There were some weaknesses in the study. The exclusion criteria for this study excluded non-naïve patients who had moderate to severe nausea with prior chemotherapy. This could have led to bias with a more favorable response in the non-naïve group. However, the results do not demonstrate such a bias. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. However, this only occurred in five patients (2 in each of the palonosetron arms, and 1 in the ondansetron arm) Although the palonosetron seems to demonstrate some efficacy at 120 hours, some factors need to be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there may be issues with multiplicity. In addition, the comparator arm ondansetron is not indicated for prevention of CINV at 120 hours. Thus, what the results may be demonstrating is that the nausea from the chemotherapy is simply wearing off.

B. Safety

In general, the palonosetron was well tolerated in this study. There was a high rate of treatment adverse events in all three study arms. The rate was highest for the patients in the palonosetron 0.75 mg group. Cancer patients undergoing chemotherapy generally have a high rate of complications and co-morbid illness so the high rate is not unexpected. The number of serious adverse events was equal in all groups.
Adverse events of the blood and lymphatic system were most common in all treatment groups. These were equally spread out in all treatment groups and were secondary to chemotherapy. Following the blood and lymphatic disorders, headache was the most frequently reported adverse event. This also was balanced in all treatment arms. The majority of adverse events in all treatment arms were of mild intensity. The rate of severe adverse events was slightly higher in the palonosetron groups compared to the ondansetron group. The body system most frequently involved for severe adverse events was neutropenia (2/187, 1.1%) for the 0.25 mg palonosetron group and leukopenia (2/188, 1.1%) for the 0.75 mg palonosetron group. All the serious adverse events in the palonosetron group were judged to be unrelated or unlikely to be related to the study drug. One patient in the 0.75 mg palonosetron arm had to withdraw from the study due to debility. This adverse event was described as severe was thought to be possibly related to the study drug. There were 4 deaths reported during the study. Three occurred in the palonosetron 0.75 mg group and 1 in the ondansetron group. All deaths were judged as either unlikely or unrelated to the study drug.

No significant safety issues were seen in vital signs, blood, or urine laboratory parameters. The majority of patients had no change in ECG. The 0.25 mg palonosetron group had the least number of patients with worsening ECG's. There were no significant differences seen between treatment groups on QTc. The 0.25 palonosetron group showed a slight decrease in QTc in some intervals when corrected with Bazett's formula. Ondansetron arm had the highest QT/QTc mean maximum change in duration. A subset of patients had underwent Holter monitor. A similar percentage of abnormalities (15% vs 14.3%) were seen in the 0.25 mg palonosetron group compared to the ondansetron group.

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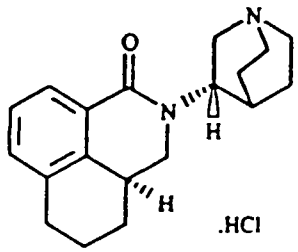
CLINICAL REVIEW

Medical Officer Review of NDA 21-372
Palonosetron

Date Submitted: 26 September 2002
Date Received: 27 September 2002
Date Assigned: October 1 2002
Date Completed: 6 June 2003

Applicant: Helsinn Healthcare SA
Via Pian Scairolo
6912 Pazzallo (Lugano) - Switzerland

Drug: Generic Name - Palonosetron
Molecular Weight - 332.87
Molecular formula - $C_{19}H_{24}N_2O.HCl$
Molecular structure –



Drug Class: 5-HT_3 antagonists

Formulation: 5-ml vial of palonosetron injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water

Route of Administration: Intravenous

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Clinical Review for NDA 21-372

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This medical officer recommends approval of palonosetron for the indication of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Approval is also recommended for prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Approval is not recommended for delayed prevention of nausea and vomiting associated of highly emetogenic cancer chemotherapy. This is a single dose regimen of 0.25 mg palonosetron administered intravenously which is being recommended for approval.

Helsinn Healthcare SA has submitted a New Drug Application (NDA) for the drug palonosetron. This new molecular entity is a member of the 5-HT_3 antagonists drug class. The applicant is requesting approval for the indications of the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy.

The applicant's submission demonstrates a favorable risk/benefit profile for this indication. This is based on three pivotal and one supportive study which demonstrated efficacy, and safety review of 18 palonosetron clinical trials. The efficacy data demonstrates that palonosetron is not inferior to other FDA approved medications for the indication of preventing nausea and vomiting associated with chemotherapy. The side effect profile is acceptable and comparable to other drugs in this class.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are some limitations of the safety data. While these limitations do not necessitate non-approval, they may addressed in Phase 4 studies and/or a risk management program. Because of concerns of QTc prolongation, the agency requested that 300 patients undergo Holter monitoring for 72 hours. The applicant had difficulty in obtaining this number due the high number of cancer patients who refused to undergo Holter monitor secondary to reasons of discomfort and inconvenience. The applicant has provided Holter data on 193 subjects for 22 hours. Although less than originally requested, this data is judged to be adequate to help establish safety. In addition, the applicant provided a retrospective analysis of ECGs obtained in Phase 1, and 2 studies. However, as with any approved new molecular entity, if an adverse event has a low enough incidence a signal may not be apparent in the safety database. Thus, to further augment what is known about palonosetron's cardiac safety profile, further pharmacokinetic/pharmacodynamic studies in which ECG and/or Holter parameters are assessed before and after drug administration may be helpful.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Palonosetron clinical development program includes a variety of clinical trials held in the United States, Europe, Mexico, Russia, and Canada. There were total of 18 clinical trials including intravenous and oral administration to chemotherapy induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV) patients or healthy volunteers, Phase 1 trials were performed in Japan, the United States and Europe. Phase 2 and 3 trials were conducted in North America, Mexico and Europe. The Phase 1 and 2 trials were conducted from 1993 to 1995 and administered by the manufacturer Syntex Laboratories. The Phase 3 trials were conducted by Helsinn and begun in 1999. In all the studies a total of 2360 patients received palonosetron. This development package contains two pivotal trials for prevention of acute and delayed nausea and vomiting following moderately emetogenic chemotherapy and one pivotal plus one supportive trial in patients receiving highly emetogenic regimens.

B. Efficacy

Palonosetron 0.25 mg given as an intravenous bolus 30 minutes prior to chemotherapy is efficacious in preventing moderately, and highly emetogenic CINV in the acute (0-24 hours) setting. The applicant also demonstrated efficacy for preventing moderately emetogenic CINV in the delayed setting (24-120 hours). Efficacy was not established for delayed prevention of highly emetogenic CINV.

Assessment of efficacy for moderately emetogenic chemotherapy is based on two adequate and well controlled pivotal Phase 3 efficacy trials, PALO-99-03 and PALO-99-04, that used standard, accepted efficacy and safety endpoints, and FDA-approved active comparators. The primary efficacy parameter was complete response (defined as no emetic episode and no rescue medication) within the first 24 hours after chemotherapy. This endpoint has been used as the basis for approval of other medications for this indication. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron and dolasetron. The lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta. These trials also demonstrated that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) of moderately emetogenic CINV.

In regards to highly emetogenic chemotherapy, the assessment of efficacy is based on the adequate and well controlled pivotal Phase 3 efficacy trial PALO-99-05 and PALO-00-01(a Phase 2 supportive trial). PALO-99-05 used standard, accepted efficacy and safety endpoints, and FDA-approved active comparators. The trial design and endpoints were identical to PALO-99-03. The results demonstrated the non-inferiority of both palonosetron 0.25 mg and 0.75 mg when compared to ondansetron. Again, the lower limit of the 97.5% confidence interval for the difference in complete response rates between the ondansetron and the palonosetron groups during the first 24 hours after chemotherapy was above the preset 15% delta. However, these trials did not establish that palonosetron 0.25 mg was efficacious for delayed prevention (24-120 hours) of highly emetogenic CINV. While the results did show non-inferiority to the comparator arms, the comparator drug is not indicated for delayed prevention of CINV. Thus, in order to show efficacy the study drug should demonstrate superiority to the comparator drug. It did not do so. There was no statistically significant difference between palonosetron and ondansetron for

delayed prevention of highly emetogenic CINV. The evidence the applicant has presented does not substantiate an efficacy claim for this indication.

C. Safety

The clinical Integrated Summary of Safety (ISS) of this NDA includes all safety data collected in 3137 unique subjects enrolled in the 18 palonosetron clinical trials of whom 2360 received palonosetron. Review of this data demonstrates that palonosetron when given as single dose prior to chemotherapy was well tolerated. A wide dose range was studied (less than 0.25 mg to approximately 6 mg). No deaths occurred that were attributable to the study drug. An extensive review of cardiac safety was conducted which included analysis of ECG (performed in 2172 subjects) and Holter tracings (143 subjects) using high-resolution methods and a centralized review by a blinded cardiologist. No dose response on QTc interval was observed. The cardiac safety profile for palonosetron is similar to that of other drugs in this class. No signal for adverse effects of the study drug on laboratory or vital signs was detected.

The most common adverse reactions seen with palonosetron (≥ 2%) were constipation and headache. Incidences of these reactions were similar across all palonosetron dose groups and the active comparator 5-HT_3 receptor antagonists, ondansetron and dolasetron. All other adverse reactions were seen at incidences equal to or less than 1%. Nearly all episodes of constipation were self-limiting and not severe. However, two subjects who took palonosetron in Phase 2 trials suffered from constipation that required treatment in a hospital. The current package insert for another already approved 5-HT_3 antagonists ondansetron states that constipation occurred in 11% of chemotherapy patients receiving multiday ondansetron. The package insert for dolasetron reports a 3.2% incidence of constipation in chemotherapy patients.

The safety database is limited in several ways. Although the numbers of patients was relatively large, a signal could not have been detected for an adverse event that has a low incidence. The majority of subjects did not have an ECG performed at CMAX when cardiac changes may be most likely to occur. The applicant was unable to recruit the requested 300 patients to undergo Holter monitoring. Despite these limitations, the applicant was able to demonstrate safety of palonosetron.

D. Dosing

The applicant proposes a dose of 0.25 mg palonosetron intravenously given over 30 seconds, 30 minutes prior to chemotherapy being dosed. This is based on the pivotal studies that demonstrated that the 0.25 mg dose of palonosetron was more efficacious than the 0.75 mg dose. Palonosetron is to be supplied as a single-use sterile, clear, colorless solution in glass 5 ml vials ready for intravenous injection.

In Phase 1 and Phase 2 trials, palonosetron was shown to be well tolerated at 30-second IV bolus doses up to 90 µg/kg. The maximum dose tested was approximately 6 mg as a fixed dose. The selection of doses for Phase 3 trials was based primarily on efficacy data. Study 2330 was a Phase 2 study in which subjects received one of the following doses of palonosetron: 0.3, 1, 3, 10, and 30 µg/kg . Based on efficacy data from this study, the 3-µg/kg and 10-µg/kg doses were selected as the doses to evaluate in Phase 3 trials. These were converted to the fixed doses of 0.25 mg and 0.75 mg in order to simplify dosing regimens in clinical practice.

E. Special Populations

The applicant has adequately evaluated the effects of gender on efficacy and safety. For the Phase 3 studies the majority of subjects were female. Subgroup analyses by gender demonstrated that male subjects had a trend for greater complete response rates during the first

24 hours after chemotherapy than female subjects. For the moderately emetogenic trials 90% of males had a complete response versus 67% for females. For the highly emetogenic trial 67% of males had a complete response versus 52% of the females. In regards, to safety no relevant difference was seen in adverse events, severe adverse events, or deaths based on gender.

Twenty three percent (316) of the 1374 adult cancer patients in clinical studies of palonosetron were over the age of 65 years. Review of this data reveals no overall differences in safety or effectiveness between these subjects and the younger subjects. There was a slightly increased incidence of selected cardiovascular AEs among older subjects than younger subjects but these AEs were not clearly related to the study drug. No alteration of the dose or special monitoring is required for geriatric patients.

There was a relative paucity of Black and Asian subjects relative to the U.S. population. The Phase 3 trials consisted of the following races:

- 65% Caucasian
- 31% Hispanic
- 1% Asian
- 3% Black
- 0.3% Other

No relevant differences in safety or effectiveness were seen based on race.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The applicant Helsinn Healthcare SA has submitted a New Drug Application (NDA) for the new molecular entity palonosetron. It does not have trade name established as of yet. Palonosetron is a new molecular entity that belongs to the drug class of 5-HT_3 antagonists. The applicant's proposed indication is for prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy. The proposed dose is a single 0.25 mg sterile injection administered intravenously. It is to be used in adults 18 years and older. Pediatric studies are still ongoing.

B. State of Armamentarium for Indication(s)

There are currently three 5-HT_3 antagonists approved for treatment of nausea and vomiting in the United States. Zofran (odansetron hydrochloride) was approved January 4, 1991. It is currently indicated for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly-emetogenic chemotherapy (cisplatin dose >50 mg/m^2). Its label states that efficacy of the single dose beyond 24 hours in these patients has not been established. Anzemet (dolasetron mesylate monohydrate) was approved September 11, 1997. It is currently indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Kytril (granisetron) was approved March 11, 1994. It is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. All three of these 5-HT_3 antagonists are available in injectable and oral formulations.

C. Important Milestones in Product Development

Palonosetron was initially developed by Syntex Laboratories Inc. The first Investigational New Drug (IND) clinical protocol (IND [redacted]) was submitted to the FDA on June 2, 1992. This was a Phase 1 escalating dose tolerance study involving the intravenous formulation of palonosetron. The target indication was "treatment of cancer chemotherapy induced nausea and emesis". On July 15, 1992, the Agency placed a clinical hold on the initial filing of IND [redacted] until additional preclinical hemodynamic and cardiac conduction data were provided. This data was supplied by Syntex Laboratories on November 9, 1992, and on December 24, 1992, the Agency notified the sponsor by letter that the clinical hold had been lifted. Please see the pharmacology/toxicology review for details.

Syntex Laboratories also [redacted] IND [redacted] In 1994, the target indication was expanded to [redacted] Between 1992 and 1995 Syntex Laboratories conducted five Phase 1 clinical trials and five Phase 2 clinical trials for both the oral and intravenous formulation of palonosetron. The last of the Phase 2 trials was completed in 1995.

In 1998, Helsinn Healthcare SA (based in Lugano, Switzerland) acquired palonosetron from Syntex Laboratories. On June 23, 1998, all rights and responsibilities related to IND's (IV palonosetron), and were transferred from Syntex Inc. to Helsinn Healthcare SA. This was conveyed to the FDA by letter on August 3, 1998. Helsinn decided to focus development solely on the indication for chemotherapy induced nausea and vomiting (CINV) and on the intravenous formulation.

On March 10, 1999, an End-of Phase 2 Meeting between Helsinn and the FDA was held with a follow-up teleconference held April 29, 1999. During the meeting the target indication was changed from to "prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy. " The Agency and Helsinn agreed that the trials PALO-99-03 and PALO-99-04 (both involving moderately emetogenic chemotherapy) and PALO-99-05 (involving highly emetogenic chemotherapy), would serve as the pivotal Phase 3 studies for efficacy. To support a claim for palonosetron in the prevention of nausea and vomiting due to highly emetogenic chemotherapy the Agency agreed with the applicant's plan to use Study PALO-99-05 (a comparison of palonosetron to ondansetron and historical control) and Study 2330 (a Phase 2 efficacy, safety, pharmacokinetics trial). The FDA also deemed acceptable the use of historical controls with a 15 % delta for these non-inferiority studies. At the follow-up teleconference, it was agreed on the inclusion of both chemotherapy naïve and non-naive patients in the efficacy trial. In addition, both parties agreed to the primary efficacy outcome measure.

Another issues raised at the End of Phase 2 meeting was the concern whether palonosetron was metabolized to a metabolite with potential cardiovascular toxicity.) On November 8, 2001, a FDA Preclinical Cardiovascular Safety meeting was held. In response to these concerns, a series of in vitro and in vivo metabolic studies were conducted by Helsinn which demonstrated that this metabolite was not present.

In late 1999, Helsinn submitted Pivotal efficacy protocols for Special Protocol Assessment. The FDA replied to these assessments in January 2000. The FDA's response contained the following pertinent points:

- Agreed with the definition of the primary efficacy endpoint "complete response"
- Agreed to the uses of concomitant dexamethasone
- Suggested a subset of patients should undergo Holter monitoring (the applicant agreed and conducted trials)

A teleconference was convened October 18, 2001, to discuss statistical concerns about the Special Protocol Assessment. There were no historical placebo complete response efficacy data for placebo use with dexamethosone for acute CINV. The applicant suggested using meta-analysis to predict the dexamethasone effect on historical placebo and the agency agreed this may be the best approach.

A final Pre-NDA meeting was held April 10, 2002. At this meeting, the applicant submitted multiple questions relating to submission format as well as various chemistry, toxicology and clinical issues. Several pertinent clinical issues were discussed with the applicant. The Agency noted that although there was a response to delayed emesis this was a secondary and not a primary endpoint. It was also noted that one investigator from a single trial initially conducted by Syntex was disqualified by the FDA. This investigator had violations that

did not affect data integrity. The Agency agreed with Helsinn's approach to exclude the efficacy data from this investigator but to include the safety data. The conclusion of the meeting was that the NDA was ready for submission. On September 27, 2002 the NDA was submitted to the FDA.

D. Other Relevant Information

Palonosetron is not approved in the United States for any other indication. It not approved in any foreign country for this or any other indication. It is currently under development for the European market.

E. Important Issues with Pharmacologically Related Agents

There are currently three approved $5HT_3$ receptor antagonists approved for use in the United States. They consist of Zofran(ondansetron hydrochloride), Kytril(granisetron), and Anzemet (dolasetron mesylate monohydrate). This class of medications is widely used for CINV. As a class, they are well tolerated and in general, safe and efficacious. Although they have been shown to affect ventricular depolarization and repolarization, no significant safety concerns have been introduced regarding this pharmacologic class since their introduction into the market.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The chemical review was conducted by Dr. Marie Kowblansky. She stated that from a chemistry standpoint this NDA could be approved pending completion of a satisfactory GMP inspection. In addition, she deferred to the toxicology reviewer a decision regarding whether the impurities [redacted] are qualified to be present at the of [redacted], as proposed by the applicant. The toxicology review was conducted by Dr. Yosh Chopra. He has stated in his review that the level of impurities was acceptable that there are no outstanding toxicological issues that interfere with approval.

The statistics reviewer was Dr. Stella Grosser. The primary issue from a statistical standpoint was the minimization allocation procedure used for randomization in the pivotal studies. Although she cited several drawbacks to this method of allocation, she concludes there is sufficient evidence that palonosetron 0.25 mg is efficacious in the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer chemotherapy. She also found that there is also sufficient evidence that it is efficacious in the prevention of delayed emesis following moderately (but not highly) emetogenic chemotherapy.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Information about the pharmacokinetics of palonosetron is based on 14 Phase 1 to 3 clinical studies. Generally, this data follows a two compartment open model with first order elimination. After intravenous infusion of palonosetron, there is an initial slow decline in plasma concentrations. Following this initial decline, several subjects had secondary peaks in drug levels two to four hours post-dosing. These were thought to be due to entero-hepatic re-circulation. The mean time to maximum plasma concentration (T_{max}) is three to four hours. The mean terminal elimination half-life of palonosetron was 37.4 hours. However, some patients had half-lives of over 100 hours. Area under the curve (AUC) was dose –proportional when given in standard

dosages. Palonosetron has a large volume of distribution with an estimated median volume of the central compartment of 632 liters (584 to 680 liters) or 6.9 to 7.9 l/kg. About 62% of palonosetron is bound to plasma proteins.

Palonosetron is metabolized primarily via CYP2D6, with a lesser role played by CYP3A and CYP1A. Fifty percent of the palonosetron is broken down into two major metabolites: N-oxide-palonosetron (M9) and 6-S-hydroxy-palonosetron (M4). These metabolites have at least 100-fold less 5-HT_3-antagonist activity than palonosetron. Studies demonstrated that subjects who were either poor or extensive metabolizers of CYP2D6 substrates did not have significant differences in clinical pharmacokinetic parameters when given palonosetron. Neither Palonosetron nor its metabolites inhibit or induce cytochrome P450 isozymes at clinically relevant concentrations.

During development, concerns were raised about ——— a compound with 5-HT_3 receptor antagonist activity and the last intermediate in the synthesis of palonosetron. ——— was associated with an arrhythmia in a normal volunteer participating in a Phase 1 trial. The applicant conducted several biotransformation studies that demonstrated that ——— is not formed from palonosetron in humans. In addition, the content of ——— in the drug product is %. This is 30,000 fold less than the safety margin for this compound.

Palonosetron is eliminated from the body with an apparent mean elimination half-life of approximately 40 hours in healthy volunteers (mean range 30.8 to 54.1 hours). Mean total clearance ranged from 1.11 to 3.90 ml/min/kg. After a single intravenous dose, 80% of the palonosetron was recovered within 144 hours in the urine. Approximately 40% of the palonosetron was excreted renally unchanged.

The applicant submitted data describing the pharmacokinetics in various subgroups. A population PK study was conducted involving 688 cancer patients. This demonstrated that race, gender, and age do not affect clearance of palonosetron. In patients with severe renal impairment, there is a reduction in renal clearance of the drug but total body clearance is unchanged. The AUC of the metabolite M9 increases 3-4 fold but this metabolite does not show any clinical activity. In patients with hepatic impairment, total body clearance and AUC values were unchanged from healthy subjects. However, patients with severe liver disease had a lower C_{max} than other groups.

Palonosetron when given as a single 0.75-mg bolus injection did not affect steady state pharmacokinetic parameters of metoclopramide. Metoclopramide, dosed to steady state, did not affect the pharmacokinetic parameters of palonosetron given as a single 0.75 mg

B. Pharmacodynamics

Cancer chemotherapy agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine thus activating 5-HT_3 receptors located on the vagal nerve and triggering the vomiting reflex. Palonosetron is a highly selective 5-HT_3 receptor antagonist. It possesses a strong affinity for this receptor and thus blocks the vomiting reflex. As with other 5-HT_3 antagonists, the dose-response curve is flat and efficacy reaches a plateau. In Phase 2 studies, the lowest effective IV dose of palonosetron was 3-μg/kg, corresponding to a fixed-dose equivalent of 0.25 mg, in CINV patients.

Like other 5-HT_3 antagonists, palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. Effects on cardiac conduction and arrhythmic episodes (no *Torsades des Pointes*) were noted *in vivo* in anesthetized rabbits at 10 mg/kg but not at lower doses in any other species. As these effects

were seen at very large, supratherapeutic doses or concentrations, clinical effects are considered very unlikely in humans. Preclinical data did show prolonged action potential duration *in vitro* in canine Purkinje fibers. This led Helsinn to conduct a retrospective review of the effect of palonosetron on ECG intervals. Seven Phase 1 and Phase 2 studies were included in this a retrospective analysis. High-resolution analysis of ECG data was done by a cardiologist at a central ECG laboratory. The conclusion was that palonosetron has no effect on QTc or other ECG intervals. This process was repeated prospectively for the three pivotal studies. All subjects underwent ECG and these were in turn reviewed at a central ECG laboratory. Again, no changes in intervals were noted from the ECG in any of these pivotal trials. Please see the safety section for a full discussion of ECG findings.

IV. Description of Clinical Data and Sources

A. Overall Data

Palonosetron clinical development program includes a variety of clinical trials held in the United States, Europe, Mexico, Russia, and Canada. There were a total of 18 clinical trials including intravenous and oral administration to CINV and PONV patients or healthy volunteers, Phase 1 trials were performed in Japan, the United States and Europe. Phase 2 and 3 trials were conducted in North America, Mexico and Europe. The Phase 1 and 2 trials were conducted from 1993 to 1995 and administered by Syntex. The Phase 3 trials were conducted by Helsinn and begun in 1999. This development package contains two pivotal trials for prevention of acute and delayed nausea and vomiting following moderately emetogenic chemotherapy and one pivotal plus one supportive trial in patients receiving highly emetogenic regimens.

B. Tables Listing the Clinical Trials

The following table displays the number of trials conducted to support this NDA. Two trials were not included in the Integrated Safety Database because they were multiple dose regimens of palonosetron and thus were not consistent with the indication for which the applicant is seeking. The results from these two trials are supplied by the applicant in a separate section of the NDA.

TABLE 1: Summary of Clinical Trials Supporting Palonosetron NDA

Trials Included in Integrated Safety Database:	**Number of Trials**
Phase 1 [2216, 2092, 0100, 0101, 2336, PALO-99-39, PALO-99-35, PALO-99-51]	8
Phase 2 [2330, 2120, 2332, 2500, 2502]	5
Phase 3 Controlled [PALO-99-03, PALO-99-04, PALO-99-05]	3
Trials NOT Included in Integrated Safety Database:	
Phase 1 [PALO-99-34]	1
Phase 3 Uncontrolled [PALO-99-06]	1

(Reference: Vol. 1, pg. 108, Table 3.8.2:1)

Table 2 displays the summary of the three pivotal and one supportive Phase 3 Efficacy trials in CINV patients.

TABLE 2: Summary of Pivotal and Supportive Efficacy Trials in CINV Performed with IV Palonosetron

Trial	Indication	Palonosetron Doses	Comparator	ITT Dose[a] Groups	Duration of Treatment	Trial Date
PALO-99-03	Moderately emetogenic CINV	0.25, 0.75 mg IV bolus dose	Ondansetron 32 mg	Palo 0.25 mg: 189 Palo 0.75 mg: 189 Onda 32 mg: 185	Single dose	August 2000 – October 2001
PALO-99-04	Moderately emetogenic CINV	0.25, 0.75 mg IV bolus dose	Dolasetron 100 mg	Palo 0.25 mg: 189 Palo 0.75 mg: 189 Dola 100 mg: 191	Single dose	May 2000 – October 2001
PALO-99-05	Highly emetogenic CINV	0.25, 0.75 mg IV bolus dose	Ondansetron 32 mg	Palo 0.25 mg: 223 Palo 0.75 mg: 223 Onda 32 mg: 221	Single dose	July 2000 – December 2001
PALO-00-01[b] (Study 2330)	Highly emetogenic CINV	Fixed Dose < 0.1, 0.25, 0.75, 2, 6 mg Weight-Based 0.3, 1.0, 3, 10, 30, 90 µg/kg IV bolus dose	Historical placebo: no active comparator	Fixed Dose[c] < 0.1 mg: 30 0.25 mg: 27 0.75 mg: 24 2 mg: 27 6 mg: 46 Weight-Based[b] 0.3-1.0 µg/kg: 31 3 µg/kg: 25 10 µg/kg: 25 30 µg/kg: 26 90 µg/kg: 47	Single dose	May 1994 – April 1995

[a] Intent-to-treat

[b] PALO-00-01 was an efficacy re-analysis of Study 2330 using fixed dose conversions from the original weight-based doses and comparison to historical placebo, and is considered supportive.

[c] Based on the Helsinn ITT data set.

Source: Final Study Reports: PALO-99-03; PALO-99-04; PALO-99-05, PALO-00-01.

(Reference: Vol. 1, Pg. 112, Table 3.8.2:3)

The first three trials were active controlled trials that evaluated the efficacy of palonosetron, administered as a single IV bolus dose over 30 seconds, 30 minutes prior to chemotherapy for the prevention of nausea and vomiting associated with moderately emetogenic (PALO-99-03 and PALO-99-04) and highly emetogenic (PALO-99-05) cancer chemotherapy. PALO-00-01 is a re-analysis of efficacy data from Study 2330. This study, a Phase 2 supportive trial for highly emetogenic CINV, was a dose-response study and did not employ a comparator agent. Since the use of placebo is not ethically acceptable in the CINV subject population, a literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data.

The applicant also included three more studies in this submission. These were described in the Integrated Summary of Efficacy (ISE) but were not considered key trials because they were either discontinued early, used oral palonosetron, or were open label. These studies are displayed in the following table.

TABLE 3: Summary of Other Efficacy Trials in CINV Described in the ISE

Study Number	Indication	Palonosetron Doses	Comparator	ITT Dose Groups	Duration of Treatment	Trial Date
PALO-99-06[a]	Moderately or highly emetogenic CINV	0.75 mg IV bolus dose	None	0.75 mg: 875	Repeat dose (up to 9 cycles)	July 2000 – January 2002
2120[b]	Highly emetogenic CINV	3 µg/kg IV bolus dose	None	3 µg/kg: 2	Single dose	December 1993 – March 1994
2332	Highly emetogenic CINV	0.3, 1, 3.0, 10, 30, 90 µg/kg Oral solution	None	169: 0.3-1 µg/kg: 32 3.0 µg/kg: 33 10 µg/kg: 35 30 µg/kg: 33 90 µg/kg: 36	Single dose	April 1994 – March 1995

[a] Open label study of subjects who participated in one of the three pivotal Phase 3 trials (PALO-99-03, PALO-99-04, PALO-99-05).
[b] Discontinued early by the sponsor due to poor enrollment
Source: Final Study Reports: PALO-99-06; 2120, and 2332.

(Reference: Vol. 1, pg. 113, Table 3.8.2:4)

C. Postmarketing Experience

Since palonosetron is a new molecular entity and is not approved in any country, there is no postmarketing experience.

D. Literature Review

The applicant submitted 12 references with this NDA. These include original research in peer reviewed journals a well as review articles and excerpts from textbooks. A complete list of references can be found in Appendix.

V. Clinical Review Methods

A. How the Review was Conducted

The applicant submitted three pivotal and one supportive trial to demonstrate efficacy in CINV patients. Study design, objectives, endpoints, efficacy and safety results as well as all other aspects of each of these trials were reviewed in detail. Three other trials were described in the ISE and these were reviewed as well.

Data from 15 other trials were reviewed for safety analysis. Thirteen of these trials were pooled and comprised the Integrated Review of Safety.

B. Overview of Materials Consulted in Review

A total of 381 volumes of written material was submitted with this NDA. This was not an electronic submission. However, the applicant submitted electronic data that included case. report forms and safety and efficacy data.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Because this is a new molecular entity with trials conducted at a variety of clinical sites an audit was requested from the Department of Scientific Investigations (DSI). In consultation with the statistician Dr. Stella Grosser, five investigative sites were provided to DSI as potential sites for auditing. The location, protocol involved, the principal investigator, indication, and reasons for auditing are cited below.

1. Site ID #044 - Protocol 99-03,
Krankenhause Paulinenstift
Geisenheimer St. 10
65187 Weisbaden, Germany
Principal investigator - Emir Selak
Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate emetogenic chemotherapy
Reason: This site had a large number of patients enrolled in a pivotal trial.

2. Site ID #221-Protocol 99-03
Arkhangelsk Regional Oncology Center
145/A Obvodniy Canal
163045 Arkhangelsk, Russia
Principal Investigator - Alexander Arkhipov
Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate emetogenic chemotherapy
Reason: This site reported a higher efficacy rate compared to other sites

3. Site ID #501-Protocol 99-04, 99-05
Pasco Pinellas Cancer Center
5347 Main Street suite 303
New Port Richey, FL 34652 U.S.A.
Principal Investigator - Julio Hajdenberg
Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate and highly emetogenic chemotherapy
Reason: This site had the largest number of patients enrolled in the United States.

4. Site ID #212 - Protocol 99-03, 99-05
St. Petersburg Oncology Center
3/5 Voraya
Berezovaya al,
St.Petersburg,
197022, Russia
Principal investigator -Georgiy Manikhas
Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate and highly emetogenic chemotherapy
Reason: This site reported a high efficacy rate compared to other sites

5. Site ID#820- Protocol 99-04, 99-05
Hospital Gerneral Mexico
Dr. Balmis 148 Col. Doctores
CP. 06720 Mexico City
Mexico D.F.
Principal investigator - Jazmin Figureoa
Indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate and highly emetogenic chemotherapy
Reason: This site had a large number of patients enrolled.

DSI selected the first four of these sites for auditing (Site ID #'s 044, 221, 501, and 212). In addition to DSI audits, all case report forms for patients with serious adverse events were reviewed. A random sampling of other case report forms were reviewed and compared with the applicants final data. [No discrepancy was found between the case report forms and the applicant's data.]

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were performed within accepted ethical standards. They were conducted under the auspices of an Institutional Review Board. Each patient signed a detailed informed consent that explained the possible complications of participation in detail. All the pivotal and supportive trials were conducted according to the last version of the Declaration of Helsinki (Edinburgh, 2000), the rules of the ICH Guidelines (1997), and U.S. FDA Regulations 21 CFR Parts 50.20-50.27 (1998).

One investigator ____ was disqualified. This investigator was involved in a trial 2330 supervised by Syntex prior to Helsinn's involvement with palonosetron. The data from this investigator was not included in analysis. Another investigator, ____ located in ____ was noted to not have adhered to applicable statutory requirements and FDA regulations governing clinical investigations. ____ was an investigator in Studies Palo-99-0-4, Palo-99-05, Palo-99-06. The sponsor discontinued ____ participation in these studies after an internal audit determined that information from this site was unreliable. This prompted a DSI site inspection in June 2002. During this site visit, it was noted that the investigator did not get proper informed consent for some subjects and failed to properly record some adverse events. This site had 14 subjects enrolled in Palo-99-04, 6 subjects in Palo-99-05 and 17 subjects in Palo-99-06. These subjects were excluded from the efficacy analysis.

E. Evaluation of Financial Disclosure

Upon review of the financial disclosure by investigators, there were no financial improprieties that would cast doubt on the findings of this study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Palonosetron 0.25 mg given as an intravenous bolus 30 minutes prior to chemotherapy is efficacious in preventing moderately, and highly emetogenic CINV in the acute (0-24 hours) setting. The applicant also demonstrated efficacy for preventing moderately emetogenic CINV in the delayed setting (24-120 hours). Efficacy was not established for delayed prevention of highly emetogenic CINV.

B. General Approach to Review of the Efficacy of the Drug

Efficacy was assessed by reviewing the data for three pivotal studies (PALO-99-03, PALO-99-04, PALO-99-05), one supportive (2330; efficacy re-analysis of 2330 versus historical placebo is provided in report PALO-00-01), one providing evidence of efficacy after repeated cycles (PALO-99-06), and one providing ancillary data with the oral route of administration (2332). The three Phase 3 pivotal trials are double-blind, randomized clinical trials in which palonosetron 0.25 mg or 0.75 mg was administered as a single IV bolus dose given over 30 seconds, 30 minutes prior to administration of moderately emetogenic (PALO-99-03, PALO-99-04) and highly emetogenic (PALO-99-05) chemotherapy.

All the pivotal studies were reviewed in detail. In addition to the information presented below, a separate review that details the results of studies 99-04 ,99-05 individually and serves as a stand alone document. The three Phase 3 pivotal trials are double-blind, clinical trials in which palonosetron 0.25 mg or 0.75 mg was administered as a single IV bolus dose given over 30 seconds, 30 minutes prior to administration of moderately emetogenic (PALO-99-03, PALO-99-04) and highly emetogenic (PALO-99-05) chemotherapy.

The study methods for three pivotal studies are nearly identical only differing in the comparator drug and the type of chemotherapy. Thus, they will be presented as a group with differences being noted.

The following tables display the pivotal studies relating to palonosetron.

TABLE 4: Summary of Pivotal and Supportive Efficacy Trials in CINV Performed with IV Palonosetron

Trial	Indication	Palonosetron Doses	Comparator	ITT Dose Groups	Duration of Treatment	Trial Date
PALO-99-03	Moderately emetogenic CINV	0.25, 0.75 mg IV bolus dose	Ondansetron 32 mg	Palo 0.25 mg: 189 Palo 0.75 mg: 189 Onda 32 mg: 185	Single dose	August 2000 – October 2001
PALO-99-04	Moderately emetogenic CINV	0.25, 0.75 mg IV bolus dose	Dolasetron 100 mg	Palo 0.25 mg: 189 Palo 0.75 mg: 189 Dola 100 mg: 191	Single dose	May 2000 – October 2001
PALO-99-05	Highly emetogenic CINV	0.25, 0.75 mg IV bolus dose	Ondansetron 32 mg	Palo 0.25 mg: 223 Palo 0.75 mg: 223 Onda 32 mg: 221	Single dose	July 2000 – December 2001
PALO-00-01[a] (Study 2330)	Highly emetogenic CINV	Fixed Dose < 0.1, 0.25, 0.75, 2, 6 mg Weight-Based 0.3, 1.0, 3, 10, 30, 90 µg/kg IV bolus dose	Historical placebo: no active comparator	Fixed Dose[b] < 0.1 mg: 30 0.25 mg: 27 0.75 mg: 24 2 mg: 27 6 mg: 46 Weight-Based[b] 0.3-1.0 µg/kg: 31 3 µg/kg: 25 10 µg/kg: 25 30 µg/kg: 26 90 µg/kg: 47	Single dose	May 1994 – April 1995

[a] PALO-00-01 was an efficacy re-analysis of Study 2330 using fixed dose conversions from the original weight-based doses and comparison to historical placebo, and is considered supportive.

[b] Based on the Helsinn ITT data set.

(Refernce:Source: Final Study Reports: PALO-99-03; PALO-99-04; PALO-99-05, PALO-00-01.

Study 2330 was a Phase 2 supportive trial for highly emetogenic CINV. It was a dose-response study and did not employ a comparator agent. A literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data, since it is not ethical to administer placebo in the setting of CINV.

B. Detailed Review of Trials by Indication

1. Objectives

The primary objective of the studies PALO-99-03, PALO-99-04 and PALO-99-05 was to compare the efficacy of single IV doses of palonosetron 0.25 mg or 0.75 mg, to ondansetron 32 mg IV or dolasetron 100 mg IV in preventing moderately or highly emetogenic CINV.

2. Study Design and Methodology

This was a double-blind clinical study to compare single IV doses of palonosetron 0.25 mg or 0.75 mg, and ondansetron 32 mg IV or dolasetron 100 mg IV, in the prevention of moderately or highly emetogenic chemotherapy-induced nausea and vomiting. The comparator drugs are FDA approved medications that are indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting in the first 24 hours after chemotherapy.

The doses of ondansetron and dolasetron are the standard doses used in clinical practice. The table on the following page lists the study procedures for the pivotal studies.

TABLE 5 : STUDY FLOW CHART

	Screening Study Day -7 to 0	Study Day 1	Study Day 2[a]	Study Day 5[b]	Study Day 6-8	Study Day 15+/- 1[c]	Study Day 15-28[d]
	Visit 1	Visit 2	Visit 3	Tele 1	Visit 4	Tele 2	Visit 5
Informed Consent	X						
Inc/Excl demographic	X						
Karnofsky's Index	X						
Past Medical History	X						
Blood Chemistry	X		X		X		
CBC with differential	X		X		X		
Urinalysis	X		X		X		
Pregnancy Test[e]	X						
Randomization[f]	X						
Study Medication		X					
Chemotherapy[g]		X					
Dexamethasone[h]		X					
Physical Exam	X		X[i]		X[i]		X
Vital Signs and Weight	X		X		X		X
12-Lead ECG	X	X[j]	X		X		
Efficacy Parameters[k]		X	X	X	X		
FLIE Questionnaire	Instruction		X[l]	X[m]	collection		
Patient's Diary and VAS[n]	Instruction	Filled in from Study Day 1 to Study Day 5 daily			collection		
Concomitant Meds	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Holter Monitoring[o]	initiation		termination				
PK [p](Holter Patients)		X			X[p]		
PK [p](selected non-Holter patients)		X	X		X[p]		X

a) Post study medication administration
b) If Study Day 5 was a holiday or weekend day, patients were contacted the previous/next business day
c) If patient was scheduled for a clinic or hospital visit on this day, this information was obtained at that time
d) Only for those patients who enrolled in the open label protocol (PALO-99-06)
e) For females of childbearing potential only
f) After all inclusion/exclusion criteria were met the patient could be randomized to one of three treatment groups
g) 30 minutes post study mediation administration
h) For PALO-04, and PALO-05 at the discretion of the investigator, dexamethasone, 20 mg IV could be given 15 minutes before the start of chemotherapy(in the event of a shortage of IV dexamethasone, a single 20 mg oral dose of dexamethasone or a single 125 mg IV dose of methylpredisolone could be given).
i) Limited physical examination only on these days
j) 15 minutes post study medication administration in Holter patents only
k) See below for efficacy parameters and assessments
l) Referring to Study Day 1 (0-24 hours)
m) Referring to Study Days 2-4 (24-96 hours)
n) Filled in on Study Days 1-5 collected on Study Day 6-8
o) Patients at selected sites were to have Holter Monitoring from at least 2 hours before to at least 22 hours after start of study medication administration
p) Blood sampling for pharmacokinetic analysis

(Reference Table 5.5-a , Page 38, volume 135)

Screening Study Day -7 to 0 (Visit 1)

Patients signed an informed consent and then had their demographic information recorded. The investigator performed an initial history and physical examination. Eligibility criteria were examined and the patient underwent laboratory studies. This included 12 lead ECG, blood chemistry, complete blood count and urinalysis. A urine pregnancy test was done for females of childbearing potential as well. Patients were instructed on how to use the diaries to record nausea and episodes of emesis. If patients were randomized to get a Holter monitor, this was started two hours before the start of the study medication administration.

Study Day 1 (Visit 2)

Study Day 1 was defined as the day the patient received a single dose of a major chemotherapeutic agent that was considered the most emetogenic (as classified by Hesketh et al., The Oncologist 1999:4:191-196). The administration of this agent was not to extend greater than 4 hours.

Each patient was randomized to 1 of 3 treatment groups

- Palonosetron 0.25 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Palonosetron 0.75 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy
- Dolasetron 100 mg given as a single dose over 30 seconds, 30 minutes prior to chemotherapy or Ondansetron 32 mg given as IV infusion over 15 minutes, 30 minutes prior to chemotherapy

Randomization was blocked by groups of three. It was stratified by gender (male or female), previous chemotherapeutic history (naive, non-naïve). A dynamic adaptive stratification type of randomization method was employed to balance the three treatment groups across these criteria. It was then checked if the study site had the supply of the selected study drug. If the kit containing the drug and dose to which the patient was randomized was not available then they would be randomly assigned to one of the other treatment arms. If the study site had only one drug available then the patient was automatically assigned to that treatment arm. The investigator called an automated telephone line and received a randomization code for the patient. Based on this randomization code, the research pharmacists would select the appropriate drug. The pharmacist would then prepare the drug for administration in unblinded fashion. The pharmacist would deliver the drug to the investigator in a blinded fashion. A double dummy technique was utilized because the volume of the two study medications was different. Each patient received two injections: one containing the active study drug, the other inactive normal saline thus ensuring everyone received the same volume infusion regardless of treatment arm. The palonosetron or the comparator was administered as an IV bolus over 30 seconds, 30 minutes prior to the chemotherapy. The patient remained in the clinic for a minimum of 3 hours after the administration of the study drug.

Medical Officer Comments: *All study sites should have been provided with ample supplies of the study drug and the active control. This would have allowed true randomization. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. However, this only occurred in a small number of patients and did not compromise the results.*

Study Day 2 (Visit 3)
Patients returned 24 hours after the study medication administration to the study site. They underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication.
Study Day 5 (Telephone contact 1)
All patients were contacted by telephone for adverse events and concomitant medication recording.
Study Day 6 to 8 (Visit 4)
Patients underwent a repeat physical examination, 12 lead ECG, laboratory evaluation and documentation of adverse events. For patients who were selected to have a Holter monitor it was removed 22 hours after the start of the study medication. At this visit, the 5-day patient diary was completed.
Study Day 15 (Telephone contact 2)
All patients were contacted by telephone, and adverse events and concomitant medication were recorded.

3. Eligibility Criteria

The following table displays the entry criteria for the pivotal studies.

TABLE 6: Entry Criteria for the CINV Clinical Program

Inclusion Criteria	Moderately Emetogenic	
	PALO-99-03	PALO-99-04
Chemotherapy naïve subjects with histologically or cytologically confirmed malignant disease.	X	X
Chemotherapy non-naïve subjects with histologically proven diagnosis of cancer.	X	X
Have a Karnofsky index of ≥ 50%.	X	X
Have a Karnofsky index of ≥ 60%.		
Scheduled to receive a single dose of at least one of the following agents administered on Day 1 of the study: any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; or methotrexate > 250 mg/m^2; or cyclophosphamide < 1500 mg/m^2 IV; doxorubicin > 25 mg/m^2 IV; or cisplatin ≤ 50 mg/m^2 IV (to be administered over 1-4 hours).[a]	X	X
Scheduled to receive a single dose of at least one of the following agents administered on Day 1: cisplatin ≥ 60 mg/m^2 (administered over 1-4 hours for doses < 70 mg/m^2, administered over 2-4 hours for doses ≥ 70 mg/m^2); cyclophosphamide > 1500 mg/m^2 IV; carmustine (BCNU) > 250 mg/m^2; dacarbazine (DTIC); or mechlorethamine (nitrogen mustard).[a]		
If a subject has a known hepatic, renal or cardiovascular impairment and is scheduled to receive the above-mentioned chemotherapeutic agents, he/she may be enrolled in this study at the discretion of the investigator.	X	X
Subjects were to be scheduled to receive a their first dose of highly emetogenic chemotherapy with either cisplatin ≥ 70 mg/m^2 (administered over 1-3 hours) or cyclophosphamide > 1100 mg/m^2 IV.		
Subjects with an acceptable hepatic reserve (transaminases < 2 times the upper limit of the reference range) and acceptable renal reserve (calculated or measured creatinine clearance ≥ 50 ml/min).		
If a subject experienced no more than mild nausea following any previous chemotherapy regimen, he/she could have been enrolled at the discretion of the investigator.	X	X

[a] The administration of the major chemotherapeutic agent (i.e., the most emetogenic agent according to the classification of Hesketh, 1999) on Study 1 4 hours.

(Reference: Table 3.8.3:2, page 119, Volume 1)The following were the exclusion criteria:

- Unable to understand or cooperate with study procedure
- Received any investigational drug 30 days prior to study entry
- Received any drug or were scheduled to receive any drug with anti-emetic efficacy within 24 hours of the start of treatment until Day 5 of the study
- Enrollment in a previous study with palonosetron
- Seizure disorder requiring anticonvulsant medication unless clinically stable and free of seizure activity
- Experienced any vomiting, retching, or NCI Common Toxicity Criteria grade 2 or 3 nausea in the 24 hours preceding chemotherapy.
- Ongoing vomiting from any organic etiology
- Experienced nausea (moderate to severe or vomiting following any previous chemotherapy. At the discretion of the investigator , a patient who experienced at maximum mild nausea following any previous chemotherapy might not be excluded from this study)
- Scheduled to receive any dose of a chemotherapeutic agent with an emetogenicity level 5 according to Hesketh et al Classification (The Oncologist 1999; 4:191-196) or were

scheduled to receive any chemotherapeutic agent with an emetogenicity level 3 or higher during Days 2-6 (This refers to Studies PALO-99-03, and 04 only)

- Known contraindication to 5-HT_3 antagonist
- Scheduled to receive radiotherapy of the upper abdomen or cranium during Study Day 2

Medical Officer Comments: *The inclusion criteria are adequate. These doses of chemotherapy are considered moderately emetogenic according to the classification by Hesketh, et al., The Oncologist 1999. The exclusion criteria are adequate with one exception. The protocol excludes patients who had previous nausea or vomiting with previous chemotherapy. This could introduce bias into the study. Patients who are not chemotherapy naïve and enter the study are subjects who tolerate chemotherapy well with respect to emetogenicity. This could make the results appear more favorable in this subset of patients. However, the Agency did agree to these criteria in a Special Protocol Assessment dated December 1999.*

4. Endpoints

The following table displays the primary and secondary endpoints.

TABLE 7: Efficacy Endpoints for the CINV Trials

	Moderately Emetogenic		Highly Emetogenic	
	PALO-99-03	PALO-99-04	PALO-99-05	2330
Primary Efficacy Endpoint				
Complete response (CR)[a] during the first 24 hours after administration of chemotherapy.	X	X	X	X
Secondary Efficacy Endpoints				
Complete response over 120 h	X	X	X	X
Complete control (CC).[b]	X	X	X	X
Total response (subjects free from emetic episodes, rescue medication, and nausea over time).				X
Number of emetic episodes.	X	X	X	
Time to first emetic episode.	X	X	X	X
Time to rescue medication.	X	X	X	X
Time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first).	X	X	X	X
Severity of nausea (Likert Scale)	X	X	X	X
Subject global satisfaction with therapy (VAS; visual analog scale).	X	X	X	X
Quality of life questionnaire (FLIE; Functional Living Index):	X	X	X	

[a] Defined as no emetic episode and no rescue medication.
[b] Defined as a complete response and no more than mild nausea.
Source: Final Study Reports: PALO-99-03; PALO-99-04; PALO-99-05, and 2330.

(Reference: Table 3.8.3.2, page 119, Volume 1)
The primary efficacy endpoint was complete response (CR), which was defined as no emetic episode and no rescue medication during the first 24 hours after administration of chemotherapy. For the Phase 3 studies, secondary measures included evaluations of complete response and complete control (defined as no emetic episode, and only mild or no nausea) for both acute and delayed nausea and vomiting daily and overall through Day 5. Other secondary measures were: number of emetic episodes, time to first emetic episode, time to rescue medication, time to treatment failure, severity of nausea, global satisfaction and quality of life.
All measurements were performed according to accepted and standard methods (visual analog scale [VAS] for the assessment of subjects' global satisfaction with antiemetic therapy, the Likert scale for assessing symptoms like nausea, and Functional Living Index [FLIE] for the measurement of quality of life).

Medical Officer Comments: All measurements used acceptable and standardized methods. The primary efficacy endpoint is identical to that used for other medications approved for the indications the applicant is seeking.

5. Statistical Analysis

PALO-99-03, 04, and 05 were an active comparator, non-inferiority analyses that employed a 15% delta. The primary efficacy parameter in these trials was the proportion of subjects considered to have achieved a complete response (CR) during the first 24 hours after administration of chemotherapy. CR is defined as no emesis and no rescue medication during the first 24 hours after chemotherapy.

The lower bound of 97.5% CI for the difference (palonosetron minus active comparator) between the proportion of subjects with a complete response during the first 24 hours after administration of chemotherapy was calculated and compared to the pre-set threshold (-15% difference) to demonstrate non-inferiority. To demonstrate that the two palonosetron doses were equal with respect to CR (0–24 hours), the bounds of the two-sided 95% CI of the difference between the proportions of CR (0–24 hours) were compared to the pre-set threshold (± 15%). The intent to treat (ITT) population was used in the primary analysis. The following table displays the various statistical methods used for the secondary efficacy parameters at various time intervals.

TABLE 8: Statistical Test Utilized for Secondary Efficacy Parameters

Parameters	Statistical Test
Complete Control (CC)	
0-24 hr	Chi-square
24-48 hr	Chi-square
48-72 hr	Chi-square
72-96 hr	Chi-square
96-120 hr	Chi-square
0-48 hr	Chi-square
0-72 hr	Chi-square
0-96 hr	Chi-square
0-120 hr	Chi-square
Number of Emetic Episodes (EE)	
0-24 hr	Kruskal-Wallis/Wilcoxon
24-48 hr	Kruskal-Wallis/Wilcoxon
48-72 hr	Kruskal-Wallis/Wilcoxon
72-96 hr	Kruskal-Wallis/Wilcoxon
96-120 hr	Kruskal-Wallis/Wilcoxon
0-120 hr	Kruskal-Wallis/Wilcoxon
Time to First EE	Log Rank
Severity of Nausea	
0-24 hr	Kruskal-Wallis/Wilcoxon
24-48 hr	Kruskal-Wallis/Wilcoxon
48-72 hr	Kruskal-Wallis/Wilcoxon
72-96 hr	Kruskal-Wallis/Wilcoxon
96-120 hr	Kruskal-Wallis/Wilcoxon

Due to ethical concerns, a placebo-controlled trial was not feasible for CINV. Thus to ensure validity, the applicant developed a meta-analysis (PALO-01-23) which used data from a published literature to predict the complete response for CINV.
A literature search was performed to select articles using placebo, dolasetron, granisetron, ondansetron and other anti-emetics for CINV). This meta-analysis database consisted of 78 treatment arms from published trials and included 7274 subjects. Helsinn used this database to perform a logistic regression to identify which covariates were relevant in predicting complete response for various treatments and produce a model to calculation of historical placebo and historical active comparator complete response.

Validity was demonstrated if:

- the lower limit of the 95% CI of complete response in the active comparator group was greater than the upper limit of the 95% CI of the complete response rate of the modeled historical placebo; and
- the complete response rate achieved in the active comparator group was similar to modeled historical comparator.

Medical Officer Comments: The Agency and the applicant agreed to this approach to validation in pre-NDA meetings and end of Phase II meetings held in spring of 1999.

6. Results

a.) Moderately Emetogenic Chemotherapy (Studies PALO-99-03, PALO-99-04)

For Study PALO-99-03, 58 centers located thoughout Europe enrolled 571 patients. Of these, 570 were randomized to one of the three treatment groups (1 patient was not randomized and did not receive treatment). For Study PALO-99-04, 61 centers located in the U.S. and Mexico enrolled 593 patients. Of these, 592 were randomized to one of the three treatment groups (1 patient was not randomized and did not receive treatment).

The treatment groups in these studies were similar with respect to demographics, baseline characteristics, and Karnofsky index. There were more females than males in these two studies (approximately 77% versus 23%, respectively). The applicant attributes this to the fact that moderately emetogenic chemotherapy is frequently used for breast cancer. The studies differed in chemotherapeutic history. In Study PALO-99-03, the majority of subjects were non-naïve as opposed to Study PALO-99-04 which consisted of a slight majority of naïve subjects. After subject recruitment was completed in Study PALO-99-03, and towards the end of Study PALO-99-04 a protocol amendment permitting use of intravenous dexamethasone was enacted. Thus, number of subjects with corticosteroid use was low. For PALO-99-03, there was no subjects received corticosteroids. The following table shows the use of corticosteroids in study PALO 99-04.

TABLE 9 – PALO-99-04: Corticosteroid Use

	Palonosetron 0.25 mg (N=189) N (%)	**Palonosetron 0.75 mg (N=189)** N (%)	**Dolasetron 100 mg (N=191)** N (%)
Corticosteroid Use			
Yes	11(5.8)	12 (6.3)	8 (4.2)
No	178 (94.2)	177(93.7)	183 (95.8)

(Reference: Table 6.3-b, pg. 76, Volume 135)

The chemotherapeutic treatment administered on Study Day 1 was similar for all the treatment groups. Cyclophosphamide was the most frequently administered chemotherapeutic agent. The following tables display the chemotherapy agent administered on Day 1 for PALO-99-03, and PALO-99-04.

TABLE 10 – PALO-99-03: Chemotherapeutic treatment administered on Study Day 1[1]

Substance	Palonosetron 0.25 mg (N=189) N (%)	Palonosetron 0.75 mg (N=189) N (%)	Ondansetron 32 mg (N=185) N (%)
Cyclophosphamide	119 (63.0)	120 (63.5)	117 (63.2)
Doxorubicin	97 (51.3)	87 (46.0)	87 (47.0)
Cisplatin	36 (19.0)	33 (17.5)	31 (16.8)
Methotrexate	23 (12.2)	32 (16.9)	36 (19.5)
Carboplatin	15 (7.9)	25 (13.2)	25 (13.5)
Epirubicin	13 (6.9)	17 (9.0)	14 (7.6)
Irinotecan	10 (5.3)	8 (4.2)	8 (4.3)
Ifosfamide	2 (1.1)	0 (0.0)	2 (1.1)
Mitoxantrone	1 (0.5)	1 (0.5)	3 (1.6)
Idarubicin	0 (0.0)	0 (0.0)	0 (0.0)

[1] Multiple answers possible
(Reference: Table 6.4.3-a, pg. 85, Volume 117)

TABLE 11 – PALO-99-04:Chemotherapeutic treatment administered on Study Day 1[1]

Substance	Palonosetron 0.25 mg (N=189) N (%)	Palonosetron 0.75 mg (N=189) N (%)	Ondansetron 32 mg (N=185) N (%)
Cyclophosphamide	119 (63.0)	120 (63.5)	117 (63.2)
Doxorubicin	97 (51.3)	87 (46.0)	87 (47.0)
Cisplatin	36 (19.0)	33 (17.5)	31 (16.8)
Methotrexate	23 (12.2)	32 (16.9)	36 (19.5)
Carboplatin	15 (7.9)	25 (13.2)	25 (13.5)
Epirubicin	13 (6.9)	17 (9.0)	14 (7.6)
Irinotecan	10 (5.3)	8 (4.2)	8 (4.3)
Ifosfamide	2 (1.1)	0 (0.0)	2 (1.1)
Mitoxantrone	1 (0.5)	1 (0.5)	3 (1.6)
Idarubicin	0 (0.0)	0 (0.0)	0 (0.0)

[1] Multiple answers possible
(Reference: Table 6.4.3-a, pg. 85, Volume 117)

The primary efficacy endpoint was complete response (defined as no emetic episode and no rescue medication) during the first 24 hours after administration of chemotherapy.The following table displays the complete response rates for the first 24 hours after chemotherapy.

TABLE 12: Complete Response Rates During the First 24 Hours After Chemotherapy: Moderately Emetogenic CINV Studies PALO-99-03 and PALO-99-04 and Pooled Data (ITT Cohort; N = 1132)

Treatment Group	Complete Response (CR) During the First 24 Hours			97.5% CI for the Difference in CR Rates During the First 24 Hours Between Palonosetron and Active Comparator	
	N	n (%)	95% CI	Palonosetron 0.25 mg Minus Active Comparator	Palonosetron 0.75 mg Minus Active Comparator
PAL0-99-03					
Palonosetron 0.25 mg	189	153 (81.0)	[74.5%, 86.1%]		
Palonosetron 0.75 mg	189	139 (73.5)	[66.6%, 79.6%]		
Ondansetron 32 mg	185	127 (68.6)	[61.4%, 75.1%]	[1.8%, 22.8%]*	[-6.1%, 15.9%]
PAL0-99-04					
Palonosetron 0.25 mg	189	119 (63.0)	[55.6%, 69.8%]		
Palonosetron 0.75 mg	189	108 (57.1)	[49.8%, 64.2%]		
Dolasetron 100 mg	191	101 (52.9)	[45.6%, 60.1%]	[-1.7%, 21.9%]	[-7.7%, 16.2%]
Pooled Data (PALO-99-03 and PALO-99-04)					
Palonosetron 0.25 mg	378	272 (72.0)	[67.1%, 76.4%]		
Palonosetron 0.75 mg	378	247 (65.3)	[60.3%, 70.1%]	–	–

CR = Complete Response (defined as no emetic episode and no rescue medication) during the first 24 hours after chemotherapy.
N = Number of subjects in treatment group.
n (%) = number and percentage of subjects with CR.
CI = Confidence Interval.
* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron or dolasetron) indicating palonosetron superiority ($p < 0.05$).
Source: Final Study Reports PALO-99-03 and PALO-99-04 (Table 7.1.1.1-a and Table 7.1.1.1-b); Section 8.8.8, ISE End-of-Text D.10.
(Reference: Table 3.8.3:3, page 122, Volume 1

Medical Officer Comments: *The palonosetron 0.25 mg group had the highest number of subjects with a complete response during the first 24 hours after chemotherapy was highest in (range 63.0% to 81.0%). The lowest number was in the active comparator group (dolasetron, 52.9%; ondansetron, 68.6%). The lower limit of the 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy was above the preset 15% delta. The comparator was adequate. The comparator drugs are FDA approved medications indicated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Based on this data, the non-inferiority of both palonosetron doses to ondansetron 32 mg and dolasetron 100 mg was demonstrated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting during the first 24 hours after chemotherapy. It is not clear why the higher dose of palonosetron seemed to have less efficacy. The results of the pooled data supported findings from the individual studies.*

For trial validation, the 95% confidence interval of the proportion of complete response in the active comparator group was compared to the complete response rate of the modeled historical placebo group and modeled history dolasetron group. The following tables display the results.

TABLE 13 : PALO-99-03 - Comparison of complete response between the ondansetron and modeled historical placebo

	Modeled Historical Ondansetron	Modeled Historical Placebo	Ondansetron (N=185)
CR	79.3%	27.3	68.6
95% CI of the proportion of patients with CR	[73.1%, 84.3%]	[21.3%, 34.6%]	[61.4%, 75.1%]

(Reference: Table 7.1.1.2 g, page 97, Volume 117)

TABLE 14: PALO-99-04-Comparison of complete response between the dolasetron and modeled historical placebo

	Modeled Historical Dolasetron	Modeled Historical Placebo	Dolasetron 100 mg (N=191)
CR	59.7%	15.1%	52.9%
95% CI of the proportion of patients with CR	[51.3%, 67.6%]	[11.3%, 20.1%]	[45.6%, 60.1%]

(Reference: Table 7.1.1.2 g, page 106, Volume 135)

Medical Officer Comments: *Since the use of placebo is not ethically acceptable in the CINV subject population, a literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data. Since the dolasetron and ondansetron performed similarly to the modeled historical dolasetron and far better than in the modeled historical placebo, the applicant demonstrated validity of the trial.*

The applicant did not pool the results from the secondary endpoints. Therefore, the pertinent results are displayed for the individual study (PALO-99-03, followed by PALO-99-04).

Secondary Efficacy Endpoint – Complete response over 120 hours

The applicant performed an analysis of complete response over time as shown in the following table.

TABLE 15: Subjects with Complete Response After Chemotherapy, By Day (Acute and Delayed): Moderately Emetogenic CINV Studies PALO-99-03 and PALO-99-04 (ITT Cohort; N = 1132)

	Number and Percentage (%) of Subjects with Complete Response			Difference in Complete Response Rates, 97.5% Confidence Intervals	
PAL0-99-03					
Time Period (Hours)	**Palonosetron 0.25 mg (N = 189)**	**Palonosetron 0.75 mg (N = 189)**	**Ondansetron 32 mg (N = 185)**	**Palonosetron 0.25 mg Minus Ondansetron 32 mg**	**Palonosetron 0.75 mg Minus Ondansetron 32 mg**
Acute[a]					
0–24	153 (81.0)	139 (73.5)	127 (68.6)	[1.8%, 22.8%]*	[-6.1%, 15.9%]
Delayed[b]					
24–48	154 (81.5)	132 (69.8)	122 (65.9)	[4.9%, 26.1%]*	[-7.5%, 15.2%]
48–72	161 (85.2)	147 (77.8)	124 (67.0)	[8.0%, 28.4%]*	[-0.1%, 21.6%]
72–96	168 (88.9)	161 (85.2)	145 (78.4)	[1.5%, 19.5%]*	[-2.6%, 16.3%]
96–120	175 (92.6)	169 (89.4)	161 (87.0)	[-2.0%, 13.1%]	[-5.6%, 10.4%]
PAL0-99-04					
Time Period (Hours)	**Palonosetron 0.25 mg (N = 189)**	**Palonosetron 0.75 mg (N = 189)**	**Dolasetron 100 mg (N = 191)**	**Palonosetron 0.25 mg Minus Dolasetron 100 mg**	**Palonosetron 0.75 mg Minus Dolasetron 100 mg**
Acute[a]					
0–24	119 (63.0)	108 (57.1)	101 (52.9)	[-1.7%, 21.9%]	[-7.7%, 16.2%]
Delayed[b]					
24–48	118 (62.4)	118 (62.4)	85 (44.5)	[6.1%, 29.7%]*	[6.1%, 29.7%]*
48–72	128 (67.7)	138 (73.0)	107 (56.0)	[0.1%, 23.3%]*	[5.6%, 28.3%]*
72–96	149 (78.8)	155 (82.0)	137 (71.7)	[-3.3%, 17.5%]	[0.1%, 20.4%]*
96–120	167 (88.4)	162 (85.7)	156 (81.7)	[-2.0%, 15.4%]	[-5.0%, 13.0%]

[a] = Primary efficacy endpoint.
[b] = Secondary endpoint.
* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron or dolasetron) indicating palonosetron superiority ($p < 0.05$).
For secondary endpoints p-values not adjusted for multiple comparisons.
Source: Final Study Reports PALO-99-03 and PALO-99-04; Table 7.1.2.1-d.
(Reference: Table 3.8.3:4, page 125, Volume 1)

Medical Officer Comments: *During all study days, complete response rates were higher in the 2 palonosetron groups than in the comparator arms. Higher rates were observed in the palonosetron 0.25 mg group compared to the 0.75 mg group. Although the palonosetron seems to demonstrate some efficacy at 120 hours some factors need to be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there may be issues with multiplicity. In addition, the comparator drugs dolasetron and ondansetron are not indicated for prevention of CINV at 120 hours. Thus, what the results may be demonstrating is that the nausea from the chemotherapy is simply wearing off. In regards to delayed prevention of CINV, palonosetron 0.25 mg showed a statistically significant difference from ondansetron only for following intervals: 24-48 hours, 48-72 hours, and 72-96 hours. There was no statistical difference between the palonosetron and ondansetron for 96-120 hours despite the fact that ondansetron is not indicated for prevention of CINV at this time interval. Palonosetron 0.25 mg showed statistical difference from dolasetron only for the intervals 24-48 hours and 48-72 hours. Like ondansetron, dolasetron in not indicated for prevention of CINV in the delayed time period (after 24 hours).*

Complete response for the cumulative time periods (0 to 48, 0 to 72, 0 to 96, 0 to 120 hours, and 24 to 120 hours) and 97.5% CIs of the differences in complete response rates are shown in the following table.

TABLE 16: Subjects with Complete Response After Chemotherapy, Cumulative Time Periods: Moderately Emetogenic CINV Studies PALO-99-03 and PALO-99-04 (ITT Cohort; N = 1132)

	Number and Percentage (%) of Subjects with Complete Response			Difference in Complete Response Rates, 97.5% Confidence Intervals	
PAL0-99-03					
Time Period (Hours)	**Palonosetron 0.25 mg (N = 189)**	**Palonosetron 0.75 mg (N = 189)**	**Ondansetron 32 mg (N = 185)**	**Palonosetron 0.25 mg Minus Ondansetron 32 mg**	**Palonosetron 0.75 mg Minus Ondansetron 32 mg**
0–24	153 (81.0)	139 (73.5)	127 (68.6)	[1.8%, 22.8%]*	[-6.1%, 15.9%]
0–48	141 (74.6)	119 (63.0)	111 (60.0)	[3.3%, 25.9%]*	[-8.8%, 14.8%]
0–72	137 (72.5)	116 (61.4)	97 (52.4)	[8.5%, 31.6%]*	[-3.0%, 20.9%]
0–96	132 (69.8)	112 (59.3)	94 (50.8)	[7.4%, 30.7%]*	[-3.6%, 20.5%]
0–120	131 (69.3)	111 (58.7)	93 (50.3)	[7.4%, 30.7%]*	[-3.6%, 20.5%]
24–120	140 (74.1)	122 (64.6)	102 (55.1)	[7.5%, 30.3%]*	[-2.4%, 21.3%]
PAL0-99-04					
Time Period (Hours)	**Palonosetron 0.25 mg (N = 189)**	**Palonosetron 0.75 mg (N = 189)**	**Dolasetron 100 mg (N = 191)**	**Palonosetron 0.25 mg Minus Dolasetron 100 mg**	**Palonosetron 0.75 mg Minus Dolasetron 100 mg**
0–24	119 (63.0)	108 (57.1)	101 (52.9)	[-1.7%, 21.9%]	[-7.7%, 16.2%]
0–48	96 (50.8)	95 (50.3)	74 (38.7)	[0.2%, 23.9%]*	[-0.4%, 23.4%]
0–72	89 (47.1)	93 (49.2)	69 (36.1)	[-0.8%, 22.8%]	[1.3%, 24.9%]*
0–96	88 (46.6)	90 (47.6)	68 (35.6)	[-0.8%, 22.7%]	[0.2%, 23.8%]*
0–120	87 (46.0)	89 (47.1)	65 (34.0)	[0.3%, 23.7%]*	[1.3%, 24.8%]*
24–120	102 (54.0)	107 (56.6)	74 (38.7)	[3.4%, 27.1%]*	[6.0%, 29.7%]*

* = 97.5% CIs for the difference between palonosetron and active comparator (ondansetron or dolasetron) indicating palonosetron superiority ($p < 0.05$).
For secondary endpoints p-values not adjusted for multiple comparisons.
Source: Final Study Reports PALO-99-03 and PALO-99-04; Table 7.1.2.1-a and Table 7.1.2.1.b.
(Reference: Table 3.8.3:5, page 128, Volume 1)

Medical Officer Comment: *When the entire time period 0-120 hours was evaluated, palonosetron a statistically significant higher proportion of patients in the palonosetron arm had complete response than patients in the comparator arms. The 97.5% CIs for the comparison of palonosetron 0.25 mg with ondansetron 32 mg did not include zero, indicating statistically superior complete response rates with palonosetron 0.25 mg compared to ondansetron 32 mg for all cumulative time periods. The comparison of palonosetron 0.25 mg to dolasetron 100 mg for complete response showed a statistical superiority for the 0 to 48, 0 to 120, and 24 to 120-hour periods. Statistical superiority of palonosetron 0.75 mg to dolasetron 100 mg was seen for the 0 to 72, 0 to 96, 0 to 120, and 24 to 120-hour periods.*

Secondary Efficacy Endpoint – Complete control over 120 hours

The following tables show the proportion of patients who were considered to have complete control. Complete control was another secondary efficacy endpoint and was defined as patient who had a complete response and no more than mild nausea.

TABLE 17: PALO-99-03- Patients with complete control after chemotherapy, overall time periods (ITT cohort, N=563)

Time Period (Hours)	Palonosetron 0.25 mg (N = 189)		Palonosetron 0.75 mg (N = 189)		Ondansetron 32 mg (N = 185)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
0-24	144 (76.2)	[69.4%, 81.9%]	134 (70.9)	[63.8%, 77.1%]	121 (65.4)	[58.0%, 72.1%]
0–48	133 (70.4)	[63.2%, 76.7%]	109 (57.7)	[50.3%, 64.7%]	101(54.6)	[47.1%, 61.9%]
0–72	124 (65.6)	[58.3%, 72.3%]	105 (55.6)	[48.2%, 62.7%]	87 (47.0	[39.7%, 54.5%]
0–96	120 (63.5)	[56.2%, 70.3%]	102 (54.0)	[46.6%, 61.2%]	84 (45.4)	[38.1%, 52.9%]
0–120	119 (63.0)	[55.9%, 69.8%]	101 (53.4)	[46.1%, 60.7%]	83 (44.9)	[37.6%, 52.3%]

(Reference: Table 7.1.2.2-a, page 109, Volume 117)

TABLE 18: PALO-99-04 - Patients with complete control after chemotherapy, overall time periods (ITT cohort, N=563)

Time Period (Hours)	Palonosetron 0.25 mg (N = 189)		Palonosetron 0.75 mg (N = 189)		Dolasetron 100 mg (N = 191)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
0-24	108 (57.2)	[49.8%, 64.2%]	100 (52.9)	[45.5%, 60.2%]	91 (47.6)	[40.4%, 55.0%]
0–48	86 (45.5)	[38.3%, 52.6%]	87 (46.0)	[38.8, 53.4%]	66(34.6)	[27.9%,41.8%]
0–72	81 (42.9)	[35.8%, 50.2%]	86 (45.5)	[38.3%, 52.9%]	63 (33.0	[26.5%, 40.2%]
0–96	80 (42.3)	[35.3%, 49.7%]	83 (43.9)	[36.8%, 51.3%]	60 (45.4)	[25.0%, 38.6%]
0–120	79 (41.8)	[34.7%, 49.2%]	81 (42.9)	[35.8%, 50.2%]	59 (30.9)	[24.5%, 38.0%]

(Reference: Table 7.1.2.2-a, page 115, Volume 135)

Medical Officer Comments: *In study PALO-99-03, both palonosetron groups demonstrated higher complete control rates at all time periods when compared to ondansetron. The*

palonosetron 0.25 mg group had a higher proportion of patients that had complete control than the 0.75 mg group. The differences between the three groups were statistically significant for the time period 0 top 48 hours (p=.004), 0 to 72 hours (p=0.001), 0 to 96 hours (p=0.002) and 0 to 120 hours (p=0.002). There was no statistical difference in the 0 to 24 hour time period (p=0.072 using Chi-Square test)

Similarly, in study PALO-99-04, both palonosetron groups demonstrated higher complete control rates at all time periods when compared to dolasetron. During the 0-24 hours period the palonosetron 0.25 mg group had a higher proportion of patients that had complete control than the 0.75 mg group. Pairwise comparison of the treatment groups revealed statistically significant differences between both palonosetron and the dolasetron for each observation period.. In Study PALO-99-04, there were no statistically significant differences between the two palonosetron groups.

Secondary Efficacy Endpoint – Number of emetic episodes over 120 hours

Number of emetic episodes was another secondary endpoint. The following tables show the number of emetic episodes during the observation period for Studies PALO-99-03, 99-04 respectively.

TABLE 19 – PALO-99-03 Number of emetic episodes during the observation period

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Ondansetron 32 mg (N=185)	
	N	(%)	N	(%)	N	(%)
ACUTE						
0–24						
0 episodes	161	(85.2)	147	(77.8)	132	(71.4)
1 episode	4	(2.1)	13	(6.9)	20	(10.8)
2 episodes	6	(3.2)	9	(4.8)	12	(6.5)
≥3 episodes	18	(9.5)	20	(10.6)	21	(11.4)
DELAYED						
24–48						
0 episodes	166	(87.8)	143	(75.7)	129	(69.7)
1 episode	11	(5.8)	24	(12.7)	30	(16.2)
2 episodes	5	(2.6)	7	(3.7)	11	(5.9)
≥3 episodes	7	(3.7)	15	(7.9)	15	(8.1)
48–72						
0 episodes	170	(89.9)	159	(84.1)	138	(74.6)
1 episode	14	(7.4)	17	(9.0)	29	(15.7)
2 episodes	2	(1.1)	4	(2.1)	8	(4.3)
≥3 episodes	3	(1.6	9	(4.8)	10	(5.4)
72–96						
0 episodes	174	(92.1)	169	(89.4)	165	(89.2)
1 episode	10	(5.3)	9	(4.8)	13	(7.0)
2 episodes	3	(1.6)	4	(2.1)	6	(3.2)
≥3 episodes	2	(1.1)	7	(3.7)	1	(0.5)
96–120						
0 episodes	178	(94.2)	176	(93.1)	173	(93.5)
1 episode	6	(3.2)	7	(3.7)	7	(3.8)
2 episodes	2	(1.1)	2	(1.1)	3	(1.6)
≥3 episodes	3	(1.6)	4	(2.1)	2	(1.1)

(Reference:Table 7.1.2.3-a, from page 112, Volume 117)

TABLE 20 : PALO-99-04 -Number of emetic episodes during the observation period

Time Period	Palonosetron 0.25 mg (N=189)		Palonosetron 0.75 mg (N=189)		Dolasetron 100 mg (N=191)	
	N	(%)	N	(%)	N	(%)
ACUTE						
0–24						
0 episodes	136	(72.0)	123	(65.1)	112	(58.6)
1 episode	19	(10.1)	21	(11.1)	25	(13.1)
2 episodes	4	(2.1)	6	(3.2)	15	(7.9)
≥3 episodes	30	(15.9)	39	(20.6)	39	(20.4)
DELAYED						
24–48						
0 episodes	134	(70.9)	142	(75.1)	110	(57.6)
1 episode	24	(12.7)	23	(12.2)	34	(17.8)
2 episodes	9	(4.8)	11	(5.8)	18	(9.4)
≥3 episodes	22	(11.6)	13	(6.9)	29	(15.2)
48–72						
0 episodes	147	(77.8)	159	(84.1)	139	(72.8)
1 episode	20	(10.6)	15	(7.9)	31	(16.2)
2 episodes	9	(4.8)	5	(2.6)	11	(5.8)
≥3 episodes	13	(6.9)	10	(5.3)	10	(5.2)
72–96						
0 episodes	170	(89.9)	168	(88.9)	158	(82.7)
1 episode	10	(5.3)	12	(6.3)	20	(10.5)
2 episodes	2	(1.1)	3	(1.6)	8	(4.2)
≥3 episodes	7	(3.7)	6	(3.2)	5	(2.6
96–120						
0 episodes	181	(95.8)	175	(92.6)	168	(88.0)
1 episode	2	(1.1)	9	(4.8)	15	(7.9)
2 episodes	2	(1.1)	1	(0.5)	2	(1.0)
≥3 episodes	4	(2.1)	4	(2.1)	6	(3.1)

(Reference: Table 7.1.2.3-a, from page 118 Volume 135)

Medical Officer Comments: *In study PALO-99-03, the palonosetron 0.25 mg group had fewer emetic episodes than the other groups for days 1,2 ,and 3. There was no difference between the groups on day 4 and 5. On these days, most patients did not experience an episode of emesis. However, the palonosetron 0.75 mg group did have more patients who had 3 or more episodes of emesis on Days 4 and 5 than the other groups.*

For study PALO-99-04, the percentage of patients without an emetic episode was higher in both palonosetron groups than in the dolasetron group. The 0.25 mg palonosetron group had

a higher rate of patients without emetic episodes on Day 1 compared to the 0.75 mg group. Pair wise testing revealed a statically significant difference between palonosetron 0.25 mg group and the dolasetron group on Study Day 1, 2 and 5. Pairwise testing revealed a difference on Day 2 and 3 between dolasetron and the 0.75 mg group. .

Secondary Efficacy Endpoint – Median time to first emetic episode

The median time to first emetic episode was above 120 hours for all groups in both studies. When the applicant performed further analysis of the first quartile of patients, they found that the first quartile showed that time to first emetic episode was longer in the 0.25 mg group. This was an unplanned analysis that was done after the primary analysis failed to show a difference. Thus, it is unclear if this is clinically significant.

Secondary Efficacy Endpoint – Severity of Nausea

The following figures display the severity of nausea for both studies PALO-99-03, and 99-04 respectively.