treatment initiation) or scheduled receipt (up to Day 5) of any medication with antiemetic effects; with nausea or vomiting with a National Cancer Institute (NCI) Common Toxicity Criteria (CTC) of grade 2 or 3 in the 24 hours before receiving study medication; or ongoing vomiting from any other

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organic etiology.

Test Product, Dose, Mode of Administration, Batch No(s): Palonosetron 0.25 mg administered as an IV bolus (lot number [redacted]) over 30 seconds, 30 minutes before chemotherapy on Day 1. Dexamethasone 8 mg IV (lot numbers [redacted] and [redacted]) administered 1 hour before chemotherapy on Day 1. Followed by the oral administration of placebo (lot numbers [redacted] and [redacted]) on Days 2 and 3.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Palonosetron 0.25 mg administered as an IV bolus (lot number [redacted]) over 30 seconds, 30 minutes before chemotherapy on Day 1. Dexamethasone (8 mg IV) (lot numbers [redacted] and [redacted]) was administered on Day 1, approximately 1 hour prior to chemotherapy, followed by the oral administration of dexamethasone 4 mg BID (lot numbers [redacted] and [redacted]) on Days 2 and 3.

Duration of Treatment: The duration of treatment was 3 days; the duration of the primary efficacy evaluation was 120 hours; and the study duration for each patient including the screening and follow up period was 19-31 days.

Criteria for Evaluation: The objective of the study was to demonstrate the non-inferiority of IV palonosetron given with IV dexamethasone on Day 1 versus the same regimen on Day 1 followed by p.o. doses of dexamethasone BID on Days 2 and 3, in preventing nausea and vomiting following the first administration of MEC.

Three populations were defined for reporting the results:

- Intent-to-Treat Population (ITT): All randomized patients who received a dose of at least MEC and any study medication were included in this population. This population was used to report efficacy results.
- Per-Protocol Population (PP): Patients in the ITT population without a major protocol violation were included in this population. The PP population was used only to report the primary endpoint.
- Safety Population: The safety population will include all randomized patients who received any study medication. This population was used to report safety results.

Efficacy

The primary efficacy endpoint was the evaluation of the number and percentage of patients with Complete Response (CR) (no emesis, no rescue medication) during hours 0–120 post chemotherapy.

All secondary efficacy endpoints were evaluated during the Acute Phase (0-24 hours), the Delayed Phase (>24-120 hours), Daily (0-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96-120 hours), and Overall Phase (0-120 hours). The secondary efficacy endpoints are listed below:

- Complete Response (no emesis, no rescue medication) (CR will not be evaluated for the overall period since this is considered the primary efficacy variable.);
- Severity of nausea (100 mm Visual Analog Scale [VAS]);
- Duration of nausea;
- Complete Control (CC, no emesis, no rescue medication, with a maximum grade of mild nausea defined as a VAS<25 mm);
- Percentage of patients with no emesis;
- Percentage of patients with no nausea defined as VAS <5 mm;
- Percentage of patients without rescue medication;
- Number of emetic episodes (categories);
- The time to first emesis;
- The time to first use of rescue medication;
- The time to treatment failure (time to first emetic episode or time to first use of rescue medication, whichever occurred first).

Other secondary endpoints for evaluation include:

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- Global Satisfaction score (100 mm VAS) assessed on Day 6 and related to the overall period (0-120 hours);
- Functional Living Index-Emesis (FLIE) score assessed in the Screening Phase (related to the period Day -5 to Day 1) and at Day 6 (related to the period Day 1-Day 5).

Safety

The number of patients with TEAEs and the number of TEAEs during the study was the safety endpoint of major interest for the study. Adverse events starting after study medication administration were defined as treatment emergent. Treatment-related AEs were defined as AEs with relationships as "possible", "probable", "definite" or "unassessable". Severe AEs were defined as "severe" and "life threatening". Overall counts and percentages by treatment group were presented for the following groups of patients in the safety population.

- Patients with any TEAE;
- Patients with any treatment-related TEAE;
- Patients with any serious TEAE;
- Patients with any serious treatment-related TEAE;
- Patients with any severe TEAE;
- Patients who discontinued due to an AE;
- Patients who died.

Other safety endpoints for evaluation included:

- Vital signs (blood pressure [BP] and heart rate [HR]) and weight;
- Laboratory assessments; and
- Physical examination.

Statistical Methods

Efficacy Analysis

For the primary and secondary parameters descriptive statistics were presented for each treatment group, for the ITT population. In addition, the CR results, including the overall period 0-120 hours (primary endpoint) were presented for the PP population. Continuous variables were summarized by sample size (n), mean, standard deviation, median, and minimum/maximum. Categorical variables were summarized by counts and percentages with 95% confidence intervals (CIs) using Fisher's exact method.

The primary efficacy analysis compared the treatment groups during the overall period (0-120 hours) for CR (no emesis, no rescue medication). The null hypothesis was that the IV palonosetron/dexamethasone on Day 1 (with no antiemetic prophylaxis on Day 2 and 3) was non-inferior to the same regimen on Day 1 followed by dexamethasone p.o. BID on Days 2 and 3. To demonstrate non-inferiority of the 1 day regimen, the lower boundary of the 2-sided 95% CI on the difference between the overall CRs for the 2 groups (1 day regimen minus 3 day regimen) must have been >-15%. This comparison was performed for the ITT and PP population. Only the result of the comparison on the ITT population was considered confirmatory; the other was only descriptive.

For the secondary efficacy parameters, all the inferential analyses were interpreted descriptively.

- Complete Response at all planned periods (with the exception of the overall period which is the primary variable) was analyzed as for the primary end-point, i.e. the 95% CI of the difference between the 2 groups. In addition for all the time periods (including 0-120 hours) the one-sided Cochran-Mantel-Haenszel test stratified by center was performed.
- Severity of nausea (VAS) for the treatment groups was compared using a one-sided Wilcoxon rank-sum test. A Kolmogorov-Smirnov test was conducted for confirming non-normality and for comparing the equality of the 2 distributions in the event the data were highly skewed.
- Duration of nausea for the treatment groups was to be compared using a one-sided t-test, provided that the Kolmogorov-Smirnov test confirmed normality. Being the data not normal the one-sided Wilcoxon rank-sum test

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(already planned) was used, instead of the t-test. A Kolmogorov-Smirnov test was conducted for comparing the equality of the 2 distributions in the event the data were highly skewed. Only patients with any duration of nausea were included in the comparison.

- Complete Control (no emesis, no rescue medication, with a maximum grade of mild nausea defined as a VAS <25mm) was analyzed with a one-sided Cochran-Mantel-Haenszel test stratified by center.
- Percentage of patients with no emesis was analyzed with the one-sided Cochran-Mantel-Haenszel test stratified by center.
- Percentage of patients with no nausea defined as VAS <5 mm was analyzed with the one-sided Cochran-Mantel-Haenszel test stratified by center.
- Percentage of patients without rescue medication was analyzed with the one-sided Cochran-Mantel-Haenszel test stratified by center. Rescue medication was summarized by categories and active ingredient.
- Number of emetic episodes was analyzed with the two-sided Cochran-Mantel-Haenszel test stratified by center.
- The time to first emesis (the time from the administration of emetogenic chemotherapy to first emesis during the overall duration) was presented by Kaplan-Meier curves and summarized by 25th percentile, median, 75th percentile, number and percent of patients with the event, number and percent censored, probability and standard error for selected time points (24, 48, 72, 96, 120 hours). For time to event variables treatment groups were compared using a log-rank test.
- The time to first use of rescue medication (the time from the administration of emetogenic chemotherapy to the first use of rescue medication during the overall duration) was analyzed as described for the time to first emesis.
- The time from chemotherapy to treatment failure (the time to first emesis or first use of rescue medication during the overall duration) was analyzed as described for the time to first emesis.

Other secondary endpoints for evaluation included:

- Global Satisfaction score (VAS) assessed on Day 6 and related to the overall period (0-120 hours) was compared for the treatment groups using a one-sided Wilcoxon rank-sum test. A Kolmogorov-Smirnov test was conducted for confirming non-normality and for comparing the equality of the 2 distributions in the event the data were highly skewed.
- Functional Living Index-Emesis (FLIE) score assessed in the Screening Phase (related to the period Day -5 to Day 1) and at Day 6 (related to the period Day 1 to Day 5) was compared for the treatment groups using a one-sided Wilcoxon rank-sum test. A Kolmogorov-Smirnov test was conducted for confirming non-normality and for comparing the equality of the 2 distributions in the event the data were highly skewed.

SYNOPSIS (CONTINUED)

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Safety Analyses

Safety analyses were performed on all randomized patients who took any study medication. Treatment-emergent adverse events (AEs on or after Day 1) recorded on the CRF through Visit 4 (Days 19-29) were included. Patients with TEAEs were summarized with counts and percentages by treatment group by body system and preferred term. In addition, patients with TEAEs were summarized by treatment group, body system, preferred term, and severity; and by treatment group, body system, preferred term, and relationship. The number of TEAEs in relevant categories were also summarized. Adverse events were listed.

Vital signs (BP and HR) were summarized by treatment group at Baseline (Day 1) (the last values prior to the administration of study medication), Post Baseline (Day 1), Visit 3 (Day 6), and Visit 4 (Days 19 to 29) for all patients in the safety population. Sample size (n), mean, standard deviation, median, and minimum/maximum were reported. In addition, changes in values from Baseline was presented. Vital signs were listed. Screening and Baseline values were listed separately if the Screening visit was not combined with the Baseline visit.

Laboratory clinically significant data recorded on the CRF were summarized for Baseline (Day 1) and Visit 3 (Day 6). Counts and percentages were reported. Shift tables showing change in clinical significance from Baseline to Visit 3 were presented. Chemistry tests including AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), sodium, potassium, chloride and creatinine were summarized. Bicarbonate was listed when available but was not part of the standard laboratory tests. Hematology tests were summarized, they included hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) including differential and platelet count. Clinically significant laboratory data were listed.

Physical examination abnormalities were summarized by treatment group at Baseline (Day 1) (the last values prior to the administration of study medication), Visit 3 (Day 6), and Visit 4 (Days 19 to 29) for all patients in the safety population. Counts and percentages were reported. Physical examination details were listed. Screening and baseline values were listed separately if Screening visit was not combined with baseline visit.

RESULTS:

Efficacy:

Efficacy results were generally similar across treatment groups showing a good prophylactic efficacy in the control of emesis and nausea. For the primary efficacy endpoint, CR (defined as no emesis and no use of rescue medication) in the overall period (0-120 hours), an almost identical percentage of responder patients was observed in the palonosetron/placebo (81/151 [53.6%]) and the palonosetron/dexamethasone (80/149 [53.7%]) treatment groups. The difference between groups was 0.0% with a 95% CI of [-11.7%; 11.6%]. Since the lower boundary of the 2-sided 95% CI (-11.7%) was >-15%, non-inferiority of palonosetron/placebo compared with palonosetron/dexamethasone was demonstrated. This result was confirmed by the result of the Cochran-Mantel-Haenszel test of difference stratified by centers (no statistically significant differences between groups were observed, $P = 0.487$).

The PP population showed similar results to the ITT population; the number and percentage of complete responders for the overall period were similar for the palonosetron/placebo (76/138 [55.1%]) and the palonosetron/dexamethasone (73/138 [52.9%]) treatment groups and no statistically significant differences between groups were observed (difference between the treatment groups was 2.2% with the relevant 95% CI of [-9.9%; 14.3%]). The Cochran-Mantel-Haenszel test stratified by centers confirmed that no statistically significant differences between groups were observed ($P = 0.635$).

Considering the results of CR in the other time intervals, evaluated as secondary efficacy variables, no statistically significant differences between the 2 treatment groups were observed in the Delayed Phase, >24-120 hours (94 [62.3%] and 98 [65.8%] respectively for palonosetron/placebo and palonosetron/dexamethasone groups) and in the daily time intervals with the exception of the >48-72 hours interval ($P = 0.039$, Cochran-Mantel-Haenszel test). In the Acute Phase (0-24 hours), in which the 2 groups received the same antiemetic prophylactic treatment, as expected, the results were equivalent.

Similar results were observed for the other secondary efficacy variables. No statistically significant differences between the 2 groups were observed in the Acute Phase (0-24 hours), in the Delayed Phase (>24-120 hours) and during the overall period (0-120 hours) for CC (defined as no emesis, no rescue medication, with a maximum grade of mild nausea), percentage of patients with no emesis, percentage of patients with no nausea, percentage of patients without rescue medication, number of

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emetic episodes and duration of nausea reported by patients.

Statistically significant differences between the 2 treatment groups, with slightly better results for the palonosetron/dexamethasone group in comparison to the palonosetron/placebo group were observed only on Day 3 (>48-72 hours) in the percentage of patients with no emesis, in the number of emetic episodes, and in the percentage of patients with CC (statistically significant differences were also observed in the >24-48 time interval).

The control of nausea (patients with no nausea) and patients who did not use rescue medication were similar between the 2 groups, with no statistically significant differences, in all the daily time intervals.

The severity of nausea, measured through a VAS, resulted in <25 mm, i.e., "no more than mild nausea", for each of the daily assessments in both treatment groups. For the cumulative time periods, the severity of nausea was calculated as the maximum severity experienced by the patient at all time intervals. In the Delayed Phase [>24-120 hours] and overall [0-120 hours] phase in both treatment groups, the median of the "maximum severity of nausea" was always <25 mm, i.e. "no more than mild nausea". The mean was slightly >25 mm for the Delayed Period in the palonosetron/placebo group and for the overall period in both treatment groups. The mean "maximum severity of nausea" in the overall period was similar for the 2 treatments groups, while in the Delayed Phase the nausea assessment was higher in the palonosetron/placebo group ($P = 0.031$).

The control of emesis (patients with no emesis) resulted very high (>70%) across both treatment groups and all time intervals. For the overall period (0-120 hours) the percentage of patients with no emesis was high and very similar between the groups (108 [71.5%] vs 108 [72.5%] for the palonosetron/placebo and the palonosetron/dexamethasone groups respectively) and the same was observed for the Delayed Phase (119 [78.8%] vs 127 [85.2%] for the palonosetron/placebo and the palonosetron/dexamethasone groups, respectively).

In the overall time period, the control of nausea (patients with no nausea) was lower than the control of emesis and similar between groups (29.8% and 33.6% for the palonosetron/placebo group and the palonosetron/dexamethasone group, respectively).

The prophylactic efficacy of both treatment regimens is confirmed by the high percentage of patients not using rescue medication (91 [60.3] vs 91 [61.1%] for the palonosetron/placebo and the palonosetron/dexamethasone groups respectively, in the overall period).

For the patients' global satisfaction assessment and for the impact of nausea and vomiting on the Quality of Life, assessed by means of the FLIE (Functional Living Index – Emesis) questionnaire, the results showed no statistically significant differences between groups, indicating that the control of nausea and vomiting was perceived as very good by the patients in all the treatments groups and with low impact on functional living.

Safety:

The percentage of patients reporting any TEAE were similar across both treatment groups: 87.4% (132/151) of patients reported 498 TEAEs and 89.3% (133/149) of patients reported 564 TEAEs in the palonosetron/placebo and palonosetron/dexamethasone treatment groups, respectively. The majority of the patients reported TEAEs that were mild in severity and unrelated to study medication. The frequency of treatment-related TEAEs was slightly lower in the palonosetron/placebo (25.2% [38/151] patients) group than in the palonosetron/dexamethasone (28.9% [43/149] patients). The most common treatment-related TEAEs were reported in the following SOCs for the palonosetron/placebo and palonosetron/dexamethasone treatment groups, respectively: nervous system disorder SOC (16.6% [25/151] and 19.5% [29/149] patients), gastrointestinal disorders SOC (7.3% [11/151] and 10.7% [16/149] patients) and for the skin and subcutaneous tissue disorders SOC (6.0% [9/151] and 6.0% [9/149] patients). Among these, the most common treatment-related TEAEs were headache (15.9% [24/151] and 18.8% [28/149] patients), constipation (2.6% [4/151] and 7.4% [11/149] patients), and erythema (5.3% [8/151] and 5.4% [8/149] patients) for the palonosetron/placebo and palonosetron/dexamethasone treatment groups, respectively.

Seven patients in the palonosetron/placebo treatment group experienced 9 SAEs. All SAEs were considered to be not related to study medication and all events resolved. No deaths were reported during the study.

One patient in the palonosetron/placebo treatment group discontinued due to a non serious, unrelated AE.

There were 12 patients in each treatment group who experienced clinically significant abnormal laboratory values. Slight shifts from baseline to post baseline (from not clinically significant to clinically significant) were observed in white blood cell counts, neutrophils and lymphocytes for both treatment groups. These changes are commonly observed in patients

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receiving chemotherapy treatments.

No clinically meaningful events were observed for any vital sign measurements or physical examination findings.

CONCLUSIONS:

Overall (0-120 hours), efficacy results suggest that palonosetron associated with dexamethasone administered on Day 1 may be as efficacious as the use of palonosetron associated with dexamethasone administered on Day 1 followed by dexamethasone orally on Days 2 and 3 in the prevention of vomiting and nausea induced by MEC in female patients with breast cancer.

The use of dexamethasone on Days 2 and 3 showed an improvement in CINV prevention, that was mainly evident in the >48-72 hours interval, but considering the Delayed Phase and the overall period the advantage of dexamethasone administration is not clinically evident.

The use of palonosetron may reduce the total dosage of dexamethasone given in association with a $5HT_3$ receptor antagonist in the prevention of CINV, offering the opportunity to reduce the number of antiemetic treatment in the Delayed Phase, to improve treatment compliance and to reduce potential corticosteroid related side effects.

Date of the Report: 18 December 2008