2 SYNOPSIS

Name of Sponsor:	Astellas Pharma Taiwan, Inc.
Name of Finished Product:	Ramosetron
Name of Active Ingredient:	Ramosetron hydrochloride 0.3 mg

Study title: A Double-blind, Randomized, Parallel, Comparative Study to Evaluate the Efficacy and Safety of Ramosetron Plus Dexamethasone Injection for the Prevention of Chemotherapy-induced Vomiting and Nausea

Study medical institutions/Investigators:

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Publication (references):

None

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Study period:	January 16, 2006 to December17, 2007	Developmental phase:
Study initiation date:	January 16, 2006 (date of obtaining informed consent from the first subject)	Registration study
Study completion date:	December17, 2007 (date of completion of 30 days follow-up of the last subject)	

Objectives: To evaluate the efficacy profile of ramosetron + dexamethasone injection in comparison to granisetron + dexamethasone for the prevention of chemotherapy-induced vomiting. The response was to be measured primarily by the proportion of patients with no vomiting (0 vomiting episodes) and no requirement of rescue drugs within 24 hours after chemotherapy.

Methodology:

This study was designed as a registration, double-blind, parallel, active-control for ramosetron + dexamethasone injection in the treatment of preventing chemotherapy-induced vomiting and nausea. Cancer subject scheduled to receive either one of four chemotherapy programs (Cisplatin, Doxorubicin, Epirubicin or Oxaliplatin) by IV infusion, alone in one single dose or combined with other chemotherapy regimens were enrolled into the study. After screening visit (-14~0 days), eligible patients were randomly assigned to receive ramosetron 0.3 mg plus dexamethasone 20 mg or granisetron 3 mg plus dexamethasone 20 mg at half hour before start of chemotherapy infusion.

Number of subjects (planned and analyzed):

1. Target number of subjects: 262 (Ramosetron group: 131, Granisetron group: 131)
2. Number of enrolled subjects: 288
3. Number of randomized subject: 287 (Ramosetron group: 145, Granisetron group: 142)
4. Subjects included in analyses:
    1) Full analysis set: 285 (Ramosetron group: 144, Granisetron group: 141)
    2) Efficacy analysis set: 274 (Ramosetron group: 137, Granisetron group: 137)
    3) Safety analysis set: 285 (Ramosetron group: 144, Granisetron group: 141)

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Diagnosis and enrolling criteria:

Patients with

1. Inclusion criteria

   (1) Subject with age between 20-74 years old (inclusive) of either sex.
   (2) Cancer subject was scheduled to receive either one of the following chemotherapy programs by IV infusion, alone in one single dose or combined with other chemotherapy regimens:
      a. Cisplatin $\geq$ 50 mg/m^2, with infusion time =2 hours±10 mins
      b. Doxorubicin $\geq$ 50 mg/m^2, with infusion time $\leq$l hour
      c. Epirubicin $\geq$ 60 mg/m^2 with infusion time $\leq$1 hour
      d. Oxaliplatin $\geq$ 65 mg/rn^2 , with infusion time =2 hours±10 mins
   (3) Subject without symptoms of vomiting for at least one week before dosing trial medication
   (4) Subject with ECOG performance status scale no greater than 2 (ECOG $\leq$2)
   (5) Subject had signed the written informed consent form

2. Exclusion criteria

   (1) Subject had received radiotherapy to the abdomen or pelvis within 4 weeks before entering this study
   (2) Subject had received chemotherapy programs including either one of four regimens, namely, Cisplatin, Doxorubicin, Epirubicin or Oxaliplatin, within 6 months before entering the study
   (3) Subject had known heart failure or myocardial infraction or with laboratory abnormalities at screening including: serum creatinine> 2 times of upper limit of normal range, GOT, GPT> 3 times of upper limit of normal range (Test results within 30 days before screening visit were acceptable)
   (4) Subject had known concurrent diseases that may cause vomiting, such as gastrointestinal tract obstruction, epilepsy, brain metastases, brain tumor or intracranial hypertension
   (5) Subject had taken medications that could influence the outcome of the study within 3 days before entering the study, such as anti-epilepsy drugs, anti-emetics, anti-psychotics, or adrenocorticoids
   (6) Subject with a history of allergy or intolerance to ramosetron, granisetron or dexamethasone
   (7) Female subject who was pregnant or breastfeeding
   (8) Subject with life expectancy less than 3 months
   (9) Subject participated other investigational drug trial within 1 month before entering this study

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Investigational Product, Dosage and Mode of Administration:

- Ramosetron: IV injection containing 0.3 mg of ramosetron hydrochloride
- Granisetron: IV injection containing 3 mg of granisetron hydrochloride

Two investigational products (ramosetron 0.3 mg, 2 ml/ampoule + dexamethasone 20 mg, granisetron 3 mg, 3ml/ampoule + dexamethasone 20 mg) were given to two treatment groups: ramosetron 0.3 mg and granisetron 3 mg groups. The investigational products were given at half hour before the start of chemotherapy.

Treatment Period:

Treatment period with the investigational products was to be 1 day.

Criteria for Evaluation:

1. Efficacy outcome measures:

   1) Primary outcome measure:
   The primary efficacy parameter, complete response rate, was defined by the proportion of patients without vomiting and no requirement for rescue drugs the 24-hour-period after the start of chemotherapy for the per-protocol set (PPS) cohort to show non-inferiority of one dose of Ramosetron to Granisetron.
   2) Secondary outcome measures:
      - Response rate of vomiting prevention as defined by the proportion of patients with no more than 2 times of vomiting episodes within 24 hours after start of chemotherapy.
      - The number of vomiting episodes during the 1^{st}, 2^{nd}, $3^{rd,}$ 4^{th}, 6-hours duration and the total 24-hours period after the start of chemotherapy.
      - The proportion of patients with vomiting during the 1^{st}, 2^{nd}, $3^{rd,}$ 4^{th}, 6-hours duration after the start of chemotherapy.
      - Time to the first vomiting episode in the 24-hour-period after the start of chemotherapy (percentage of subjects without vomiting episode up to 24-hour).
      - The nausea degree evaluated by patient's 10-cm visual analogue scale (VAS) during the 1^{st}, 4^{th} 6-hours duration and the total 24-hours-period after the start of chemotherapy.
      - The anorexia severity evaluated by subject's 10-cm VAS during the 1^{st}, 4^{th} 6-hours duration and the total 24-hours period after the start of chemotherapy.
      - No significant nausea proportion (VAS < 25 mm during the 24-hour-period after the start of chemotherapy)
      - No nausea rate (VAS < 5 mm during the 24-hour-period after the start of chemotherapy)
      - Complete protection rate (no vomiting + nausea VAS < 25 mm during the 24-hour-period after the start of chemotherapy)
      - Total control rate (no vomiting + nausea VAS < 5 mm during the 24-hour-period after the start of chemotherapy)
      - The proportion of subjects had received rescue drug(s) during the 24-hour-period after the start of chemotherapy.

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2. Safety outcome measures:

The evaluation was performed on FAS.

- Adverse event incidence
- Clinical laboratory tests
- Vital signs

Statistical Methods:

1. Efficacy
   1) The primary efficacy outcome measure, complete response rate was analyzed by using the method of confidence interval based on pooled data from all centers regardless chemotherapy regimen. Ramosetron + dexamethasone treatment group were declared as non-inferior if the lower limit of the 95% two-sided confidence interval (based on normal approximation with continuity correction to the binomial distribution) for the between treatment difference (ramosetron + dexamethasone group minus granisetron + dexamethasone group) was greater than -15%.
   2) As for secondary efficacy outcome measures, categorical endpoints were analyzed by CMH test stratified by center and chemotherapy regimen. Time to the first vomiting episode was analyzed by Cox model; Kaplan-Meier estimate of vomiting free rate was also presented. For the other secondary continuous endpoints, including number of vomiting, VAS of nausea and VAS of anorexia were analyzed by using ANOVA.

2. Safety
   Safety outcome measures included adverse event incidence, clinical laboratory values and vital signs.
   Adverse events were reported by treatment groups and by physiological systems as appropriate. Incidence of adverse events between treatments was analyzed by Fisher's exact test. The categories of adverse event severity and the relationship to trial medication drug were tabulated. The coding system used was the MedDRA version 10.0. Changes from pre-treatment in laboratory test results and changes in urinalysis were also summarized by descriptive statistics. Vital signs were also summarized descriptively.

Summary Results

1. Patient Disposition:
   Four centers enrolled a total of 288 patients in this study, but 3 subjects did not receive study medication. Hence, both the safety cohort and full-analysis set cohort contained 285 subjects where 144 subjects treated with Ramosetron plus dexamethasone and 141 subjects treated with Granisetron plus dexamethasone. As for the per-protocol set cohort, 11 patients (7 subjects in Ramosetron group; 4 subjects in Granisetron group) were excluded from PPS due to protocol violations/deviations. There were 137 subjects in each treatment group of PPS cohort.

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2. Demographics and Baseline Characteristics :

Of the 285 subjects, the average age was 51.8 years old of Ramosetron group, ranging from 29.0 to 73.0 years old; of Granisetron group, average age was 51.5 years old, ranging from 22.0 to 74.0 years old. The number of male/female was 54/90 in Ramosetron group and 56/85 in Granisetron group. The mean weight and height of subjects in this study were 60.8 kg and 160.1 cm in Ramosetron group, and 59.7 kg and 160.8 cm in Granisetron group, respectively. Only 16 patients (5.6%) had ECOG performance status higher than 1; 7 in Ramosetron group and 9 in Granisetron group. Other than cisplatin, the most frequently administered chemotherapeutic agent was doxorubicin.

Of the FAS cohort, two treatment groups were well balanced concerning age, sex, weight, height, ECOG performance status, and baseline characteristics, such as AST, ALT and serum creatinine. Demographics and baseline characteristics for the per-protocol (PPS) cohort were comparable to the FAS cohort.

3. Efficacy results:

The statistical analysis of PPS cohort showed that primary efficacy parameter, the complete response rate, was 77.37% of Ramosetron group and 81.75% of Granisetron group. For comparison of Ramosetron and Granisetron, the lower limit of the 95% confidence interval for the difference in complete response rate was -14.64% which was above the pre-set threshold (-15%). Thus, non-inferiority of Ramosetron 0.3 mg to Granisetron 3 mg can be demonstrated for the prevention of emetogenic chemotherapy-induced vomiting and/or retching during the first 24 hours after chemotherapy. Besides, for the patients treated with non-cisplatin in PPS cohort, the lower limit of the 95% confidence interval for the difference in complete response rate between Ramosetron and Granisetron was -14.73%, but the non-inferiority can not be demonstrated for patients treated with cisplatin in PPS cohort since the lower limit of the 95% confidence interval for the difference was -24.63%.

Concerning the secondary efficacy parameters, the effects of Ramosetron were not significant different from Granisetron for vomiting prevention, No. of vomiting episodes, the time to first vomiting, nausea degree, anorexia severity, nausea proportion and rate, complete protection, total control, and the proportion of subject received rescue drug.

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4. Safety result:

Both treatments were well tolerated. Most adverse events were assessed as unlikely to be related to study medication and mild to moderate in intensity, but rather to the patient's underlying cancer or chemotherapeutic treatment. Of patients in the Ramosetron and Granisetron groups, 52 (36.11%) and 33 (23.40%) experienced at least one adverse event occurred within 24 hours after administration of study medication. AEs occurring greater than 1% within 24 hours were reported more frequently in Ramosetron group than that in Granisetron group with statistically significant difference p=0.0203. Hiccups, constipation, anorexia were the adverse events most frequently occurring in the two treatment groups. Though Ramosetron tended to experienced more adverse events, the incidence in adverse reactions (i.e., AEs considered to be treatment related) was comparable between treatment groups. Adverse reactions occurred in 2.08% of patients in the Ramosetron group and in 2.84% of patients in the Granisetron group. None of the deaths or serious adverse events was assessed as related to the study medication. There were no significant treatment-related changes in laboratory measures or vital signs.

5. Conclusions:

In conclusion, whereas the lower limit of the 95% confidence interval for the difference was -14.64% which was above the pre-set threshold (-15%), the result demonstrated that Ramosetron plus dexamethasone was non-inferior to Granisetron plus dexamethasone in complete response rate during the first 24 hours after chemotherapy, the primary efficacy parameter. For the patients treated with non-cisplatin, Ramosetron plus dexamethasone was also non-inferior to Granisetron plus dexamethasone since the lower limit of the 95% confidence interval for the difference was -14.73%. Nevertheless, the non-inferiority could not be demonstrated for patients treated with cisplatin since the lower limit of the 95% confidence interval for the difference was -24.63%. Safety profile also showed a similar pattern in the treatment groups. There were no safety concerns associated with the results of laboratory values and vital signs. AEs occurring greater than 1% within 24 hours were reported more frequently in Ramosetron group than that in Granisetron group with statistically significant difference p=0.0203. It is thus recommended that in comparison to Granisetron, a combination of Ramosetron 0.3 mg plus dexamethasone 20 mg can be as an alternative given to prevent chemotherapy-induced nausea and vomiting.

Date of report:
Nov. 13, 2008