

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-233

CROSS DISCIPLINE TEAM LEADER REVIEW



Clinical Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROENTEROLOGY PRODUCTS MEDICAL TEAM LEADER'S SECONDARY REVIEW

Date: August 16, 2008

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HFD-180

To: Division Files, NDA 22-233
Palonosetron [Aloxi®], a 5-HT₃ receptor antagonist
Sponsor: Helsinn Healthcare SA

Regulatory Contact: Dr. Craig Lehmann
August Consulting, Inc
515 Capital of Texas Highway
Austin, TX 78746

Formulation: Oral Capsules

Proposed Dosing Regimen: 0.50 mg

Requested Indication: Prevention of acute (b) (4)
chemotherapy induced nausea and vomiting (CINV) associated
with the administration of moderately emetogenic
chemotherapeutic agents (MEC)

Relevant INDs/NDAs IND 39,797 [palonosetron injection]; IND 42,886 [oral palonosetron]
NDA 21,372 [ALOXI® (palonosetron hydrochloride) injection]

Subject: Recommendation for Regulatory Action

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I. EXECUTIVE SUMMARY

The object of the current review is palonosetron [Aloxi®], a serotonin receptor subtype 3 (5-HT₃) antagonist that is approved in more than 50 countries, including the US. The approved indications for the recommended dose of 0.25 mg I.V. dose are: the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy [prevention of CINV], including highly emetogenic chemotherapy. Through NDA 22-233, the sponsor [Helsinn Healthcare SA] is requesting approval of an oral formulation of palonosetron 0.5 mg for (b) (4) the prevention of acute (b) (4) chemotherapy-induced nausea and vomiting [N&V] associated with initial and repeat courses of moderately emetogenic chemotherapeutic [MEC] agents. In support of this application, the sponsor submitted results of two Phase 3 efficacy trials, one pivotal, the other supportive.

PALO-03-13 [n = 651] was a multi-center, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, non-inferiority phase 3 study which designed to assess the efficacy and the safety of single, oral doses of palonosetron, 0.25 mg, 0.50 mg or 0.75 mg, versus a single I.V. dose of palonosetron 0.25 mg [the active comparator] in the prevention of MEC-induced N&V. The primary endpoint of efficacy in this non-inferiority trial was the proportion of patients with Complete Response [CR]. The pivotal study had a non-inferiority (NI) design, in which three oral doses of palonosetron were compared with the approved 0.25 mg I.V. dose, the active comparator. The primary efficacy endpoint was CR from 0 to 24 hours after administration of MEC. As per the non-inferiority design, the oral formulation would demonstrate efficacy by showing that it is not less effective than the control by a margin of -15%.

PALO-03-14 [n = 217] was a multi-center, open-label, repeated cycle, and uncontrolled phase 3 trial to assess the safety and the efficacy of single oral doses of palonosetron 0.75 mg in the prevention of MEC-induced N&V in repeated and consecutive moderately emetogenic chemotherapy cycles. Enrolled patients received a single oral dose of palonosetron 0.75 on Day 1 before each moderately emetogenic chemotherapy cycle, up to a maximum of four consecutive cycles. There were total of 654 cycles observed which consisted of 171 cycles with dexamethasone and 483 cycles without dexamethasone.

Recommendations/remarks on approvability and pivotal contributions from individual discipline reviewers participating in the customary multidisciplinary approach are listed in Table 1. Clinical and Statistics recommend that the 0.5 mg capsule be approved for the prevention of MEC-induced N&V only. It is noted that, in study PALO-03-13, each of the three oral doses of palonosetron is non-inferior to the I. V. dose, as measured by CR during the acute phase (0 to 24 h) and a non-inferiority margin of 15% but none of the oral doses shows non-inferiority to the I.V. for CR for the delayed phase (24 to 120 h). According to this evaluation, results based on other secondary endpoints should be considered exploratory.

Although the MTL agrees with the recommendation to approve the 0.5 mg oral form of palonosetron for the prevention of acute N&V induced by MEC, (b) (4)

In this application, the efficacy trials did not include a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of oral doses of palonosetron to I.V. palonosetron, the sponsor conducted a meta-analysis of results from publications which constitute

historical placebo CINV studies for the acute phase (0 to 24 h). In response to a DGP request, on July 25, 2008, the sponsor submitted data from historical placebo-controlled trials for the delayed phase [> 24 h], so as to differentiate delayed from acute results. In response to our request¹, the sponsor submitted an analysis and interpretation of results from historical placebo-controlled trials for delayed phase [> 24 h], so as to differentiate delayed phase from acute results² [Sponsor's Appendices #2 and #3]. The MTL agrees with the sponsor that the publications and the FDA MOR reviews³ constitute all known historical placebo CINV studies available to Helsinn Healthcare SA that provide such historical placebo response data in the delayed phase⁴. Methods to identify published historical placebo data are described in sponsor's Appendix 2. One or more of the following efficacy endpoints must have been available from the publication for any time period from > 24 to 120 h after the administration of moderately emetogenic chemotherapy for the proportion of patients in the placebo study arm with:

- a. No emetic episodes and no rescue medication
- b. No emetic episodes, no rescue medication and no more than mild nausea
- c. No emetic episodes and no more than mild nausea
- d. No emetic episodes
- e. No emetic episodes and no nausea

The MTL agrees with the sponsor that these efficacy endpoints are consistent with those used in study PALO-03-13. It is true that, as pointed out by Dr. Snow, there were some differences with respect to type of cancer treated, chemotherapeutic agent, gender, previous chemotherapy history, and corticosteroid use. In addition, efficacy was measured on single days, rather than for the entire delayed phase of 24 to 120 hours. However, except for corticosteroid use, which makes it necessary to analyze the data as a function of dexamethasone use, the MTL believes that this historical placebo response is relevant. As noted by Dr. Snow, these data are useful in so far as they provide a larger database for the active comparator.

It worth noting that, as a general principle, the use of a historical placebo response to assess efficacy is not recommended. In reality, use of historical placebo response data for the assessment of efficacy of palonosetron in the acute phase is not needed because the results for the 0 to 24 h period in Study PALO-03-13 show that the oral 0.5 mg palonosetron is clearly non-inferior to 0.25 mg I.V. palonosetron, the active comparator. However, the MTL believes that, in this particular instance, comparison of the results of study PALO-03-13 with historical placebo response data identified for the delayed phase of moderately emetogenic CINV is very useful. One reason for this belief is that although these placebo comparison studies were carried out in the 80s and early 90s, no additional placebo comparison data from studies carried out in the United States are available. This is because by now, placebo-controlled studies may no longer be considered ethical. The supplemental data, which the sponsor submitted to support CR in the delayed phase, pooled data from historical I.V. CINV pivotal trials, with the 0.25 mg I.V. arm in PALO-03-13.

¹ Letter from Division to sponsor, dated June 20, 2008.

² Letter from sponsor to Division, dated July 25, 2008.

³ Indeed, among the sources of information reviewed by the sponsor are the following reviews of NDAs : N20-007 I.V. ondansetron, FDA MOR, Study S3A-354 (1990); N20-103 Ondansetron Tablets, FDA MOR, Study S3A-361 (July 2, 1991); N20-103 Ondansetron Tablets, FDA MOR, Study S3A-362 (July 2, 1991); N20-103 Ondansetron Tablets, MOR, Study S3A-T17 (July 2, 1991), N20-239 I.V. Granisetron, FDA MOR (Jan 15, 1993), N20-305, Granisetron Tablets, FDA MOR (Jan 12, 1994). The MOR of these NDAs was Dr. Hugo E Gallo-Torres, who is also the author of the current Secondary Review. This list of publications is included in Sponsor's Appendix 4 of their July 25, 2008 submission.

⁴ Copies of the source publications and FDA's Medical Officer's reviews were submitted in Sponsor's Appendix 3.

Salient items to be addressed by the current reviewer include:

- Approvability of palonosetron for the prevention of acute MEC-induced CINV
- Recommended dose for the above indication
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Approvability of palonosetron for the prevention of initial and repeat courses of MEC-induced CINV

Approvability of palonosetron for the prevention of acute MEC-induced CINV

The MTL agrees with the recommendation to approve oral palonosetron for the prevention of acute MEC-induced N&V. This recommendation is based on the CR results of randomized, double-blind, active-comparator, non-inferiority study PALO-03-13 where all three dosages of orally administered palonosetron were associated with a similar proportion of patients that did not experience N or V, or require rescue medication. Furthermore, all three doses of the oral drug fell within the prespecified non-inferiority margin.

Recommended dose for the above indication

The recommended dose for the prevention of acute MEC-induced CINV is 0.5 mg. Although a similar proportion of patients did not experience N or V with the 0.25 mg dose level, the adverse reaction profile of these two dose levels of the drug and that of 0.75 mg is similar.

(b) (4) (4)

Approvability of palonosetron for the prevention of initial and repeat courses of MEC-induced CINV

The MTL strongly recommends that oral palonosetron be approved not only for the initial but also for the repeat courses of MEC-induced N&V. The Division has not traditionally required data from well-designed, well-executed trials to approve drugs intended for the prevention of the delayed phase MEC-induced N&V. After the initial cycle, the cancer patients are no longer naïve and assessments of data obtained at the 2nd, 3rd, 4th, cycle, etc. have addressed safety rather than efficacy. Nonetheless, the sponsor submitted results of Study PALO-03-04. This trial evaluated the safety of palonosetron in up to 4 cycles of chemotherapy, but only cycle 1 data were included in the Integrated Summary of Safety. All in all, the incidence of cycles with adverse effects decreased slightly from cycle 1 to cycle 3, and remained about the same in cycle 4.

II. BACKGROUND/INTRODUCTION

Palonosetron [Aloxi®] is a serotonin receptor subtype 3 (5-HT₃) antagonist that is structurally unrelated to other 5-HT₃ receptor antagonists⁵. I.V. palonosetron is approved in 53 countries around the world including the US. The approved indications for the recommended dose of 0.25 mg I.V. dose are: the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy [prevention of CINV], including highly emetogenic chemotherapy.

Through NDA 22-233, the sponsor [Helsinn Healthcare SA] is requesting approval of an oral formulation of palonosetron 0.5 mg for (b) (4); the prevention of acute (b) (4) chemotherapy-induced nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapeutic [MEC] agents. Clinically, MEC is classified as acute [N&V occurring within 24h after chemotherapy administration and delayed [N&V occurring from 24 h and up to 120 h after chemotherapy administration].

In support of this application, the sponsor submitted results of two Phase 3 efficacy trials:

PALO-03-13 was a multi-center, randomized, balanced, stratified, double-blind, double-dummy, parallel group, active control, non-inferiority phase 3 study which designed to assess the efficacy and the safety of single, oral doses of palonosetron, 0.25 mg, 0.50 mg or 0.75 mg, versus a single I.V. dose of palonosetron 0.25 mg [the active comparator] in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. The study included 651 patients from 46 centers in five countries between the ages of 20 and 100, of whom 639 patients received the test medication.

PALO-03-14 was a multi-center, open-label, repeated cycle, and uncontrolled phase 3 trial 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 in repeated and consecutive moderately emetogenic chemotherapy cycles. The study included 217 patients in 22 study centers in four countries. All enrolled patients received a single oral dose of palonosetron 0.75 on Day 1 before each moderately emetogenic chemotherapy cycle, up to a maximum of four consecutive cycles. There were total of 654 cycles observed which consisted of 171 cycles with dexamethasone and 483 cycles without dexamethasone.

In this application, the efficacy trials did not include a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of oral doses of palonosetron to I.V. palonosetron, the sponsor conducted a meta-analysis of results from publications which constitute historical placebo CINV studies for the acute phase (0 to 24 h). In response to a DGP request, on July 25, 2008, the sponsor submitted data from historical placebo-controlled trials for the delayed phase [> 24 h], so as to differentiate delayed from acute results.

III. MULTIDISCIPLINARY REVIEWS

Recommendations/remarks on approvability from individual discipline reviews are listed in Table 1.

⁵ Other commercially available 5-HT₃ receptor antagonists used to prevent CINV are ondansetron, granisetron, and dolasetron.

Table 1
NDA 22-233 [ALOXI®; palonosetron]
List of Individual Reviews

REVIEWER/ [DISCIPLINE]	REMARKS
1. Dr. Nancy Snow [CLINICAL]	The reviewer concludes that efficacy in the acute phase for the prevention of CINV was demonstrated for all 3 oral palonosetron dose levels [0.25, 0.50, and 0.75 mg] based on: (1) proportion of patients with Complete Response [CR] and (2) non-inferiority to I. V. palonosetron. The reviewer notes that in the delayed phase, CR rates were similar to the I.V. form. None of the oral dosage forms demonstrated non-inferiority to the active comparator but the 0.5 mg dose came closest to the non-inferiority margin. The reviewer recommends that the 0.5 mg oral capsule be approved for the prevention of N&V in the acute [0 to 24 h] phase (b) (4).
2. Dr. Kate Dwyer, Dr. Wen-Jen Chen [STATISTICS] NOTE: At the time the current review was finalized the complementary Statistical Review by Dr. Chen, mentioned in Dr. Dwyer's draft review, was not yet available.	The reviewer notes that results from study PALO-03-13 show that each of the three oral doses of palonosetron is non-inferior to the I. V. dose, as measured by CR during the acute phase (0 to 24 h) and a non-inferiority margin of 15%. However, none of the oral doses showed non-inferiority to the I.V. for CR for the delayed phase (24 to 120 h). The results based on other secondary endpoints should be considered exploratory. The reviewer concluded that from a statistical perspective, this study has demonstrated comparable efficacy between the oral and I.V. administrations of palonosetron for the acute phase only.
3. Dr. Insook Kim [CLINICAL PHARMACOLOGY] (Review dated 07/23/2008)	Dr. Kim found the CP & B information acceptable provided 1) the DSI inspection currently scheduled in the week of 11th of August finds the BE study acceptable and 2) a mutual agreement regarding the label language can be reached between the sponsor and the Agency. CP recommends that the dose be reduced to 0.25 mg from the proposed 0.5 mg. The dose of 0.25 mg was found to be effective and no dose-response relationship was demonstrated among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg. This recommendation is consistent with the finding that the absolute bioavailability of oral capsules was 97% and the approved dose for I.V. administration for the prevention of (b) (4) acute and delayed CINV is 0.25 mg. (b) (4) CP also recommend that the dose be reduced to 0.25 mg because no dose-response relationship was evident among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg for CR 24-120.
4. Dr. David Joseph (06/25/2008Review) [PHARMACOLOGY/TOXICOLOGY]	The reviewer recommends: 1) Approval of the application; 2) no additional non-clinical studies; 3) labeling revisions
5. Dr. Zhengfang Ge [CHEMISTRY]	The reviewer concludes that “the sponsor has provided adequate information in the original submission and subsequent amendments to assure identity, strength, purity, and the quality of the drug product. From a CMC perspective, the NDA is approvable, pending satisfactory facility inspections.”
6. Richard Abate [MEDICATION ERRORS PREV.] (Review dated 08/04/2008)	The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks they have identified can be addressed and has provided recommendations to be sent to the applicant; These are listed under Sections 5.2.1 General Comments; 5.2.2 Container Label; 5.2.3 Carton Labeling; and 5.2.4 Insert Labeling of the DMEPA 8/4/8 review.
7. Dr. Sharon R Mills [DRISK] (Review dated July 31, 2008)	Recommends revisions to the Patient Package Insert. The MTL agrees with all DRISK recommendations.

IV. HIGHLIGHTS of REVIEWS from INDIVIDUAL DISCIPLINES

Included in this Section of the MTL's review are salient comments/conclusions/ recommendations from individual disciplines [Table 1] regarding approvability of the submission and Labeling and Patient Labeling revisions.

Salient items to be addressed, summarized and expended in the Executive Summary include:

- Approvability of palonosetron for the prevention of acute MEC-induced CINV
- Recommended dose for the above indication
- (b) (4)
- (b) (4)
- Approvability of palonosetron for the prevention of initial and repeat courses of MEC-induced CINV

1. CLINICAL

The Clinical reviewer, Dr. Nancy Snow concludes that efficacy in the acute phase for the prevention of CINV was demonstrated for all 3 oral palonosetron doses, based on: (1) the percentage of patients with complete response (CR; no emesis and no rescue medications), (2) non-inferiority to the active control, I.V. palonosetron. In the delayed phase, CR rates were similar to the I.V. formulation, but none of the oral dosage forms demonstrated non-inferiority to the active comparator. **Of the three oral dosage forms tested, the 0.50 mg dose came closest to the non-inferiority margin [actually, with the 0.5 mg dose, the non-inferiority margin was borderline].** Based on demonstrating non-inferiority to the I.V. approved formulation for all three oral dose levels in the acute phase, but failure to show non-inferiority in the delayed phase, the medical reviewer recommends that the 0.50 mg oral capsule be approved for the prevention of nausea and vomiting in the acute (0 to 24 hour) phase (b) (4). Included below are highlights from Dr. Snow's Clinical Review.

The primary efficacy measure for Phase 3 studies was complete response (no emetic episodes, no rescue medication) during 0 to 24 hours after administration of moderately emetogenic chemotherapy. The key secondary efficacy measure was CR during 24 to 120 hours after MEC. Other secondary efficacy parameters included complete control (CR and no more than mild nausea), daily number of emetic episodes, and time to first emetic episode.

Results from PALO-03-13 showed that the number of patients with CR in the 0 to 24 hour period was comparable in the three oral palonosetron treatment groups (less than 3% difference between the individual oral treatment groups), and slightly higher than with the I.V. formulation. In all 3 oral palonosetron doses the lower limit of the 98.3% CI was above the non-inferiority margin of -15%, implying with reasonable certainty that the proportion of complete responders to palonosetron was no more than 15% less than the proportion seen with the comparator. No clear dose response relationship was observed in the oral palonosetron studies, or in the earlier studies conducted with the I.V. formulation.

During the 24 to 120 hour time frame the highest percentage of patients with CR was seen with I.V. palonosetron (65.4%), followed by the 0.50 mg oral palonosetron dose (62.5%). As with the acute phase, oral doses of palonosetron were compared in a non-inferiority manner to the approved I.V. formulation. Since the lower limit of the CI for the oral doses was below the pre-set threshold of -15%, none of the oral doses were statistically non-inferior. Thus for all oral dose levels studied in the delayed time period, the proportion of complete responders to palonosetron fell outside the -15% margin. The 0.50 mg dose performed best, and came closest to the margin. From a safety perspective there were no major differences in adverse events that would support one dose over another with respect to the 0.25 and 0.50 mg doses.

Dr. Snow notes that although PALO-03-14 evaluated the safety of palonosetron in up to 4 cycles of chemotherapy, only cycle 1 data was included in the Integrated Summary of Safety. Overall, the incidence of cycles with adverse events decreased slightly from cycle 1 to cycle 3, and remained about the same in cycle 4.

Another conclusion from Dr. Snow's review is that special patient population PK studies involving the I.V. palonosetron formulation indicate that no dosage adjustment is required for elderly patients, or patients with impaired renal or hepatic function. However the PKs of palonosetron have not been studied in patients with end-stage renal disease. Because there are no adequate and well-controlled studies in pregnant women and during lactation, palonosetron is not recommended for use during pregnancy or in nursing women.

The following comment was included in Dr. Snow's review. The American Society of Clinical Oncologists (ASCO) Guidelines for antiemetics in Oncology recommends a 5-HT₃ receptor antagonist, along with dexamethasone for patients receiving chemotherapy of moderate emetic risk other than anthracycline and cyclophosphamide. A three drug combination of a 5-HT₃ receptor antagonist, dexamethasone, and an NK-1 receptor antagonist is recommended for patients receiving anthracycline and cyclophosphamide, and for highly emetogenic regimens. At no time is palonosetron to be used alone to prevent MEC or HEC.

CR for the lowest oral dose level was higher, and for the second dose level lower than expected. Therefore the sponsor concluded that the lowest fully effective oral dose may lie between 3µg/kg (0.25 mg) and 10 µg/kg (0.75 mg).

To augment results from PALO-03-13, and provide support for the secondary efficacy endpoint of complete response (CR) in the delayed phase (24 to 120 hours), further investigations were done, pursuant to 21 CFR 314.126(b)(2)(v).

- Historical pooled analyses, PALO-07-36
- Exploratory analysis, PALO-07-35 (non-inferiority test of proportions)

21 CFR 314.126(b)(2)(v) states:

*“Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, **historical control designs are usually reserved for special circumstances**. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).”*

MTL Comment

*The MTL believes that, when assessing effectiveness of palonosetron in the prevention of MEC-induced N&V, the use of a historical placebo control **represent a special circumstance**. This is because all available data from placebo comparisons in support of this indication were carried out in the 80s and early 90. Because of ethical reasons, no additional studies have been carried out. As a consequence, an important but realistic constraint when comparing palonosetron data to historical placebo control is that the available placebo data are not contemporaneous to those results from recently carried out studies.*

As noted by Dr. Snow's during the course of the review the FDA requested additional information from the sponsor, including historical placebo controlled trials specific to the delayed phase. These items were also reviewed with the NDA and provide additional data for the efficacy review.

In her review, Dr. Snow included the following Medical Officer's Comments:

In NDA 22-233 the most useful and robust data comes from pivotal study PALO-03-13. Supportive Phase 3 study PALO-03-14 provides limited efficacy data since the trial did not evaluate the 0.50 mg dose and was uncontrolled. Phase 2 study 2332 evaluated CR in the acute phase only, for patients receiving highly emetogenic chemotherapy (HEC).

The supplemental data, which the sponsor submitted to support CR in the delayed phase, pooled data from historical I.V. CINV pivotal trials, with the 0.25 mg I.V. arm in PALO-03-13. These data are useful in so far as they provide a larger database for the active comparator, but since dexamethasone was not the standard of care when these studies were conducted, fewer patients received dexamethasone than in the current studies. In addition this evaluation was not part of the original statistical analysis plan, and was done post-hoc.

The historical placebo data provides additional information about efficacy beyond 24 hours by comparing the percentage of patients on placebo (derived from earlier studies) who did not have emesis with patients receiving 0.50 mg oral palonosetron. Data were presented for days 2, 3, and 4-5. On day two 23% of placebo patients did not have emesis, compared to 75% of palonosetron patients. On day three 40% of placebo patients were emesis-free, compared to 84% observed with palonosetron.

The endpoints measured, no emesis, are not the primary, or key secondary endpoints used in PALO-03-13. Further there were differences with respect to type of cancer treated, chemotherapeutic agent, gender, previous chemotherapy history, and corticosteroid use. In addition, efficacy was measured on single days, rather than for the entire delayed phase of 24 to 120 hours.

The most sensible definition of delayed response is the overall post-24 hour four-day value: it does not include the acute response but does include information from all subsequent days, in particular the final day of observation when the emetogenicity of the chemotherapy is most muted.

PALO-03-14

PALO-03-14 was a multicenter, open-label, repeated cycle, uncontrolled trial to assess safety and efficacy of single oral capsules of palonosetron 0.75 mg in the prevention of MEC in repeated and consecutive moderately emetogenic chemotherapy cycles. Patients enrolled were allowed to continue in the study until a maximum of four consecutive chemotherapy cycles per patient had been evaluated, and until at least 600 cycles were available as a total.

Oral palonosetron 0.75 mg was administered on Study Day 1 in an open-label fashion in the form of a soft gelatin capsule 60 minutes before the start of the first emetogenic chemotherapeutic agent. A single I.V. or oral 8 mg dose of dexamethasone could be given at the discretion of the investigator 30 minutes before the start of chemotherapy. If a patient received dexamethasone during the first study cycle, he/she was to continue to receive dexamethasone with subsequent cycles. The interval between 2 consecutive study drug administrations was at least 7 days.

At each cycle efficacy was assessed daily by the patient during the 0 to 120 hour time period from the administration of chemotherapy. Patient diaries were used to record emetic episodes, use of rescue medication, severity of nausea, and patients' global satisfaction with anti-emetic therapy.

PALO-07-36 Historical Pooled Analysis

Prevention of Delayed CINV

The proportion of patients with CR in the 24 to 120 hour time period was analyzed as a key secondary efficacy variable. Results of this analysis show that during the 24 to 120 hour period the highest number of patients with CR was seen in the I.V. palonosetron group (65.4%) followed by the 0.50 mg oral palonosetron dose group (62.5%).

Table 7.1-l shows data from the delayed phase of 24 to 120 hours.

Table 7.1-l: Patients with complete response during the 24-120 hour time period from 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 (%)
92	59.4	[51.2, 67.1]	100	62.5	[54.5, 69.9]	95	60.1	[52.0, 67.7]	106	65.4	[57.5, 72.6]

Source: Appendix B-1.2.1, Table 15.1.1, Table 15.1.2

CI = confidence interval

N = number of patients in specific group

n = number of patients with complete response

% = percentage based on N

A further breakdown of the (b) (4) into 24 hour intervals (as was done in the I.V. palonosetron review), is shown in sponsor Table 7.1-p.

Table 7.1-p: Patients with complete response after start of chemotherapy, per day (Full analysis set, N = 635)

Time period	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 (%)
>24 – 48 h	107	69.0	[61.0, 76.1]	113	70.6	[62.8, 77.4]	117	74.1	[66.4, 80.5]	123	75.9	[68.5, 82.1]
>48 – 72 h	118	76.1	[68.5, 82.4]	118	73.8	[66.1, 80.2]	120	75.9	[68.4, 82.2]	130	80.2	[73.1, 85.9]
>72 – 96 h	126	81.3	[74.1, 86.9]	125	78.1	[70.8, 84.1]	121	76.6	[69.1, 82.8]	133	82.1	[75.1, 87.5]
>96 – 120 h	130	83.9	[76.9, 89.1]	140	87.5	[81.1, 92.0]	138	87.3	[80.9, 91.9]	141	87.0	[80.6, 91.6]

Source: Appendix B-1.2.1, Table 15.1.1, Table 15.1.2

CI = confidence interval

N = number of patients in specific group

n = number of patients with complete response

% = percentage based on N

As pointed out by Dr. Snow, these data show variability at each of the 24 hour time periods, and no clear cut advantage of one dose level over the other.

As with the acute phase, efficacy of palonosetron capsules in the delayed phase was based on showing that the proportion of complete responders to palonosetron was no more than 15% less than the proportion seen with the I.V. comparator. In other words, non-inferiority in the delayed phase was demonstrated if the lower bound of the two-sided 98.3% confidence interval of the difference in the percentage of patients with complete response between each of the oral treatment groups and the I.V. treatment group was above the pre-set threshold of -15%.

Sponsor's Table 7.1-m. shows (b) (4)

Source: Appendix B-1.2.1, Table 15.1.3

(b) (4)

Dr. Snow commented that *“The Historical Pooled Analysis or the Exploratory Analysis were post-hoc analyses, not pre-specified in the SAP. A full analyses of these studies can be found in a separate Statistical Review of this NDA submission”*.

From her review of the evidence, Dr. Snow arrived at the following conclusions. Study PALO-03-13 demonstrated that palonosetron 0.25mg, 0.50 mg, and 0.75 mg were non-inferior to the active comparator, I.V. palonosetron 0.25 mg, for CR during the 0 to 24 hour time interval. For the 24 to 120 hour time interval the sponsor has not been able to demonstrate that, at any dose level of oral palonosetron capsules, there is a reasonable certainty that the proportion of complete responders in the 24 to 120 hour time period would be no more than 15% less than the comparator. From a clinical perspective one may conclude that from 0 to 24 hours patients can be expected to receive the same protection from CINV with oral palonosetron as they currently derive from the marketed I.V. formulation. For later time periods oral palonosetron may be effective in preventing nausea or emesis in a percentage of patients, but may not perform at the same level of I.V. palonosetron.

Dr. Snow’s Recommendation on Regulatory Action are listed below.

The medical reviewer recommends the approval of 0.50 mg palonosetron oral capsules for the prevention of chemotherapy induced nausea and vomiting during the acute, 0 to 24 hour, time period.

The sponsor is requesting the indication of prevention of acute (b) (4) nausea and vomiting associated with the administration of chemotherapeutic agents of moderate emetogenic potential, during initial and repeat administrations of chemotherapy for 0.50 mg palonosetron oral capsules. Acute CINV is defined as nausea and vomiting that occur within 24 hours of receiving chemotherapy, (b) (4)

Efficacy in the acute phase was demonstrated for all 3 oral palonosetron dosages, based on a demonstration of non-inferiority to the active control, I.V. palonosetron with respect to the efficacy parameter of complete response. No oral dosages were showed non-inferiority to the active comparator in the delayed phase.

The safety of palonosetron was established in the trials supporting the I.V. formulation, and in post-marketing data. In the current submission adverse events were consistent with those already known to be associated with this drug.

A dosage of 0.50 mg is recommended for marketing due to its favorable safety and efficacy profile.

- *The MTL agrees with the recommendation to approve the Aloxi® [palonosetron] oral capsule for the prevention of N&V induced by moderately emetogenic chemotherapeutic agents in the acute [0 to 24 h] after chemotherapy administration] phase.*
- *The MTL believes that the sponsor's request for approval of Aloxi® [palonosetron] for the prevention of (b) (4) N&V needs further consideration [See below].*
- *Also needed is further discussion about the recommended dose for the prevention of acute MEC-induced N&V (b) (4) [0.50, as proposed by the sponsor, vs. 0.25, as proposed by Clinical Pharmacology].*

2. STATISTICS

The bulk of the Statistical review was carried out by Dr. Kate Dwyer. Additional Statistical evaluations were carried out by Dr. Wen-Jen Chen. Included below are highlights excerpted from Dr. Dwyer's draft review.

Dr. Dwyer concluded that the results from study PALO-03-13 show that each of the three oral doses of palonosetron is non-inferior to the I.V. dose, as measured by complete response during the acute phase (0 to 24 h) and a non-inferiority margin of 15%. However, none of the oral doses showed non-inferiority to the I.V. for complete response for the delayed phase (24 to 120 h). According to Dr. Dwyer, the results based on other secondary endpoints should be considered exploratory. From a statistical perspective, this study has demonstrated comparable efficacy between the oral and I.V. administrations of palonosetron for the acute phase only.

1.3 Statistical Issues and Findings [from Dr. Dwyer's review]

This reviewer has concern regarding the dynamic adaptive allocation procedure used in PALO-03-13. This scheme does not correspond to what is usually thought of as randomization in a clinical trial. A further analysis was done regarding this dynamic adaptive randomization approach; please refer to the supplemental review by Wen Jen Chen for details.

Another concern is that the complete response rates were different between US and non-US regions. However, due to small numbers of patients enrolled in US, no clear conclusions can be drawn regarding US and non-US differences.

In this application, the efficacy trials did not include a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of oral doses of palonosetron to I.V. palonosetron, the sponsor conducted a meta-analysis of results from publications which constitute historical placebo CINV studies for the acute phase (0-24 hours).

Exploratory analysis of PALO-07-35 and historical pooled analysis PALO-07-36 submitted by sponsor are post-hoc analyses and should be considered exploratory and not providing any measurable support for efficacy assessment of oral Palonosetron. Please refer to the supplemental review by Wen-Jen Chen for additional comments.

The results from study PALO-03-13 support the effects of the three oral doses are non-inferior to that of I.V. dose for the acute phase (0 to 24 hours), assessed by non-inferiority margin of 15%. However, for the delayed phase (24 to 120 hours), none of the three oral doses is non-inferior to IV dose, assessed by non-inferiority margin of 15%.

This review also conducted the patient enrollment study by country. It should be noted that the study enrollment duration for Romania was only 21 days which was much less than any other country. Additional information was request. According to the response from the Sponsor, Romania was added toward the end of the study due to enrollment behind schedule.

3.1.1.1 Efficacy Results for Primary and Key Secondary Endpoints

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, whereas complete response during the 24-120 hour period after administration of chemotherapy was the key secondary efficacy variable.

The 95% confidence intervals for primary and key secondary endpoints are presented in Table 1 for FAS set. The confidence intervals for differences between the oral and I.V. treatment groups are showed in Table 2, also for FAS set.

Table 1: Proportion of patients achieving CR during first 24 and 24 -120 hours from start of chemotherapy (Full analysis set, N = 635)

Time Period	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	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)	n	CR%	95% CI (%)
0 – 24 Hr	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)
24 – 120 Hr	92	59.4	(51.2, 67.1)	100	62.5	(54.5, 69.9)	95	60.1	(52.0, 67.7)	106	65.4	(57.5, 72.6)

Table 2: Complete response during the first 24 and 24-120 hours: confidence intervals for differences between oral and I.V. treatment groups (Full analysis set, N = 635)

Time Period	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg 98.3% Confidence Interval
0 – 24 Hr	(-9.5, 15.8)	(-6.5, 18.2)	(-8.9, 16.3)
24 – 120 Hr	(-19.7, 7.5)	(-16.3, 10.5)	(-18.8, 8.2)

According to the statistical hypothesis, non-inferiority of the oral palonosetron doses to the I.V. palonosetron dose was demonstrated if the lower bound of the two-sided 98.3% confidence interval of the difference in the percentage of patients with complete response between each of the oral treatment groups and the I.V. treatment group was above the pre-set threshold of -15%. As showed in Table 2, the non-inferiority of the three oral doses to I.V. dose are achieved when assessed by the primary endpoint for both FAS and PP set. However, for the delayed phase (24-120 hours), none of the lower bounds for the three oral doses on the complete response rate differences is above -15% of the non-inferiority margin. It indicates that none of the three oral doses is non-inferior to I.V. dose when assessed by the key secondary endpoint. Since the complete response rate of 0.75 mg is not significantly larger than that of 0.50 mg, dose response is not supported.

This reviewer has concern regarding the dynamic adaptive allocation procedure including a randomization component was applied in order to balance the four treatment groups with or without dexamethasone across the gender and previous chemotherapeutic history (naïve or non-naïve). This scheme does not correspond to what is usually thought of as randomization in a clinical trial. As stated in ICH E9 this type of procedure “should be avoided” (ICH E9, p.13). A further analysis was done regarding this dynamic adaptive randomization approach; please refer to secondary review by Wen Jen Chen for details.

Other Special/Subgroup Populations

4.1.1 Region

We conducted analysis for primary and key secondary endpoints by US vs. non-US in addition to by country which was submitted by sponsor. The results are presented in Table 3 and Table 4. In general, the highest percentages of patients with complete response in all treatment groups were found in Romania, whereas in USA the percentages of patients with complete response were lowest. Non-inferiority was shown for Non-US and for the oral palonosetron 0.50 mg versus the I.V. palonosetron group in Mexico, while in all the other countries all three oral doses failed to show noninferiority versus the I.V. palonosetron dose. Since the low patient numbers per country, we cannot draw any conclusion from this study.

Table 3: Patients with complete response during 0 to 24 and 24 to 120 hour time period from start of chemotherapy (Full analysis set, subgroups: region, N = 635)

Time Period	Region	Oral Palonosetron 0.25 mg				Oral Palonosetron 0.50 mg				Oral Palonosetron 0.75 mg				IV Palonosetron 0.25 mg			
		N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)
0 – 24 Hr	US	32	19	59.4	(40.8, 75.8)	30	17	56.7	(37.7, 74.0)	26	18	69.2	(48.1, 84.9)	37	20	54.1	(37.1, 70.2)
	Non-US	123	95	77.2	(68.6, 84.1)	130	105	80.8	(72.7, 86.9)	132	99	75.0	(66.6, 81.9)	125	94	75.2	(66.5, 82.3)
	Czech Republic	25	18	72.0	(50.4, 87.1)	29	19	65.5	(45.7, 81.4)	25	17	68.0	(46.4, 84.3)	28	19	67.9	(47.6, 83.4)
	Poland	29	21	72.4	(52.5, 86.6)	27	23	85.2	(65.4, 95.1)	33	23	69.7	(51.1, 83.8)	30	25	83.3	(64.5, 93.7)
	Romania	27	26	96.3	(79.1, 99.8)	32	30	93.8	(77.8, 98.9)	29	28	96.6	(80.4, 99.8)	27	26	96.3	(79.1, 99.8)
	Mexico	42	30	71.4	(55.2, 83.8)	42	33	78.6	(62.8, 89.2)	45	31	68.9	(53.2, 81.4)	40	24	60.0	(43.4, 74.7)
24 – 120 Hr	US	32	16	50.0	(32.2, 67.8)	30	15	50.0	(31.7, 68.3)	26	14	53.8	(33.7, 72.9)	37	18	48.6	(32.2, 65.3)
	Non-US	123	76	61.8	(52.6, 70.3)	130	85	65.4	(56.5, 73.4)	132	81	61.4	(52.5, 69.6)	125	88	70.4	(61.5, 78.1)
	Czech Republic	25	14	56.0	(35.3, 75.0)	29	19	65.5	(45.7, 81.4)	25	14	56.0	(35.3, 75.0)	28	21	75.0	(54.8, 88.6)
	Poland	29	16	55.2	(36.0, 73.0)	27	22	81.5	(61.3, 93.0)	33	21	63.6	(45.1, 79.0)	30	23	76.7	(57.3, 89.4)
	Romania	27	21	77.8	(57.3, 90.6)	32	24	75.0	(56.2, 87.9)	29	22	75.9	(56.1, 89.0)	27	25	92.6	(74.2, 98.7)
	Mexico	42	25	59.5	(43.3, 74.0)	42	20	47.6	(32.3, 63.4)	45	24	53.3	(38.0, 68.1)	40	19	47.5	(31.8, 63.7)

Table 4: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and I.V. treatment groups (Full analysis set, subgroups: region, N = 635)

Time Period	Region	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg
		98.3% Confidence Interval	98.3% Confidence Interval	98.3% Confidence Interval
0 – 24 Hr	US	(-26.1, 36.7)	(-29.5, 34.8)	(-17.2, 47.6)
	Non-US	(-11.7, 15.7)	(-7.6, 18.7)	(-13.9, 13.5)
	Czech Republic	(-29.7, 38.0)	(-35.6, 31.0)	(-34.3, 34.6)
	Poland	(-39.9, 18.1)	(-24.7, 28.4)	(-41.9, 14.6)
	Romania	(-16.0, 16.0)	(-19.4, 14.3)	(-15.2, 15.7)
	Mexico	(-15.9, 38.7)	(-7.7, 44.9)	(-18.2, 36.0)
24 – 120 Hr	US	(-30.4, 33.1)	(-31.0, 33.7)	(-28.6, 39.0)
	Non-US	(-23.7, 6.5)	(-19.7, 9.7)	(-23.9, 5.8)
	Czech Republic	(-53.5, 15.5)	(-41.7, 22.8)	(-53.5, 15.5)
	Poland	(-53.6, 10.6)	(-24.4, 34.0)	(-43.4, 17.3)
	Romania	(-41.1, 11.5)	(-42.9, 7.7)	(-42.8, 9.3)
	Mexico	(-16.5, 40.6)	(-28.7, 28.9)	(-22.4, 34.1)

4.1.2 Use of Dexamethasone

The complete response during the 0-24 and 24-120 hour time period are summarized by use of dexamethasone in Table 5 and Table 6. For complete response in the 0-24 hour time period, non-inferiority of the respective oral palonosetron doses to the I.V. palonosetron dose was shown for all oral palonosetron doses in both dexamethasone and no dexamethasone subgroups, except for oral palonosetron 0.25 mg in the subgroup using dexamethasone.

Table 5: Patients with complete response during 0-24 and 24-120 hour time period from start of chemotherapy (Full analysis set, subgroups: use of dexamethasone, N = 635)

Time Period	Dex	Oral Palonosetron 0.25 mg				Oral Palonosetron 0.50 mg				Oral Palonosetron 0.75 mg				IV Palonosetron 0.25 mg			
		N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)	N	n	CR%	95% CI (%)
0 – 24 Hr	Dex	78	60	76.9	(65.8, 85.4)	79	68	86.1	(76.0, 92.5)	80	68	85.0	(74.9, 91.7)	82	68	82.9	(72.7, 90.0)
	Non-Dex	77	54	70.1	(58.5, 79.8)	81	54	66.7	(55.2, 76.5)	78	49	62.8	(51.1, 73.3)	80	46	57.5	(46.0, 68.3)
24 – 120 Hr	Dex	78	45	57.7	(46.0, 68.6)	79	50	63.3	(51.6, 73.6)	80	51	63.8	(52.2, 74.0)	82	56	68.3	(57.0, 77.9)
	Non-Dex	77	47	61.0	(49.2, 71.7)	81	50	61.7	(50.2, 72.1)	78	44	56.4	(44.7, 67.4)	80	50	62.5	(50.9, 72.9)

Table 6: Complete response (0-24 and 24-120 hours): confidence intervals for differences between oral and I.V. treatment groups (Full analysis set, subgroups: use of dexamethasone, N = 635)

Time Period	Dex	Oral Palonosetron 0.25 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.50 mg – IV Palonosetron 0.25 mg	Oral Palonosetron 0.75 mg – IV Palonosetron 0.25 mg
		98.3% Confidence Interval	98.3% Confidence Interval	98.3% Confidence Interval
0 – 24 Hr	Dex	(-22.4, 10.4)	(-11.7, 18.0)	(-12.9, 17.1)
	Non-Dex	(-6.8, 32.0)	(-10.3, 28.6)	(-14.5, 25.2)
24 – 120 Hr	Dex	(-30.0, 8.8)	(-24.1, 14.1)	(-23.5, 14.4)
	Non-Dex	(-21.3, 18.3)	(-20.3, 18.7)	(-26.0, 13.8)

5. SUMMARY AND CONCLUSIONS [FROM STATISTICS]

Statistical Issues and Collective Evidence

This reviewer has concern regarding the dynamic adaptive allocation procedure used in PALO-03-13. This scheme does not correspond to what is usually thought of as randomization in a clinical trial. A further analysis was done regarding this dynamic adaptive randomization approach; please refer to the supplemental review by Wen-Jen Chen for details.

Another concern is that the complete response rates were different between US and non-US regions. However, due to small numbers of patients enrolled in US, no clear conclusions can be drawn regarding US and non-US differences.

In this application, the efficacy trials did not include a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of oral doses of palonosetron to IV palonosetron, the sponsor conducted a meta-analysis of results from publications which constitute historical placebo CINV studies for the acute phase (0-24 hours).

Exploratory analysis of PALO-07-35 and historical pooled analysis PALO-07-36 submitted by sponsor are post-hoc analyses and should be considered exploratory and not providing any measurable support for efficacy assessment of oral Palonosetron. Please refer to the supplemental review by Wen-Jen Chen for additional comments.

The results from study PALO-03-13 support the effects of the three oral doses are non-inferior to that of I.V. dose for the acute phase (0-24 hours), assessed by non-inferiority margin of 15%.

However, for the delayed phase (24-120 hours), none of the three oral doses is non-inferior to I.V. dose, assessed by non-inferiority margin of 15%.

Conclusions and Recommendations [Statistics]

The results from study PALO-03-13 show that each of the three oral doses of palonosetron is non-inferior to the I.V. dose, as measured by complete response during the acute phase (0-24 hours) and a non-inferiority margin of 15%. However, none of the oral doses showed non-inferiority to the I.V. for complete response for the delayed phase (24-120 hours). The results based on other secondary endpoints should be considered exploratory. From a statistical perspective, this study has demonstrated comparable efficacy between the oral and I.V. administrations of palonosetron for the acute phase only.

3. CLINICAL PHARMACOLOGY

In the Executive Summary of her 07/23/2008 review, Dr. Insook Kim states that the sponsor is seeking an approval of single oral dose of palonosetron hydrochloride 0.5 mg for the prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy (MEC). An injection form of palonosetron has been approved. The sponsor proposed to support the oral product by a single pivotal phase 3 trial based on the similar dose-response relationship between oral administration and intravenous administration observed in phase 2 and 3 trials. In the single pivotal phase 3 trial, the non-inferiority of oral administration of 0.25 mg, 0.5 mg and 0.75 mg compared to 0.25 mg I.V. administration was demonstrated for the prevention of acute nausea and vomiting associated with initial course of MEC. (b) (4)

According to Dr. Kim, the clinical pharmacology and biopharmaceutics information was reviewed by the division of clinical pharmacology III and found acceptable provided 1) the DSI inspection currently scheduled in the week of 11th of August finds the BE study acceptable and 2) a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

Should the proposed product of palonosetron be approved for the prevention of acute CINV, CP recommends that the dose be reduced to 0.25 mg from the proposed 0.5 mg. The dose of 0.25 mg was found to be effective and no dose-response relationship was demonstrated among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg. Dr. Kim states that this recommendation is consistent with the finding that the absolute bioavailability of oral capsules was 97% and the approved dose for I.V. administration for the prevention of both acute and delayed CINV is 0.25 mg.

If the clinical division determined that there was clinically meaningful efficacy for oral palonosetron in the prevention of (b) (4)

(b) (4) we also recommend that the dose be reduced to 0.25 mg because no dose-response relationship was evident among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg for (b) (4). Summarized below are some highlights excerpted from Dr. Kim' CP and B review.

Summary of Clinical Pharmacology and Biopharmaceutics Findings

In support of the new oral formulation of palonosetron HCl, included were the final study reports of nine phase 1 and 2 studies: oral ADME, dose-proportionality, single dose pharmacokinetics, bioavailability and bioequivalence studies, food effect and drug interaction studies, pharmacokinetics in CINV and PONV patients and in the healthy elderly subjects. (b) (4)

The

single pivotal phase 3 study and an open-label phase 3 safety study were submitted to support the efficacy and the safety of oral capsules of palonosetron.

For some early phase 1 and 2 studies, the IV formulation was used as a drinkable oral solution for the body-weight based doses while oral capsule formulation was used for later studies including phase 3 trials conducted for the fixed doses.

PK characteristics

After oral administration, palonosetron is well-absorbed with an absolute bioavailability of 97 to 100%. The peak plasma concentrations are generally achieved within 4-6 h and the C_{max} and AUC after oral solution administration are generally dose-proportional over 1 to 80 µg/kg dose range in healthy subjects. Mean plasma half-life after oral dosing is ca. 40 h in healthy subjects and 40 to 60 h in CINV patients. The systemic exposure to palonosetron was higher in cancer patients by about 26 to 86% in terms of AUC than in healthy subjects (Table 1). (It should be noted that the data in Table 1 were gathered from three separate studies.)

Ca. 40% of orally administered palonosetron was cleared renally as unchanged drug and approximately 50% of palonosetron is metabolized. Two primary metabolites M9 and M4 were excreted in the urine amounting to about 12.1% and 17.2% of the administered dose, respectively. Estimates of renal clearance ranged from 4.06 to 6.29 l/h.

Dr. Kim's Table 1. PK parameters for palonosetron after a single-dose administration in healthy subjects and cancer patients

Dose	Parameters	Healthy Mean (SD)	Cancer patients Mean (SD)
0.25 mg ¹ capsule	C _{max} (ng/ml)	n/a	0.55 (0.23)
	T _{max} ² (h)	n/a	6 (1-47.4)
	AUC _∞ (ng·h/ml)	n/a	34.2 (13.6)
0.5 mg capsule	C _{max} (ng/ml)	0.81 (0.16)	0.93 (0.34)
	T _{max} ¹ (h)	5.0 (2-8)	3.5 (1-23.4)
	AUC _∞ (ng·h/ml)	38.2 (11.7)	49.7 (12.2)
0.75 mg capsule	C _{max} (ng/ml)	1.2 (0.32)	1.42 (0.36)
	T _{max} ¹ (h)	4.5 (2-12)	4 (1-23.3)
	AUC _∞ (ng·h/ml)	58.3 (18.1)	103.3 (37.3)

¹ PK following a 0.25 mg dose capsule administration was not studied in healthy subjects. The closest dose studied in healthy subject was 3 µg/kg which corresponds to 0.21 mg (70 kg BW) using an oral solution.

² median (min-max)

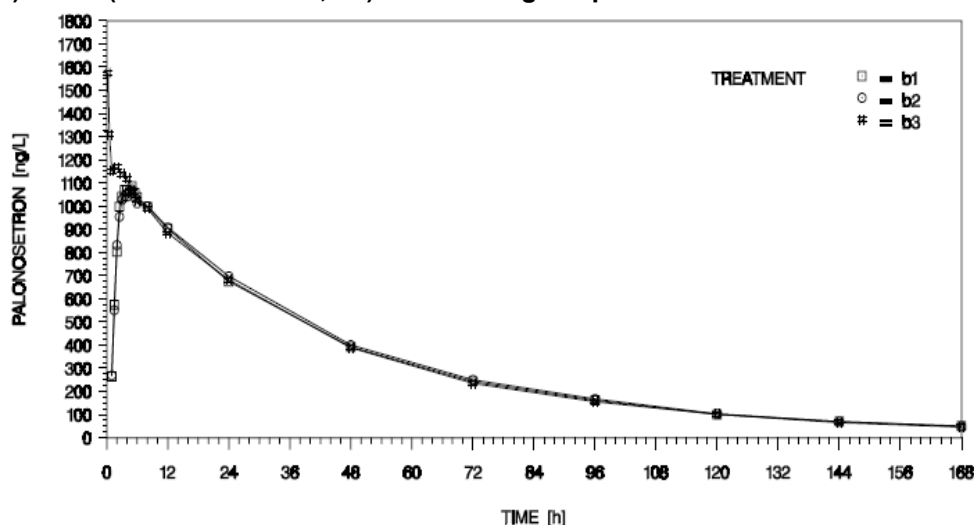
The absolute bioavailability of palonosetron after 0.75mg oral capsule administration was 97%. The C_{max} of palonosetron after oral administration was 28% lower than after intravenous administration. Following oral absorption, the elimination profile of palonosetron was similar to those after I.V. injection (Figure 1).

Pharmacokinetic characteristics after oral administration of palonosetron HCl was studied only in white subjects except one phase 1 PK study in Japanese male subjects. According to cross-study comparisons the 25% higher apparent total body clearance of palonosetron was observed in Japanese males than in white males.

The mean AUC of palonosetron is approximately 20-38% higher in females compared to males. The mean AUC of a metabolite M9 was 10-30% higher in females but 15% higher in males than in females for the elderly. The M4 exposure was variable and there was no consistent difference in M4 exposure by gender. No dosage adjustment based on gender is needed.

Following oral administration of 0.75 mg palonosetron under fasting, the mean AUC of palonosetron in elderly subjects aged over 65 years was similar to younger subjects aged 18-45 years and the mean C_{max} was 13% lower than in the young. There is no need for dosage adjustment in the elderly.

Dr. Kim's Figure 1. Arithmetic mean concentration time curves for 0.75 mg capsule: formulations a (phase 3; b1) and b (to-be-marketed*; b2) and 0.75 mg I.V. palonosetron



b1: 0.75 mg palonosetron softgel capsule (Formulation A; phase 3 clinical trial formulation)
b2: 0.75 mg palonosetron softgel capsule (Formulation B; proposed commercial formulation)
b3: 0.75 mg intravenous palonosetron (reference, 3 x 0.25 mg i.v. Aloxi®)

* Proportionally similar with the proposed to-be-marketed formulation for 0.5 mg strength

The to-be-marketed formulation (TBM) was modified from a clinical trial formulation used in the phase 3 trial and some phase 1 and 2 trials to improve the shelf-stability. The total formulation change of (b) (4) was agreed to be SUPAC-IR level 2 change in a previous communication with the Agency. The bioequivalence between TBM and trial formulation was demonstrated in a two-way crossover in vivo bioequivalence study. The 90% confidence interval of point estimate ratio for AUC and Cmax fell within the bioequivalence criteria of 80-125% (table 2).

Dr. Kim's Table 2. ANOVA CVs, point estimates, 90% confidence intervals for (log-transformed) palonosetron pharmacokinetic parameters; Bioequivalence Assessment (N=36 subjects)

Pharmacokinetic parameter palonosetron	Ratio	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
AUC _(0-t) [ng·h/L]	b ₂ / b ₁	8.7	102.3	98.9 - 105.9
AUC _(0-∞) [ng·h/L]	b ₂ / b ₁	8.7	102.0	98.6 - 105.6
C _{max} [ng/L]	b ₂ / b ₁	7.9	103.7	100.5 - 107.0

b1: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation A, clinical trial formulation)

b2: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation B, proposed commercial formulation)

Source: Final Report PALO-06-16, Table 11.4-8.

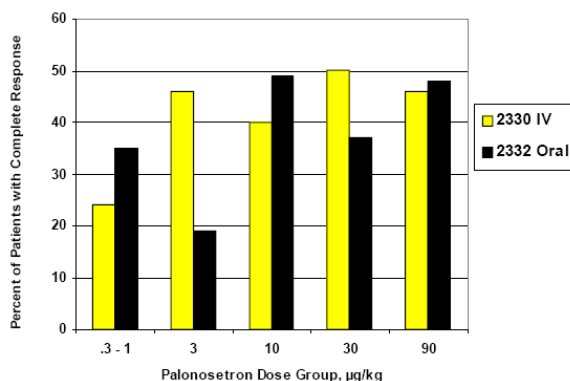
Concomitant antacid (Maalox®) and high fat diet did not affect AUC and Cmax of palonosetron. Therefore, palonosetron can be taken without regard of meal intake.

Exposure (Dose)-Response Relationship

Efficacy- The dose of 0.25 mg was the lowest effective dose among doses studied in phase 3 trial for the prevention of acute CINV while the efficacy for the prevention of (b) (4) has not been demonstrated in a statistically meaningful manner (b) (4).

In study 2332, dose-response relationship for efficacy over doses 0.3, 1, 3, 10, 30 and 90 µg/kg was studied in chemotherapy naïve patients who were scheduled to receive their first doses of highly emetogenic chemotherapy. The primary endpoint was the proportion of patients with no emetic episodes and no rescue medication for a period of time i.e. 0-24 hours (CR 0-24) for acute CINV and 24-120 hours (CR 24-120) for delayed CINV after the initiation of chemotherapy. Only CR 0-24 was collected in the phase 2 trial. The clinical response appeared to reach a plateau at a dose of 10 µg/kg (approximately 0.7 mg for 70 kg BW). The dose-response relationship for CR 0-24 of oral administration was comparable for three high doses with I.V. administration while the lowest oral dose cohort had a higher CR 0-24 and 3 µg/kg oral dose cohort had a significantly lower CR 0-24 than I.V. administration (Figure 2). The doses of 0.25 mg, 0.5 mg and 0.75 mg were chosen for the phase 3 trial since the efficacy of 0.25 mg was proven in the IV development program for moderately emetogenic chemotherapy (MEC) and the absolute BA of oral administration was greater than 90%.

Dr. Kim's Figure 2: Comparison of complete response for 0-24 hours post-chemotherapy between oral and IV palonosetron



4. ANIMAL PHARMACOLOGY/TOXICOLOGY

Dr. Joseph notes that no nonclinical studies were submitted, as per an agreement between the Sponsor and the Division of Gastroenterology Products (letter dated June 7, 2007 under IND 42,886). A review of the nonclinical studies is found in the Pharmacology/Toxicology review of NDA 21,372 (Aloxi® Injection) dated July 11, 2003. The nonclinical section of the present application contains only a summary of the studies submitted in NDA 21,372. The nonclinical information is briefly summarized in Dr. Joseph's review, of which, the Section under Discussion and Conclusions is reproduced below. Although intravenous and oral toxicology studies of palonosetron are available, the toxicology summary in Dr. Joseph's review is limited to the oral studies, since these are more relevant to the safety of Aloxi Capsules.

2.6.6.8 Discussion and Conclusions

In repeat-dose oral toxicity studies, palonosetron was tolerated at doses of up to 60 mg/kg/day in rats and mice (3-month studies) and 20-40 mg/kg/day in dogs (4-week and 3-month studies). Adverse effects in rats occurred at 120 and 180 mg/kg/day po (4-week and 3-month studies). The major effects included anemia, hepatocellular swelling and glycogen deposition, decreased bone marrow cellularity, decreased femoral trabecular bone, multiple lesions in testes, immature spermatogenic cells in the epididymis, atrophy of lymphoid tissues, and chronic nephrosis. In the 3-month rat study, oral administration of 180 mg/kg/day produced tremor, convulsions, and mortality. The no effect doses in repeat-dose intravenous toxicity studies were in the range of 3 to 7 mg/kg/day. CNS appeared to be a target organ of toxicity in both rats and dogs, based on

the incidence of convulsions, ataxia, and reduced activity. Vomiting and loose feces also occurred in dogs. In the 6-month intravenous study in rats, administration of 14 mg/kg/day produced convulsions, reduced activity, and death

There are no recommendations for additional non-clinical studies.

A. Recommendations on labeling

In Dr. Joseph's review, recommendations are given for revisions to the following sections and subsections of the labeling:

"INDICATIONS AND USAGE" section under the "HIGHLIGHTS OF PRESCRIBING INFORMATION", "DRUG INTERACTIONS", "Pregnancy", "Nursing Mothers", "OVERDOSAGE", "Mechanism of Action", "Pharmacodynamics", and "NONCLINICAL TOXICOLOGY" (Carcinogenesis, Mutagenesis, Impairment of Fertility).

- *The labeling should be revised as described in the "EXECUTIVE SUMMARY" section of Dr. Joseph's review.*

5. CHEMISTRY

The following statement is included in Dr. Ge's CMC review of NDA 22-233, under 4.1.1 A. Recommendation and Conclusion on Approvability. The sponsor has provided adequate information in the original submission and subsequent amendments to assure identity, strength, purity, and the quality of the drug product. Therefore, from a CMC point of view, **this NDA may be approvable pending satisfactory facility inspection.**

6. DIVISION OF MEDICATION ERRORS PREVENTION

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors.

The medication error prevention staff believes the risks they have identified can be addressed and has provided recommendations to be sent to the applicant [These are listed under **Sections 5.2.1 General Comments; 5.2.2 Container Label; 5.2.3 Carton Labeling; and 5.2.4 Insert Labeling**]

7. DRISK: REVIEW of PATIENT LABELING

In response to our consult request, the reviewer, Ms. Sharon R Mills [DRISK review dated July 31, 2008], proposed several modifications to the PPI, all of which are acceptable to this MTL. Ms Mills proposed revisions to the Patient Information and the MTL comments to DRISK's comments are shown in Appendix 1.

V. 4-MONTH SAFETY UPDATE

This document was submitted on August 1, 2008. A detailed review of this document is included in Dr. Snow's Clinical Review. In the meantime, the MTL agrees with the sponsor that the Summary Update of Clinical Safety Data, a Literature Search Update on the Safety of Palonosetron and a Summary Update of Relevant Animal Safety Data show that this Safety Update identifies no additional safety concerns for palonosetron; the safety profile of the drug has not changed.

VI. PEDIATRIC PLAN

A detailed review of the Sponsor's proposed Pediatric Plan is included in Dr. Snow Clinical Review.

VII. PHASE 4 COMMITMENTS

No Phase 4 commitments are recommended.

Hugo E Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastroenterology Products

APPENDICES

3 pp withheld in full immediately after this page as (b)(4) Draft Labeling.

APPENDIX 2

Below is the Question-Based Review Section excerpted from Dr. Kim's Clinical Pharmacology and Biopharmaceutics review, dated 07/23/2008.

2 QUESTION-BASED REVIEW

1.1.1 2.2.4 Exposure-Response Evaluation

1.1.1.1 2.2.4.1 What are the characteristics of the exposure (dose)-response relationships for efficacy?

In phase 2 study (study 2332), dose-response relationship for efficacy was studied in chemotherapy naïve patients who were scheduled to receive their first doses of highly emetogenic chemotherapy e.g. cisplatin ($> 70 \text{ mg/m}^2$) or cyclophosphamide ($> 1100 \text{ mg/m}^2$). All patients included in efficacy analysis were received cisplatin-based chemotherapy while all patients were included in safety analysis.

Reviewer's comments: *The proposed indication is the prevention of CINV associated with moderately emetogenic chemotherapy.*

Twenty-six to 35 patients were treated with one of the doses of 0.3, 1, 3, 10, 30 and $90 \mu\text{g/kg}$. Because the lowest dose of $0.3 \mu\text{g/kg}$ was discontinued during the study due to apparent lack of efficacy, its results were combined with $1 \mu\text{g/kg}$ dose cohort. For analysis purposes, the efficacy of each dose was compared with the efficacy of the lowest dose (the combined cohort of patients treated with 0.3 or $1 \mu\text{g/kg}$). The clinical response appeared to reach a plateau at a dose of $10 \mu\text{g/kg}$ (corresponding to 0.7 mg for 70 kg BW) and the clinical response at $10 \mu\text{g/kg}$ was higher than two lower dose cohorts, 0.3- $1 \mu\text{g/kg}$ and $3 \mu\text{g/kg}$ (corresponding to 0.21 mg for 70 kg BW) (Figure 2 in page 4). The doses of 0.25 mg, 0.5 mg and 0.75 mg were chosen for the phase 3 trial since the efficacy of 0.25 mg was proven in the IV development program for moderately emetogenic chemotherapy (MEC) and the absolute BA of oral administration was greater than 90%.

In phase 3 study PALO-03-13, the percentage of patients with CR 0-24 after moderately emetogenic chemotherapy was 73.5%, 76.3% and 74.1% for 0.25 mg, 0.50 mg and 0.75 mg oral doses, respectively (Figure 3 in page 5). All three oral doses 0.25, 0.5 and 0.75 mg for CR 0-24 was shown to be non-inferior to 0.25 mg palonosetron IV administration. Nonetheless, the dose-response relationship among 0.25 mg, 0.5 mg and 0.75 mg was not evident. For the prevention of delayed CINV as defined by CR 24-120, none of the three doses met the pre-specified non-inferiority criteria to 0.25 mg IV administration. (b) (4)

(For details, please, see the clinical review by Dr. Nancy Snow in Division of Gastroenterology Product).

In general, males showed a higher response CR 0-24 rate than females and in male patients, there was a slight increase in the percentage of patients with CR 0-24 with increasing dose (87.5%, 90.5% and 93.2% respectively for 0.25 mg, 0.50 mg and 0.75 mg), but not as consistently for CR 24-120. In female patients, no dose dependence was evident regarding the percentage of patients with CR; all treatment groups had similar CR 0-24 and 24-120.

The sponsor proposes to support the NDA by the sole pivotal efficacy trial considering similar dose-response curves for oral and IV palonosetron over the doses and similar ADME of palonosetron between

oral and IV administration as clinical safety and efficacy data of Aloxi for injection (NDA 21-372) are substantially applicable to oral palonosetron.

Reviewer's comments: Please, see the section 2.2.4.4. for discussion

1.1.1.2 2.2.4.2. 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

The dose-response relationship of oral administration for the prevention of CINV in acute phase was found to be similar for CR 0-24 to I.V. administration.

In a phase 2 study (study 2332), the dose-response relationship for CR 0-24 at the three higher doses was similar between oral and IV palonosetron while at the two lowest doses it seemed different. The sponsor noted an unexpectedly high response rate for the lowest 0.3-1 µg/kg dose cohort and it also seems that the 3 µg/kg had unexpectedly lower response rate compared to other dose cohorts. The percentage of free from emetic episodes up to 12hr post-dose was similar between the two low doses (69.2% for 0.3-1µg/kg and 71.9% for 3 µg/kg) while it was 88.6%, 80% and 84.8% for 10, 30, and 90 µg/kg, respectively. On the other hand the percentage of free from emetic episodes for the 3 µg/kg dose cohort dropped significantly to 25% between 12 to 24h while for other doses including the lowest dose cohort the percentage was 46.7 to 57.6%. This was unlikely due to pharmacokinetics since the plasma concentration of PAL at 24 h obtained from a subset of patients increased generally in a dose-proportional manner. Rather the difference in gender distribution in subjects may have contributed to either unexpected high or low response rate in two lower doses. The 3 µg/kg dose cohort had more females (52%) while the lowest dose 0.3-1 µg/kg dose cohort had a significantly less females (19%) compared to other dose cohorts (38-42%) and about 20% higher response rate in males than in females for all treatments was observed in phase 3 study. Furthermore, the response rate at 0.25 mg oral administration was comparable with IV administration within a study and across studies rendering the difference of the response rate at 3 µg/kg between oral administration and IV administration insignificant (Table 6).

Table 6. Patients with complete response by gender during 0-24 and 24-120 after start of chemotherapy

	Oral Palonosetron 0.25 mg (n=155)	Oral Palonosetron 0.50 mg (n=160)	Oral Palonosetron 0.75 mg (n=158)	I.V. Palonosetron 0.25 mg (n=162)
CR 0-24 (95% CI)				
Total	73.5% (65.8-80.2)	76.3% (68.8-82.5)	74.1% (66.4-80.5)	70.4% (62.6-77.1)
Male	87.5% (72.4-95.3)	90.5% (76.5-96.9)	93.2% (80.3-98.2)	82.2% (67.4-91.5)
Female	68.7% (59.3-76.8)	71.2% (62-79)	66.7% (57.1-75)	65.8% (56.4-74.2)
CR 24-120 (95% CI)				
Total	59.4% (51.2-67.1)	62.5% (54.5-69.9)	60.1% (52-67.7)	65.4% (57.5-72.6)
Male	72.5% (55.9-84.9)	85.7% (70.8-94.1)	77.3% (61.8-88)	75.6% (60.1-86.6)
Female	54.8% (45.3-64)	54.2% (44.8-63.4)	53.5% (44-62.8)	61.5% (52.1-70.2)

The proposed dose for prevention of acute (b) (4) CINV is 0.5 mg based on the analysis that 0.5 mg met the pre-specified non-inferiority criteria to 0.25 mg I.V. administration while dose of 0.25 mg is the lowest effective dose for prevention of acute CINV. However, 0.5 mg dose met the criteria only after post-hoc exploratory analysis by combination of historic I.V. controls to increase a number of subjects in

a comparator arm (For details, please see the clinical review by Dr. Nancy Snow). As such for the efficacy of oral palonosetron for the prevention of delayed CINV has not been demonstrated in a statistically meaningful manner and the dose of 0.25 mg is appropriate for the prevention of acute CINV as an effective dose.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation and the trial formulation are bioequivalent

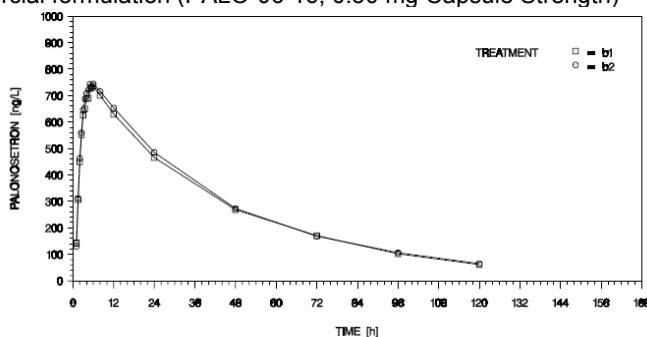
The to-be-marketed (TBM) formulation was modified from the phase 3 trial formulation to improve shelf-life stability (b) (4)

the formulation change was determined as SUPAC-IR level 2 change in a previous communication between the sponsor and the Agency.

The two formulations of 0.5 mg strength were compared in a two-way cross-over in vivo bioequivalence study. Thirty-six healthy subjects were enrolled (18 males and 18 females) and all of them completed the study. The ratio of AUC_t and AUC_∞ of PAL after administration of TBM and the phase 3 trial formulation (trial formulation hereafter) was 102.3% (90% CI: 98.9-105.9%) and 102.0% (90% CI: 98.6-105.6%), respectively and the ratio of C_{max} of PAL after administration of TBM and the phase 3 formulation was 103.7% (90% CI: 100.5-107.0%) (Figure 15, Table 22-23). As such the comparison of pharmacokinetic parameters met the bioequivalence criteria, 90% CI: 80-125% and the bioequivalence between TBM and trial formulation was demonstrated.

The bioequivalence was also demonstrated between trial formulation and the TBM for (b) (4) mg strength such that the ratio C_{max} and AUC_∞ of TBM to trial formulation were 98.4% (90% CI: 93.4-103.6%) and 102% (96.5-107.8) respectively.

Figure 15. Arithmetic Mean Concentration versus Time profiles for palonosetron Formulation b1= phase 3 clinical formulation and b2= commercial formulation (PALO-06-16, 0.50 mg Capsule Strength)



Source: Final Report PALO-06-16, Figure 11.4-1

The sponsor also conducted BE and absolute BA study with 0.75 mg strength, the highest phase 3 trial dose and the sponsor conducted a pivotal BE study with 0.5 mg strength because it is a proposed commercial dose.

Reviewer's comment: This reviewer think that this pivotal BE study for the commercial strength after conducting at a higher strength could have been waived because PK in the range is dose-proportional, the formulation is proportionally similar such that the formulation change due to the active ingredient content as a free base is less than 0.3% of total filled liquid weight which remained constant.

Table 22. PK parameters following a single-dose of 0.5 mg palonosetron oral capsule

Pharmaco-kinetic parameter Palonosetron [unit]		0.50 mg Palonosetron oral administration (formulation A) N=36	0.50 mg Palonosetron oral administration (formulation B) N=36
AUC ₀₋₄ [ng·h/L]	Mean (SD)	34076 (9874)	35106 (11012)
	Geo. Mean (Geo. SD)	32766 (1.33)	33530 (1.36)
	Median	33641	34981
	Minimum-Maximum		
AUC _{0-∞} [ng·h/L]	Mean (SD)	37099 (10141)	38176 (11698)
	Geo. Mean (Geo. SD)	35834 (1.30)	36555 (1.35)
	Median	36859	37627
	Minimum-Maximum		
C _{max} [ng/L]	Mean (SD)	785.241 (182.437)	810.176 (165.985)
	Geo. Mean (Geo. SD)	765.702 (1.25)	793.900 (1.23)
	Median	750.344	816.457
	Minimum-Maximum		
t _{max} [h]	Median	5.500	5.000
	Minimum-Maximum		
t _{1/2λz} [h]	Mean (SD)	36.248 (9.565)	37.264 (12.015)
	Median	34.378	35.262
	Minimum-Maximum		

Table 23. ANOVA CVs, point estimates, 90% confidence intervals for (log-transformed) palonosetron pharmacokinetic parameters; bioequivalence assessment (N=36 subjects)

Pharmacokinetic parameter palonosetron	Ratio	ANOVA CV [%]	Point estimate Test/Ref. ratio	90% Confidence interval
AUC _(0-t) [ng·h/L]	b ₂ / b ₁	8.7	102.3	98.9 - 105.9
AUC _(0-∞) [ng·h/L]	b ₂ / b ₁	8.7	102.0	98.6 - 105.6
C _{max} [ng/L]	b ₂ / b ₁	7.9	103.7	100.5 - 107.0

b1: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation A, clinical trial formulation)

b2: oral administration of 0.50 mg palonosetron as a softgel capsule (formulation B, proposed commercial formulation)

Source: Final Report PALO-06-16, Table 11.4-8.

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/s/

Hugo Gallo Torres
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