2 SYNOPSIS

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Title of Study: Open-Label Pilot Study to Evaluate the Efficacy of Palonosetron Associated with Aprepitant (Emend) and Dexamethasone in Preventing Nausea and Vomiting Induced by Highly Emetogenic Chemotherapy (HEC).

Investigator(s) and Study Sites: Six sites in the United Kingdom were to participate, however only 4 could be initiated. A total of 5 investigators at 4 sites received IRB approval to participate in this study; at least 1 patient was enrolled at all sites.

Publication(s): None to date

Study Period: 21 July 2006 to 18 March 2007 **Clinical Phase:** IV

Objectives: To evaluate the efficacy of intravenous (IV) palonosetron when given together with oral (p.o.) aprepitant and p.o. dexamethasone on Day 1, followed by p.o. aprepitant and dexamethasone on Days 2 and 3 and p.o. dexamethasone only on Day 4 in preventing acute and delayed nausea and vomiting induced by HEC.

To evaluate the safety of a single IV dose of palonosetron when given together with p.o. aprepitant and dexamethasone on Day 1 followed by p.o. aprepitant and dexamethasone on Days 2 and 3 and p.o. dexamethasone only on Day 4.

Methodology: This was a Phase IV, open-label, pilot study in chemotherapy-naïve patients, 18 years or older receiving HEC containing cisplatin ≥70 mg/m^2. The following treatments were administered:

Treatment Day	**Treatment**
DAY 1:	Palonosetron 0.25 mg IV Aprepitant 125 mg p.o. Dexamethasone 12 mg p.o.
DAYS 2 and 3:	Aprepitant 80 mg p.o. Dexamethasone 8 mg p.o.
DAY 4:	Dexamethasone 8 mg p.o.

On Day 1, palonosetron was given as a single IV bolus (0.25 mg) over 30 seconds, 30 minutes prior to receiving chemotherapy. Aprepitant (125 mg p.o.) was administered on Day 1, approximately 1 hour prior to chemotherapy administration and in the morning of Days 2 and 3 at a dose of 80 mg. Dexamethasone (12 mg p.o.) was administered on Day 1, approximately 1 hour prior to chemotherapy and then on Days 2 to 4 at a dose of 8 mg p.o. given once daily.

Patients were followed from Day 1 to Day 6 to allow assessment of the anti-emetic response in the Acute Phase (0-24 hours post chemotherapy) and the Delayed Period (>24-120 hours post chemotherapy). Additionally, the anti-emetic response was evaluated on each single day and the overall study period.

Number of Patients: Approximately 60 patients were planned for inclusion; however, due to a lengthy study approval process and slow patient enrollment, it was subsequently decided to prematurely discontinue the study. Only a total of 15 patients were enrolled. The delay in timelines for the availability of study results made the continuation of this pilot study somewhat obsolete. Since the time the study was planned, the commercial status of palonosetron and aprepitant changed as both drugs became available in several European countries; therefore, this combination treatment became commonly used in normal clinical practice in preventing CINV induced by HEC as well as in moderately emetogenic chemotherapy (MEC).

- **Diagnosis and Main Criteria for Inclusion:** Male and female patients; age ≥18 years; with histologically or cytologically confirmed malignant disease; who were naïve to chemotherapy; had a Karnofsky Performance Status grade of ≥60; who were scheduled for receipt of a single dose of HEC regimen containing cisplatin ≥70 mg/m^2 on Day 1; with acceptable hepatic function (alanine transaminase and aspartate transaminase values ≤ 2 times the upper limit of normal [ULN]) and renal function (creatinine ≤1.5 times the ULN).
- **Main exclusion criteria:** patients scheduled receipt of MEC, or 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; nausea or vomiting with a National Cancer

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Institute Common Toxicity Criteria of grade 2 or 3 in the 24 hours before receiving study medication; or ongoing vomiting from any other organic etiology.

Test Product, Dose, Mode of Administration, Batch No(s):

Test Product:
Palonosetron 0.25 mg (batch number [redacted]) administered as an IV bolus over 30 seconds, 30 minutes before chemotherapy on Day 1.

Concomitant Therapy:
Aprepitant 125 mg (batch number [redacted]) p.o. administered on Day 1, 1 hour prior to chemotherapy and in the morning of Days 2 and 3 at a dose of 80 mg.
Dexamethasone 12 mg (batch number [redacted]) p.o. administered on Day 1, 1 hour prior to chemotherapy and then on Days 2 to 4 at a dose of 8 mg p.o. given once daily.

The batch number for the patient medication packs containing all medications listed above and prepared for this study was [redacted] (expiration date [redacted]).

Duration of Treatment: The duration of treatment was 4 days. The overall study duration was 19-29 days including the screening and follow-up periods.

Criteria for Evaluation:

Efficacy

The primary efficacy endpoint for this study was the overall (0–120 hours) Complete Response (CR) (no emesis, no rescue medication). Secondary efficacy endpoints were to be evaluated in the Acute Phase (0-24 hours), Delayed Phase (>24-120 hours) on a daily basis (0-24 hours, >24-48 hours, > 48-72 hours, >72-96 hours, >96-120 hours) and for the overall period (0-120 hours). Secondary efficacy endpoints were planned to include severity and duration of nausea, CR, complete control (no emesis, no rescue medication and mild nausea only), percentage of patients with no emesis and no nausea, time to first episode of emesis and use of rescue medication, global satisfaction score and functional living index emesis score (FLIE). Since the study was prematurely terminated, the only secondary efficacy summaries that were conducted were for CR for the Acute Phase (0-24 hours), the Delayed Phase (>24-120 hours), and Daily (0-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96-120 hours).

Due to the small number of patients, the parameters such as: episodes of emesis and nausea, maximum severity of nausea, duration of nausea, and use of rescue medication were listed.

Safety

The incidence of treatment-emergent adverse events (TEAEs) during the assessment phase was the primary safety endpoint for the study. Adverse events beginning on or after Day 1 were defined as treatment-emergent. Since the study was prematurely terminated, the only safety analysis summary was for overall summary of patients with TEAEs. Overall counts and percentages were presented for the following groups of patients in the safety population: Patients with any TEAE; patients with any treatment-emergent study medication-related AE; patients with any treatment-emergent serious adverse event (SAE); patients with any treatment-emergent study medication-related SAE; patients who discontinued due to an AE; and patients who died.

The adverse events were listed.

Statistical Methods: The following study populations were defined:

- The Intent-to-Treat (ITT) Population included all patients who received a unique dose of cisplatin at doses ≥ 70 mg/m^2 as chemotherapy and at least 1 dose of study medication. This population was used for reporting efficacy results.
- The Safety Population comprised patients who received at least 1 dose of study medication.

The following reduced analysis was conducted since patient enrollment was not sufficient to conduct a full analysis.

Disposition of patients were presented as the number of patients that entered the study, the number and percentage of patients that completed or discontinued active treatment and the specific reason for early treatment discontinuation. Demographic and baseline characteristics were summarized for all patients in the efficacy and/or safety population. Demographic and baseline characteristics included age, gender, race, height, weight, alcohol consumption, tobacco consumption and Karnofsky Performance Status.

Efficacy Analysis

Efficacy analysis was based on the post chemotherapy time period starting with administration of emetogenic chemotherapy and continuing through Day 5. For the primary and secondary analyses descriptive statistics were

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presented. The primary efficacy analysis summarized counts and percentages with 95% confidence interval for CR (no emesis, no rescue medication in the overall period [0-120 hours]). The secondary efficacy analysis summarized counts and percentages with 95% confidence intervals for CR (no emesis, no rescue medication) for the Acute Phase (0-24 hours), the Delayed Phase (>24-120 hours), and Daily (0-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96-120 hours).

Maximum severity of nausea, episodes of emesis and nausea, duration of nausea, and use of rescue medication for the Acute Phase (0 24 hours), Daily (0-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96-120 hours) and for the Overall Phase (0-120 hours) were listed.

Safety Analysis

Safety was assessed for all patients who received at least 1 dose of study medication. Treatment-emergent was defined as AEs on or after Day 1. Treatment-emergent adverse events recorded on the CRF through visit 4 (days 19-29) were included. Treatment-emergent adverse events were summarized with counts and percentages for patients who experienced an AE, a drug-related AE, an SAE, a drug-related SAE or patients who withdrew due to an AE. Due to the premature termination of the study, vital signs, physical examination findings and clinical laboratory evaluations were not evaluated.

RESULTS:

Efficacy

As this study was prematurely terminated with 15 patients enrolled instead of 60, efficacy analyses were limited to the primary endpoint and to a limited set of secondary endpoints, and namely the CR for the Acute Phase (0-24 hours), the Delayed Phase (>24-120 hours), and Daily (0-24 hours, >24-48 hours, >48-72 hours, >72-96 hours, >96-120 hours).

Maximum severity of nausea, episodes of emesis and nausea, duration of nausea, and use of rescue medication were presented as listings.

As for the primary endpoints, the CR in the overall period (0-120 hours) showed that 8 (53.3%) patients achieved a CR, which also reflected a wide 95% confidence interval (26.6% to 78.7%).

As for the secondary endpoints, in the Acute Phase (0-24 hours), 15 (100%) patients achieved a CR while on combination therapy (palonosetron, aprepitant and dexamethasone). In the >24-48 hour post chemotherapy period, 13 (86.7%) patients reached a CR, while in the >48-72 hour time period, 12 (80.0%) patients maintained a CR. In the >72-96 hour time period when only dexamethasone treatment was given, the number of patients with a CR was 10 (66.7%). Between the >96-120 hour time period, in which the patients did not receive prophylactic therapy, a CR was observed in 9 (60.0%) patients. Globally, in the Delayed Phase, 8 (53.3 %) patients reached a CR.

The data on patients with no vomiting were very positive and in line with the data observed for CR. In the Acute Phase (0-24 hours), 100% of patients with no vomiting were observed. This percentage remained very high with a value of 86.7% (13/15) in the Delayed Phase (>24-120 hours) and for the overall period (0-120 hours).

The evaluation of the presence of nausea showed that 12 (80.0%) and 8 (53.3%) patients did not experienced nausea in the Acute Phase (0-24 hours) and the Delayed Phase (>24-120 hours), respectively. During the overall period, 7 (46.7%) patients did not experience nausea.

Considering the use of rescue medication, all 15 patients (100%) did not take rescue medication in the Acute Phase (0-24 hours), while the percentage of patients with no use of rescue medication was 53.3% (8/15) in the Delayed Phase (>24-120 hours) and the same for the overall period (0-120 hours).

Safety

A total of 14 (93.3%) patients experienced TEAEs. Three of these patients experienced treatment-related AEs. The majority of TEAEs were non-serious, mild or moderate in severity and unrelated or unlikely related to be related to study treatment. One patient ([redacted]) experienced a treatment-emergent SAE, (dyspnea) concurrently with other TEAEs (cyanosis and lymphedema). All events for this patient were considered unrelated to study treatment. There were no deaths during the study or discontinuations due to AEs. Laboratory parameters were not evaluated due to the premature termination of the study.

CONCLUSIONS:

Overall, due to the premature termination of this study and the small number of patients treated, it is difficult to draw a firm conclusion about the efficacy and the safety and risk benefit relationships for this study.

During the Acute Phase (0-24 hours) it was evident that the combination regimen palonosetron, aprepitant and dexamethasone was very effective and all treated patients reached a CR.

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Considering the overall study period (0-120 hours), 8 (53.3%) patients achieved a CR which also reflected a wide 95% confidence interval (26.6% to 78.7%) Eight patients were also observed to not use rescue medication during the overall period (0-120 hours). Additionally during the same time period, the percentage of patients with no emetic episodes was high (86.6%), while the percentage of patients with no nausea was lower (46.6 %). Overall, with the limited small sample size evaluated, the combination regimen of palonosetron, aprepitant and dexamethasone showed to be effective in preventing chemotherapy induced nausea and vomiting in naïve patients receiving high-dose cisplatin based chemotherapy. The treatment was generally well tolerated.		
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