

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS
DIVISION OF BIOMETRICS II**

**STATISTICAL REVIEW AND EVALUATION
Clinical Studies**

NDA: 21915

Name of drug: Ondansetron HCL Injection

Applicant: Baxter Healthcare Corporation

Indication: Prevention of Nausea and Vomiting Associated with Initial and Repeated Courses of Emetogenic Cancer Chemotherapy

Dates: Received April 5, 2005

Review Priority: Standard

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

From the statistical perspective, based upon the **remarks stated in the section of “Statistical Issues and Collective Evidence”, the literature submitted by the applicant does not provide** substantial evidence to support that the efficacy of ondansetron 8 mg is equivalent to that of an approved drug for the prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy.

1.2 Brief Overview of Clinical Studies

The applicant indicated that ondansetron (ZOFTRAN®) was originally developed by GlaxoSmithKline. In the United States, ondansetron has been approved for the treatment of emesis and nausea following single high-dose chemotherapy and for the treatment of postoperative nausea and vomiting. The recommended US dosing regimen for prevention of chemotherapy-induced emesis in adults is 32 mg administered 30 minutes prior to chemotherapy, or three 0.15 mg/kg doses (administered 30 minutes prior to, and four and eight hours after chemotherapy).

The purpose of this submission is to seek approval to market ondansetron injection, USP in PL 2408 Plastic Container. Baxter is seeking approval of two premixed presentations of ondansetron injection, USP, 8 mg and 32 mg in 50 mL IntraVia flexible plastic containers.

For ondansetron injection 32 mg, the applicant highlighted that the excipients in the Baxter preparation were identical to that in the currently-marketed 32 mg dose formulation, except that the ondansetron active drug substance is presented in a 0.9% saline diluent, rather than a 5% dextrose diluent, to reflect current clinical preference. Since the only review issues for ondansetron injection 32 mg are clinical, this review focuses on the efficacy issues for ondansetron injection 8 mg. The medical review will discuss both doses.

To support the efficacy of ondansetron injection 8 mg used for the proposed indication, the applicant submitted reports of four well controlled studies (Italian Group for Anti-emetic Research [IGAR], Seynaeve, Ruff, and Beck/Hainsworth) published in the literature. In the cover letter, the applicant further emphasizes that the four studies submitted to support the indication were not conducted by or for the applicant, and the applicant does not have a right-of-reference to them.

In the four studies submitted by the applicant, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours. All four studies were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients enrolled were naïve to chemotherapy and were receiving cisplatin-containing (≥ 50 mg/m²) treatment. However, unlike other three studies, in Study IGAR, the study drug ondansetron 8 mg and the reference drug granisetron 3mg included concomitant administration

of 20 mg dexamethasone. Since the efficacy of ondansetron 8mg plus dexamethasone 20 mg may be different from that of ondansetron 8 mg examined by the other three studies, data provided by Study IGAR is considered inadequate to support ondansetron 8 mg for the proposed indication and is not further reviewed. In this review, the other three studies (Seynaeve, Ruff, and Beck/Hainsworth) are the focus.

The primary endpoint defined by the authors for the two studies Ruff and Seynaeve was either emesis complete or major responses (i.e., ≤ 2 emetic episodes) while for study Beck/Hainsworth, the primary endpoint was number of emetic episodes. **However, in the applicant's submission, the efficacy analysis was mainly focused on the emesis complete + major responses.**

1.3 Statistical Issues and Findings

As indicated by this reviewer in the beginning of **section 3.2 "Evaluation of Efficacy"**, the issues of equivalence claim for ondansetron 8 mg versus granisetron 3 mg and ondansetron 8 mg versus ondansetron 0.15 mg/kg x 3 are similar to those of ondansetron 8 mg versus ondansetron 32 mg. In this section, the statistical issues and collective evidence are discussed for the efficacy comparison between ondansetron 8 mg and ondansetron 32 mg.

- The applicant claimed the efficacy equivalence/similarity of ondansetron 8 mg to ondansetron 32 mg based upon the non-significant result shown in the superiority analysis reported by the three selected trials (Ruff, Beck/Hainsworth, and Seynaeve). However, it is well known to the statistician that the inability to reject the null hypothesis of no efficacy difference between ondansetron 8 mg and 32 mg dose not mean we accept the null hypothesis and assert that the efficacy of the two treatments are equivalent. It only indicates that there is not sufficient data to reject the null hypothesis of no treatment difference and to support the alternative hypothesis of treatment difference. Therefore, this result does not support the equivalence of the two drugs.
In order to demonstrate the equivalence of the two drugs ondansetron 8 mg and ondansetron 32 mg, the applicant should have selected an adequate margin (Δ) and shown that the 95% two-sided confidence interval on the difference of probabilities for patients with 0 to 3 emeses and no rescue therapy between ondansetron 8 mg and 32 mg was included in the interval, $(-\Delta, \Delta)$, formulated by the margin of Δ . It follows that the equivalence claim based upon the non-significant result shown in the superiority analysis made by the applicant was not based upon a valid equivalence analysis and is not acceptable.
- After examining data for the three trials (Studies Ruff, Beck, and Seynaeve), the applicant had lost the opportunity to identify a just equivalence margin and is no longer able to perform a valid equivalence analysis.
- The applicant mainly employed complete response plus major control (i.e., 0 to 2 emeses) and no rescue therapy as the primary endpoint to assess the efficacy of ondansetron 8 mg for the submitted three trails (Studies Ruff, Beck, and Seynaeve). However, the medical reviewer, Dr. Lolita Lopez, deems that the primary endpoint should be no emesis and no rescue therapy. Accordingly, the equivalence claim of

ondansetron 8 mg to ondansetron 32 mg made by the applicant based on the efficacy results assessed by the proportions of 0 to 2 emeses shown by the three submitted trials may not fully characterize the proposed indication.

- Only the summary data reported in the literature on demographics, baseline characteristics, and efficacy comparisons for treatment groups were provided. Without detail information (raw data) for individual patients enrolled by the three studies (Seynaeve, Ruff, and Beck/Hainsworth), the Agency can not assess the quality and credibility of the data collected and the analyzed results reported by the three studies by performing imperative efficacy analyses (for example, treatment by center interaction, treatment efficacy by center, prognostic analysis to identify baseline variable affected the primary endpoint, etc). If any of the three trials were improperly conducted, the reference drug ondansetron 32 mg may not be effective in that trial. In addition, due to lack of placebo arm in any of the three studies, the concern about the lack of effectiveness of ondansetron 32 mg can not be ruled out.

Finally, since these three trials were designed for superiority analysis, no equivalence margin was selected by authors or by the applicant based upon the principle recommended by ICH E10. Accordingly, the concern of lack of assay sensitivity for ondansetron 32 mg embedded in the three trials (Seynaeve, Ruff, and Beck/Hainsworth) and no equivalence margin pre-selected before conducting the three trials result in the equivalence claim made by the applicant for ondansetron 8 mg versus ondansetron 32 mg being not statistically meaningful.

- It was possible that there may be more literature (published or un-published) which compared the efficacy between ondansetron 8 mg versus ondansetron 32 mg which were not selected by the applicant. The efficacy differences on the primary endpoint for the two treatments studied by those published/unselected literatures may be worse than the three trials selected by the applicant. As a consequence, the true efficacy difference on the primary endpoint (complete + major responses) may not be represented by the three trails (Studies Ruff, Beck, and Seynave) submitted by the applicant.

2.0 INTRODUCTION

2.1 Overview

The applicant indicated that ondansetron (ZOFTRAN®) was originally developed by GlaxoSmithKline. In the United States, ondansetron has been approved for the treatment of emesis and nausea following single high-dose chemotherapy and for the treatment of postoperative nausea and vomiting. The recommended US dosing regimen for prevention of chemotherapy-induced emesis in adults is 32 mg administered 30 minutes prior to chemotherapy, or three 0.15 mg/kg doses (administered 30 minutes prior to, and four and eight hours after chemotherapy).

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To support the efficacy of ondansetron injection 8 mg used for the proposed indication, the applicant submitted reports of four well controlled studies (Italian Group for Anti-emetic Research [IGAR], Seynaeve, Ruff, and Beck/Hainsworth) published in the literature. In the cover letter, the applicant further emphasizes that the four studies submitted to support the indication were not conducted by or for the applicant, and the applicant does not have a right-of-reference to them.

In the four studies submitted by the applicant, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours. All four studies were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients enrolled were naïve to chemotherapy and were receiving cisplatin-containing (≥ 50 mg/m²) treatment. However, unlike other three studies, in Study IGAR, the study drug ondansetron 8 mg and the reference drug granisetron 3mg included concomitant administration of 20 mg dexamethasone. Since the efficacy of ondansetron 8mg plus dexamethasone 20 mg may be different from that of ondansetron 8 mg examined by the other three studies, data provided by Study IGAR is considered inadequate to support ondansetron 8 mg for the proposed indication and is not further reviewed. In this review, the other three studies (Seynaeve, Ruff, and Beck/Hainsworth) are the focus.

The primary endpoint defined by the authors for the two studies Ruff and Seynaeve was either emesis complete or major responses (i.e., ≤ 2 emetic episodes) while for study Beck/Hainsworth, the primary endpoint was number of emetic episodes. **However, in the applicant's submission, the efficacy analysis was mainly focused on the emesis complete + major responses.**

2.2 Data Sources

To assess the clinical efficacy of ondansetron injection used for prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, this reviewer reviewed NDA submission dated April 5, 2005. **As indicated in the "Overview" section, no study was conducted by the applicant to explore the efficacy of ondansetron injection used to prevent nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy. Therefore, no raw data on efficacy was provided by the applicant for the Agency to review. The three studies (Seynaeve, Ruff, and Beck/Hainsworth) published in the literature to demonstrate the efficacy of ondansetron 8 mg were the focus.**

3. STATISTICAL EFFICACY EVALUATION

3.1 Evaluation of Efficacy

3.1, Part A Studies Selected from Literature

In order to assess the applicant's efficacy claim on the use of ondansetron injection in the prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, this reviewer summarizes the study design, adverse events, and the efficacy results for each of the three studies selected by the applicant from literatures. Then, comments on the issues related to the study design and its efficacy results follow. Since the statistical issues on the efficacy analysis presented by the three studies are similar, instead of evaluating the efficacy of ondansetron 8 mg by each study, the assessment of the efficacy for the test drug ondansetron 8 mg is performed after presenting the summaries for the three studies.

The summary of the chemotherapy doses and efficacy results of the three studies are presented in Table 3.1.1 (extracted from Table 5 at page 8 of the applicant's proposed labeling). The full references for these three studies are listed in Appendix A.

Table 3.1.1 (Applicant's) Summary of the chemotherapy doses and efficacy results on the four Studies

Study	Ondansetron 8 mg IV SD	Granisetron 3 mg IV SD	Ondansetron 32 mg IV SD	Ondansetron 0.15 mg/kg x 3
Ruff				
Total Number of Patients:	165	169	162	NS
Cisplatin Dose				
<50 mg/m ²	25 (15%)	22 (13%)	21 (13%)	
50 mg/m ² - <70 mg/m ²	45 (27%)	54 (32%)	56 (35%)	NS
70 mg/m ² - <100 mg/m ²	72 (44%)	65 (38%)	65 (40%)	
≥100 mg/m ²	23 (14%)	28 (17%)	20 (12%)	
Emesis Complete Response (0 emetic episodes)	59% ^{†,‡}	56% [‡]	51% ^{†,‡}	NS
Emesis Complete + Major Response (≤2 emetic episodes)	76% ^{†,‡}	78% [‡]	74% ^{†,‡}	NS
No or Mild Nausea	71% [‡]	73% [‡]	69% ^{†,‡}	NS
Beck/Hainsworth				
Total Number of Patients: [§]	245	NS	220	234
Cisplatin Dose				
50 mg/m ² - 70 mg/m ²	107 (48.2%)	NS	93 (47.7%)	101 (50.2%)
≥100 mg/m ²	115 (51.8%)	NS	102 (52.3%)	100 (49.8%)
Emesis Complete Response (0 emetic episodes)	94 (42.3%)	NS	117 (60.0%)	103 (51.2%)
Emesis Complete + Major Response (≤2 emetic episodes)	139 (62.6%)	NS	156 (80.0%)	133 (66.2%)
No or Mild Nausea	NR	NS	NR	NR
Seynaeve				
Total Number of Patients:	173	NS	180	NS
Cisplatin Dose				
<50 mg/m ²	10 (6%)		6 (3%)	
50 mg/m ² - <70 mg/m ²	70 (40%)	NS	66 (37%)	NS
70 mg/m ² - <100 mg/m ²	66 (38%)		62 (34%)	
≥100 mg/m ²	27 (16%)		46 (26%)	
Complete + Major Response (≤2 emetic episodes)	74% [‡]	NS	78% [‡]	NS
No or Mild Nausea [†]	75% [‡]	NS	75% [‡]	NS

SD = Single Dose NS = Not Studied NR = Not Reported;

[†] 164 evaluable patients for the 8 mg dose (emesis); 160 evaluable patients for the 32 mg dose (emesis & nausea)

[‡] Results based on assessable patients: Ondansetron 8 mg (n = 222); Ondansetron 32 mg (n = 195); Ondansetron 0.15 mg/kg (n = 201)

[§] Results reported as percentages only; [§] Twenty-four hours post-dose.

The review order for the three trials shown below is based upon the order of these trials presented in Table 3.1.1.

3.1.a.1 Study Ruff, et al

Study Design and Endpoints

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, single-dose study. A total of 496 patients who were scheduled to receive their first course of cisplatin chemotherapy (≥ 50 mg/m²) were enrolled at 42 centers in seven countries. Patients were randomly assigned to receive a single dose of one of three IV anti-emetic regimens: ondansetron 8 mg, ondansetron 32 mg or granisetron 3 mg. Each loading dose was diluted to 50 mL in normal saline and administered over 15 minutes starting 20 minutes prior to the cisplatin infusion.

An emetic episode was defined as a single vomit or retch. Emetic episodes were, by definition, separated by the absence of vomiting or retching for at least 1 minute. Emesis control during the first 24 hours was scored as follows: complete response - 0 episodes; major response, 1-2 episodes; and failure, > 2 episodes, rescued or withdrawn due to lack of response. Nausea graded on a four-point scale (none, mild, moderate and severe) was evaluated at 24 hours following chemotherapy. Global satisfaction was recorded by the patient at 24 hours after the start of cisplatin using a 100 mm VAS. The applicant indicated that the primary endpoint for this study was complete or major control of acute (within 24 hours post-treatment) emesis.

Male and female patients, aged at least 18 years, who were scheduled to receive their first dose of cisplatin chemotherapy at a dose of ≥ 50 mg/m² administered as a single intravenous infusion given over a period of up to four hours either alone or in combination with other cytotoxics were enrolled. Patients were excluded if they had received non-cisplatin chemotherapy during the previous 6 months, had a severe concurrent illness (other than cancer), had other etiologies for emesis (e.g., GI obstruction, CNS metastases), had received anti-emetic therapy 24 hours prior to chemotherapy, had received benzodiazepines (except for night sedation), or concurrent corticosteroids (except for physiological supplementation, bone metastases or respiratory problems), had vomited within 24 hours prior to chemotherapy, or were pregnant.

Statistical Methodologies

The determination of study size was based on the assumption that complete or major control of emesis would be achieved in 75% of patients in the ondansetron 32 mg group. Using two-sided tests at an overall 5% significance level and a power of 0.8, approximately 450 patients (150 patients in each treatment group) would be required to detect a difference of at least 15% between ondansetron 32 mg and either of the other two treatment groups (ondansetron 8 mg and granisetron 3 mg).

The primary analysis was performed on the intent-to-treat population (i.e., all patients who were randomized and who received study antiemetic treatment and cisplatin chemotherapy). The safety analysis was performed on all patients who were randomized and who received study anti-emetic treatment. All analyses of efficacy data were stratified by cluster of centers. Clusters were based on country and, where appropriate, geographical region within the country and ranged in

size between 33 and 73 patients. The proportions of patients showing (1) complete emetic response, (2) complete or major emetic response or (3) no emesis and no nausea were compared between treatments using stratified Mantel-Haenszel chi-squared tests. Nausea grades and global satisfaction scores were compared between treatments using stratified Wilcoxon rank sum tests.

Patient Disposition

Patients were recruited at 42 centers in seven countries: Denmark, France, Germany, The Netherlands, South Africa, Switzerland, and the United Kingdom. Data concerning screening failures or early withdrawals were not presented. A total of 497 patients were included in the final safety analysis. One patient did not receive cisplatin and was excluded from the intent-to-treat analysis.

Demographics and Baseline Characteristics

The applicant indicated that the three treatment groups were well matched for age, gender, body surface area, alcohol use, tumor site, cisplatin dose, and concomitant chemotherapy. Overall, 44% of the patients were women; the most common malignancy (30%) in all three treatment groups was gynecological tumors.

Efficacy Results and Conclusions Provided by Applicant

Based upon the efficacy results reported by the literature for this study, the applicant indicated that there were no statistically significant differences between the three treatment groups regarding the number of patients experiencing complete or major emesis control (range of 74% to 78%) or mild or no nausea (range of 69% to 73%). Then, based upon the non-significant results from the efficacy comparisons for the three anti-emetic treatment groups, the applicant concluded that ondansetron 8 mg, ondansetron 32 mg, and granisetron 3 mg are equally effective in controlling acute emesis and nausea following cisplatin chemotherapy. Table 3.1.1.1 presented the results on emesis and nausea control.

Table 3.1.1.1 (Applicant's) Analysis results on emesis and nausea control

	Ondansetron 8 mg IV SD N = 165	Ondansetron 32 mg IV SD N = 162	Granisetron 3 mg IV SD N = 169
Emesis Control (a)	N = 164	N = 160	N = 169
Complete	59%	51%	56%
Major	17%	23%	22%
Complete + Major	76%	74%	78%
Nausea	N = 168	N = 160	N = 169
None	56%	48%	56%
Mild	15%	21%	17%
None + Mild	71%	69%	73%

(a) Complete = no emetic episodes; major = 1-2 emetic episodes.

Safety Evaluation

The applicant indicated that the most commonly reported drug-related adverse events were headache, diarrhea, constipation and dizziness; no differences were observed between treatment groups. No severe or unexpected drug-related adverse events were observed with ondansetron or granisetron. No further safety information was presented.

3.1.a.2 Study Beck TM, et al./Hainsworth JD, et al

Study Design and Endpoints

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, multiple- and single-dose study. The purpose of this study was to evaluate the efficacy of two fixed single-dose ondansetron regimens (8 mg and 32 mg) to the approved divided dose regimen (0.15 mg/kg x 3).

Chemotherapy-naïve adult cancer patients scheduled to receive moderate-dose (50 to 70 mg/m²) or high-dose (≥ 100 mg/m²) cisplatin chemotherapy were recruited at 26 centers. Patients were stratified according to their dose of cisplatin and then randomized (1:1:1) to receive either three 0.15 mg/kg IV doses (pre-dose and 4 and 8 hours post-dose), a single 8 mg IV dose administered 30 minutes prior to cisplatin, or a single 32 mg IV dose administered 30 minutes prior to cisplatin. Cisplatin was administered as a single IV infusion during a period of three hours or less. Other concomitant chemotherapy was allowed with the exception of the following: cyclophosphamide (> 500 mg/m²), nitrogen mustard (mechlorethamine), dacarbazine (DTIC), procarbazine, carmustine (BCNU), ifosfamide (> 1.5 g/m²), or carboplatin.

An emetic episode was defined as a single episode of vomiting, a single episode of retching, or any number of continuous vomits and/or retches. Emetic episodes by definition were separated by at least a one minute absence of both vomiting and retching. Emesis control during the first 24 hours was scored as follows: complete response, 0 episodes; major response, 1-2 episodes; minor response, 3-5 episodes; and failure, > 5 episodes, requirement for rescue anti-emetic therapy, or withdrawal from the study. Nausea which was graded using a visual analog scale (0, no nausea; 100, nausea as bad as it could be) was evaluated at 24 hours following chemotherapy. The primary endpoint in this study was the number of episode of acute emesis (within 24 hours post-treatment).

Chemotherapy-naïve cancer patients, aged 18 years or older, were eligible for the study if they had a Karnofsky performance status of at least 60%. Patients were excluded if they had impaired renal function (serum creatinine > 2 mg/dL or creatinine clearance ≤ 50 mL/min), ALT > 2 times the upper limit of normal, or if they had vomited or retched within 24 hours prior to the study. Patients could not have received any anti-emetic medication 24 hours prior to- or during the study period, or received radiation therapy to the abdominal or pelvic region 48 hours prior to- or during the study period.

Statistical Methodologies

The determination of sample size was not specified in either of the study reports. The Treatment groups were compared with regard to the number of emetic episodes using the Wilcoxon rank sum test. Patients who reported more than five emetic episodes or who were rescued or withdrawn for any reason were assigned the same arbitrarily high value (> 5) for number of emetic episodes. Treatments were also compared with respect to the proportion of patients with a complete response and the proportion of patients who were considered to have undergone unsuccessful treatment using the Mantel-Haenszel test. Additionally, treatment groups were compared with respect to time to first emetic episode using the Wilcoxon rank-sum test. The Wilcoxon rank-sum test also was used to compare treatment groups with respect to severity of nausea.

The applicant indicated that the authors stratified the analyses based on the dose of cisplatin received. In an analysis conducted by Baxter, when combining the medium and high dose cisplatin, the dose by treatment interaction effect was evaluated by the Statistical Analysis System (SAS) procedure CATMOD with the factors of dose, treatment, and dose by treatment interaction. The applicant indicated that the dose by treatment interaction was absent ($p=0.577$ and 0.542 for complete and complete + major emesis, respectively). Therefore, the treatment effect (32 mg, 8 mg, and continuous) was judged to be homogeneous between the cisplatin dosage groups, thus justifying the pooling across dosage groups. Baxter therefore conducted an analysis combining the high and medium dose cisplatin results.

Using assumptions similar to the other primary studies that complete or major control of emesis would be achieved in 75% of patients in the ondansetron 32 mg group, and using two-sided tests at an overall 5% significance level and a power of 0.8, the applicant showed that approximately 450 patients (150 patients in each treatment group) would be required to detect a difference of at least 15% between ondansetron 32 mg and either of the other two treatment groups (ondansetron 8 mg and ondansetron 0.15 mg/kg x 3).

Patient Disposition

Patients were recruited at 26 different centers in the United States. A total of 703 patients were enrolled, and 699 patients received active medication: 234 received the weight-based dose, 245 received a single 8 mg dose, and 220 received a single 32 mg dose. Six hundred eighteen (618) patients (317 receiving high-dose cisplatin and 301 receiving low dose cisplatin) were included in the efficacy analyses; 15 patients with violations of the inclusion/exclusion criteria and 66 patients with protocol violations were excluded from the analysis.

No information concerning the number of patients who completed the study was available.

Demographics and Baseline Characteristics

The three treatment groups were similar with regard to age and gender distribution. Patients ranged in age from 20 to 87 years, and more males ($\geq 65\%$ in each treatment group) than females ($\leq 35\%$ in each treatment group) were enrolled. Lung cancer was the most common malignancy.

Efficacy Results and Conclusions Provided by Applicant

The applicant indicated that the publication presents efficacy data for an evaluable population of 618 patients. The investigator indicated analyses were also performed for the 699 intent-to-treat patients, and that similar reports were found.

Following high-dose and medium-dose cisplatin regimens, the 32 mg single dose was statistically significantly superior to the 8 mg single dose for total number of emetic episodes, complete emetic response, and failure rate with p-values less than the significance level of 0.05. In addition, the applicant indicated that the 32 mg single dose was as effective as the 0.15 mg/kg x 3 dosing regimen with regard to complete response (medium-dose cisplatin), number of emetic episodes (high-dose cisplatin). The 8 mg single dose was as effective as the 0.15 mg/kg x 3 dosing regimen with regard to total number of emetic episodes, complete response and failure rate ($P > 0.1$).

For median changes in nausea scores, the 32 mg single dose was more effective than the 8 mg single dose when moderate doses of cisplatin were administered ($P=0.008$), but not when high doses of cisplatin were administered ($P=0.092$). There were no statistically significant differences between the 8 mg ondansetron dose and the 0.15 mg/kg dosing regimen for both moderate and high dose cisplatin administration ($P > 0.1$).

As indicated in the section of Statistical Methodologies, the applicant also conducted an analysis on emesis after pooling the medium and high dose cisplatin groups. The results of the efficacy analyses on emesis and nausea control along with the pooling analysis on emesis were presented in Table 3.1.2.1.

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Table 3.1.2.1 (Applicant's) Analysis results on emesis and nausea control

	Ondansetron 0.15 mg/kg x 3	Ondansetron 8 mg IV SD	Ondansetron 32 mg IV SD
HIGH-DOSE CISPLATIN			
Emesis Control N,%(a)	N = 100	N = 115	N = 102
Complete	41 (41%)	40 (35%)	49 (48%)
Major	19 (19%)	25 (22%)	25 (25%)
Complete + Major	60 (60%)	65 (57%)	74 (73%)
Minor	4 (4%)	11 (10%)	8 (8%)
Failure	36 (36%)	39 (34%)	20 (20%)
Nausea Score (b)			
Median Change	23.0	26.5	16.0
MEDIUM-DOSE CISPLATIN			
Emesis Control N,%(a)	N = 101	N = 107	N = 93
Complete	62 (61%)	54 (50%)	68 (73%)
Major	11 (11%)	20 (18%)	14 (15%)
Complete + Major	73 (72%)	74 (69%)	82 (88%)
Minor	6 (6%)	8 (7%)	3 (3%)
Failure	22 (22%)	25 (23%)	8 (9%)
Nausea Score (b)			
Median Change	9.0	14.0	3.0
COMBINED-DOSE CISPLATIN			
Emesis Control N,%(a)	N = 201	N = 222	N = 195
Complete	51.2%	42.3%	60.0%
Complete + Major	66.2%	62.6%	80.0%

(a) Complete = no emetic episodes; major = 1-2 emetic episodes; minor = 3-5 episodes; failure = >5 episodes or withdrawn/rescued.

(b) Visual analog scale (0, no nausea; 100, nausea as bad as it could be).

Based upon the results of combined-dose cisplatin shown by Table 3.1.2.1, the applicant made the following statements:

- **The 8 mg single dose was comparable to the 0.15 mg/kg x 3 dosing regimen for both complete and complete + major responses;**
- **The 32 mg single dose was comparable to the 0.15 mg/kg x 3 dosing regimen with regard to complete response, and more effective than the 0.15 mg/kg x 3 dosing regimen with regard to complete + major response (p<0.05);**
- **The 32 mg single dose was more effective than the 8 mg single dose (p<0.05) with regard to complete and complete + major response.**

Finally, based upon the non-significant results on the efficacy comparisons, the applicant made the following conclusions:

- the 8 mg single dose was comparable to the 0.15 mg/kg x 3 dosing regimen for both complete and complete + major anti-emetic response;
- the 32 mg single dose was comparable to the 0.15 mg/kg x 3 dosing regimen with regard to complete response, and more effective than the 0.15 mg/kg x 3 dosing regimen with regard to complete + major response (p<0.05);

- the 32 mg single dose was more effective than the 8 mg single dose ($p < 0.05$) with regard to complete and complete + major response.

Safety Evaluation

Ondansetron was well tolerated. The most common adverse events were headache, fever, and diarrhea. Headache occurred in a greater number of patients in the 32 mg group; otherwise, no differences were noted between the treatment groups. No significant differences were observed among the three treatment groups with respect to laboratory indices of safety, which included transaminase elevations. However, there was an approximate 10-fold increase in the incidence of clinically significant transaminase elevations when high-dose cisplatin was administered compared to medium-dose cisplatin.

3.1.a.3 Study Seynaeve C, et al

Study Design and Endpoints

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, multi-dose study. A total of 535 patients who were scheduled to receive their first course of cisplatin chemotherapy (50 - 120 mg/m²) were enrolled: 182 patients received ondansetron 8 mg IV 30 minutes prior to chemotherapy, followed by 1 mg/hr IV for 24 hours; 180 patients received ondansetron 32 mg IV 30 minutes prior to chemotherapy, followed by placebo for 24 hours; and 173 patients received ondansetron 8 mg IV 30 minutes prior to chemotherapy, followed by placebo for 24 hours.

An emetic episode was defined as a single vomit or retch, or any number of continuous vomits or retches that were separated by the absence of symptoms for at least one minute. Emesis control during the first 24 hours was scored as follows: complete response, 0 episodes; major response, 1-2 episodes; minor response, 3-5 episodes; and failure, > 5 episodes. Patients who experienced ≥ 3 episodes and were rescued with additional anti-emetic medication were considered treatment failures. Nausea graded on a four-point scale (none, mild, moderate and severe) was evaluated at 8 and 24 hours following chemotherapy. The applicant indicated that the primary endpoint for this study was complete and major control of acute (within 24 hours post-treatment) emesis.

Male or female patients, aged at least 18 years, who were scheduled to receive their first course of chemotherapy with cisplatin at a dose of 50-120 mg/m² given over a period of up to four hours, either alone or in combination with other cytotoxic drugs, were eligible for the study. Patients were excluded if they experienced nausea or vomiting and/or received anti-emetic therapy in the 24-hour period prior to the start of treatment, had a serious concurrent illness other than cancer or another etiology for emesis, and concurrently used corticosteroids (except for physiological supplementation) or benzodiazepines (unless given for night sedation).

Statistical Methodologies

The applicant indicated that the required number of patients was calculated under the assumption that complete and major anti-emetic control would be achieved in 75% of the patients with the continuous infusion schedule (8 mg+1 mg/hr). Using two-sided tests at an overall 5% significance level and a power of 0.8, 170 (of which 150 could be expected to be evaluable) would be required in each group to detect a difference of at least 15% between the continuous infusion regimen and the either of the single dose regimens (8 mg and 32 mg).

All analyses were performed on the total population (intent-to-treat analysis) providing efficacy data were available. The proportions of patients showing a complete or a complete plus major response were compared between treatments using a two-sided Mantel-Haenszel chi-squared test stratified by center. The time to first emetic episode was compared for all pairs of treatment using Wilcoxon rank sum analysis. A separate analysis was also carried out after stratification by country, using the Van Elteren method for combining Wilcoxon statistics over strata. The grades of nausea for the 8 and 24 hr after chemotherapy were analyzed using the stratified, extended Mantel-Haenszel method. Subset analysis for the difference in gender, cisplatin dose and concurrent chemotherapy was carried out using the chi-squared test of 2x2, 2x3 and 2x4 tables.

Patient Disposition

The applicant indicated that a total of 535 patients were enrolled by more than 25 investigators in 11 countries: Austria, Belgium, Germany, Finland, Holland, Denmark, Iceland, Israel, Luxembourg, Spain, and the United Kingdom. The number of subjects who failed screening was not specified.

Forty-two (42) patients did not fully comply with the protocol: 18 received an incorrect cisplatin dose schedule, 12 received concurrent anti-emetics, seven were not naïve to chemotherapy, four had severe concurrent illnesses, and one was withdrawn due to an adverse event that was unrelated to ondansetron. Details concerning early withdrawal from the study were not provided.

Demographics and Baseline Characteristics

The applicant indicated that the three treatment groups were well matched for age, gender, alcohol intake, primary tumor site, cisplatin dose, duration of cisplatin infusion, and concomitant chemotherapy. Overall, 51% of the patients were women.

Efficacy Results and Conclusions Provided by Applicant

Based upon the efficacy results reported by the literature for this study, the applicant indicated that there were no statistically significant differences between treatments regarding the number of patients experiencing mild or no nausea at 8 hours ($\geq 85\%$) or 24 hours ($\geq 75\%$) post-chemotherapy. Similarly, no differences were noted in the percentage of patients that

experienced complete + major emesis control over the 24-hour post-dosing period (74% - 78% in all three treatment groups).

The efficacy analysis results on emesis and nausea were presented in Table 3.1.3.1.

Table 3.1.3.1 (Applicant's) Efficacy analysis results on emesis and nausea

	Ondansetron 8 mg IV + 1 mg/hr for 24 hr N = 182	Ondansetron 32 mg IV SD N = 180	Ondansetron 8 mg IV SD N = 173
Emesis Control - Complete + Major	74%	78%	74%
Nausea (None + Mild)			
8 hr	88%	87%	85%
24 hr	77%	75%	75%
Complete emesis control and none or mild nausea	52%	53%	51%

(a) Complete = 0 emetic episodes; Major = 1-2 emetic episodes

Finally, base upon the non-significant results on the efficacy comparisons, the applicant concluded that a single intravenous dose of 8 mg ondansetron given prior to chemotherapy was as effective as a 32 mg daily dose given as either a single dose or a continuous infusion in the prophylaxis of acute cisplatin-induced emesis.

Safety Evaluation

The applicant indicated that all three ondansetron dosing regimens were well tolerated. The most commonly reported events considered by the investigator to be possibly, probably or almost certainly related to ondansetron was headache (11% of all patients), followed by diarrhea and changes in laboratory values (both 3% of all patients). No patients were withdrawn from the study due to adverse events related to ondansetron. Details concerning the one subject withdrawn due to an unrelated adverse event were not provided.

Events that were identified as being possibly related to ondansetron were severe constipation, Pseudo-membranous colitis, and elevations in ALT and AST. Both the constipation and colitis resolved spontaneously. Transient changes in ALT and AST were noted for four patients following the 8 mg infusion, seven patients following the 32 mg single dose and two patients following the 8 mg single dose. All changes resolved at follow-up, and none were associated with any clinical signs or symptoms.

3.1, Part B Evaluation of Efficacy

Besides the efficacy comparisons between ondansetron 8 mg and ondansetron 32 mg reported by three studies (Ruff, Beck/Hainsworth, and Seynaeve), the efficacy comparisons for ondansetron 8 mg versus granisetron 3 mg (Ruff) and ondansetron 8 mg versus ondansetron 0.15 mg/kg x 3 (Beck/Hainsworth) were respectively, reported by Studies Ruff and Beck/Hainsworth. However,

based upon the literature submitted by the applicant, the statistical issues for the efficacy comparisons for ondansetron 8 mg versus granisetron 3 mg and ondansetron 8 mg versus ondansetron 0.15 mg/kg x 3 were similar to that of ondansetron 8 mg versus ondansetron 32 mg. Accordingly, the efficacy comparison between ondansetron 8 mg versus ondansetron 32 mg **reported by three literatures is the focus on the reviewer's efficacy evaluation. For the evaluations on the efficacy comparisons of ondansetron 8 mg versus granisetron 3 mg and ondansetron 8 mg versus ondansetron 0.15 mg/kg x 3, refer to that of ondansetron 8 mg versus ondansetron 32 mg, given by the section of "Reviewer's Comments" below.**

In order to validate the efficacy claim made by the applicant, this reviewer comments on the following four issues with regard to the study design along with its statistical analysis provided by the literatures submitted by the applicant: 1) invalid equivalence analysis, 2) inadequate primary endpoint, 3) quality of the three studies and 4) incomplete literature search.

Reviewer's Comments

1) Issue on the invalid equivalence analysis

As noted by this reviewer in the sub-section of **"Efficacy Results and Conclusions Provided by Applicant" at pages 9, 13, and 16, of this review**, the applicant treated the non-significance results for testing the null hypothesis of no efficacy differences between ondansetron 8 mg and ondansetron 32 mg as demonstrating efficacy equivalence/similarity for ondansetron 8 mg to 32 mg. However, it is well known to the statistician that not rejecting the null hypothesis of no efficacy difference between ondansetron 8 mg and 32 mg in the superiority analysis does not mean we accept the null hypothesis and assert that the efficacy of the two treatments are equivalent. It only indicates that no sufficient data evidence to reject the null hypothesis of no treatment difference and to support that the efficacy of the two treatments is different. Therefore, this non-significant result does not provide data evidence to support the equivalence of the two drugs. In other words, as the superiority analysis, the equivalence for the two treatments ondansetron 8 mg versus 32 mg should be put in the alternative hypothesis. Then, in order to claim the equivalence for ondansetron 8 mg to 32 mg, the null hypotheses of non-equivalence for the two treatments should be rejected.

In order to correct the invalid equivalence claim for the two treatments (ondansetron 8 mg versus ondansetron 32 mg) made by the applicant, this reviewer gives comments on the following two issues: criteria used for the equivalence analysis and loss of the opportunity for equivalence margin selection.

- Issue on the criteria used for equivalence analysis

From ICH E10, "Guidance for Industry, E10 choice of Control Group and Related Issues in Clinical Trials", one learns that the equivalence trials are designed to demonstrate that the efficacy of a new drug is similar in efficacy to a standard agent. Most of these are actually non-inferiority trials, attempting to show that the new drug is not less effective than the control by

more than a defined amount, generally called margin. ICH E10 also emphasizes that prior to the trial, the equivalence or non-inferiority margin, sometimes called *delta*, is selected. This margin is the degree of inferiority of the test treatments to the control that the trial will attempt to exclude statistically. In addition, theoretically, it is always possible to choose an equivalence margin leading to a conclusion of equivalence if it is chosen after the data have been inspected. Accordingly, the equivalence analysis along with its margin should be pre-specified at the protocol stage before conducting the study.

As to the principle of margin selection, E10 states that the margin chosen for an equivalence trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. The margin generally is identified based on past experience (historical studies) in placebo-controlled trials of adequate design under conditions similar to those planned for the new trial.

Based on the information provided by E10, instead of using non-significant results from the literature to claim equivalence of two treatments (ondansetron 8 mg versus 32 mg), the applicant first should have conducted studies based upon a delta margin ($\Delta > 0$) pre-specified in the protocol and selected by following the principle stated in E10. Then, with the selected margin (Δ), in order to demonstrate clinical equivalence between ondansetron 8 mg and ondansetron 32 mg, the following two null hypotheses formulated by complete or major control of acute emesis need to be rejected:

$$H_{01}: P_{\text{ondansetron-8mg}} - P_{\text{ondansetron-32mg}} \leq -\Delta \text{ or } H_{02}: P_{\text{ondansetron-8mg}} - P_{\text{ondansetron-32mg}} \geq \Delta;$$

where $P_{\text{ondansetron-8mg}}$ and $P_{\text{ondansetron-32mg}}$ are probabilities of complete or major control of acute emesis for ondansetron 8 mg and ondansetron 32 mg, respectively.

Finally, a 95% two-sided confidence interval on the difference of the two probabilities, $P_{\text{ondansetron-8mg}}$ and $P_{\text{ondansetron-32mg}}$, can be constructed to test the two one-sided null hypotheses $H_0: \cup_{i=1, 2} H_{0i}$ each at significant level of 0.025. If the 95% two-sided confidence interval is included in the interval $(-\Delta, \Delta)$, then the applicant can claim that the efficacy of ondansetron 8 mg is equivalent to that of ondansetron 32 mg.

As a result, to demonstrate the equivalence of the two drugs ondansetron 8 mg and ondansetron 32 mg, the applicant should have selected an adequate margin (Δ) and shown that the 95% two-sided confidence interval on the difference of the two probabilities, $P_{\text{ondansetron-8mg}}$ and $P_{\text{ondansetron-32mg}}$, was included in the interval $(-\Delta, \Delta)$. Thus, the equivalence claim based upon the non-significant results made by the applicant is not a valid equivalence analysis.

- Loss of opportunity for equivalence margin selection

Since the statistical method employed by the three literatures for the efficacy comparison of ondansetron 8 mg versus ondansetron 32 mg was the superiority analysis, no equivalence margin was pre-specified by the authors before conducting the trials. As indicated in the previous sub-section of **“Issue on the criteria used for equivalence analysis”**, in order to perform a valid equivalence analysis, the margin should be pre-specified in the protocol stage before the trial was conducted.

However, after examining data for the three trials (Studies Ruff, Beck, and Seynaeve), the applicant has lost the opportunity to identify a credible equivalence margin and is no longer able to perform a valid equivalence analysis. The invalidity of the post-hoc non-inferiority analysis can be attributed to the following three issues:

a) Loss of credibility on the selection of non-inferiority margin

After inspecting data, the margin selected is influenced by the efficacy data reported by the three studies (Studies Ruff, Beck, and Seynaeve). As a result, the selected non-inferiority margin is biased in favor of the study drug (ondansetron 8 mg) and thus, loses its credibility to assess the non-equivalence of ondansetron 8 mg versus ondansetron 32 mg. As indicated by this reviewer in the previous sub-section of **“Issue on the criteria used for equivalence analysis”**, in theory, it is always possible to choose an equivalence margin leading to a conclusion of equivalence if it is chosen after the data have been inspected.

b) Loss of position for equivalence analysis as the confirmatory hypothesis

As indicated by the authors for the literatures regarding the three trials, superiority efficacy comparisons for ondansetron 8 mg versus 32 mg on prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy assessed by complete response and no rescue therapy were planned before conducting the trial. The applicant employed these three trials as the phase III studies to support the equivalence of ondansetron 8 mg versus 32 mg. It is well known that a phase III study is a confirmatory clinical trial. It means that a phase III study is designed to confirm that ondansetron 8 mg has efficacy for the proposed indication by testing a pre-specified null hypothesis formulated based upon superiority or equivalence setting to answer whether or not the study drug ondansetron 8 mg is effective to prevent nausea and vomiting associated with associated with initial and repeated courses of emetogenic cancer chemotherapy. Therefore, if the applicant decided on applying equivalence analysis to confirm that ondansetron 8 mg is effective for the proposed indication, the equivalence null hypothesis along with its delta margin should have been pre-specified during the protocol stage. In this regard, instead of selecting literatures of superiority trials, the applicant should have been selected literatures of equivalence trials with margin properly selected based upon the recommendation of ICH E10.

In contrast, if the equivalence margin is selected after data is examined, not only is the non-equivalence null hypothesis not formulated before conducting the trial, but also the selected

margin is data dependent and is biased. Thus, the applicant has lost the opportunity to make the non-equivalence null hypothesis as the confirmatory hypothesis.

c) Significance level of the non-inferiority analysis inflated

As commented in the above issue, after un-blinding data codes, the post-hoc equivalence margin selected may be directly or indirectly influenced by examination of the three trial data (Studies Ruff, Beck, and Seynaeve). As a result, the significance level for testing the null hypothesis of ondansetron 8 mg non-equivalent to ondansetron 32 mg is inflated. For detail discussion on the issue for the inflation of the significance level, refer to Hung HMJ and Wang SJ, "Multiple testing of non-inferiority hypotheses in active controlled trials", *Journal of Biopharmaceutical Statistics* 14(2), 327-335, 2004.

2) Inadequate primary endpoint

As noted by this reviewer, the applicant mainly employed complete response plus major control (i.e., 0 to 2 emeses) and no rescue therapy as the primary endpoint to assess the efficacy of ondansetron 8 mg by the submitted three trials (Studies Ruff, Beck, and Seynaeve). However, the medical reviewer, Dr. Lolita Lopez, deems that the primary endpoint should be no emesis and no rescue therapy. Thus, the equivalence claim for ondansetron 8 mg versus ondansetron 32 mg made by the applicant based on the efficacy results assessed by the proportions of 0 to 2 emeses shown by the three submitted trials may not be clinically meaningful.

In addition, since the applicant did not provide data for the primary endpoint defined by the medical reviewer, in order to demonstrate the flaw of the equivalence margin selection after un-blinding data code, this reviewer performs the two-sided 95% confidence interval on the proportion difference of zero emesis and no rescue therapy (primary endpoint recommended by medical reviewer) for ondansetron 8 mg minus ondansetron 32 mg. In other words, the purpose of performing this equivalence analysis is to emphasize that after examining data for the three trials (Studies Ruff, Beck, and Seynaeve), the applicant has lost the opportunity to identify a credible equivalence margin and is no longer able to perform a valid equivalence analysis.

Due to no zero emesis data reported by study Seynaeve, the 95% two-sided confidence is performed separately using data from the two other two studies (Studies Ruff, Beck). Table 3.2.1 presents the analysis results.

Table 3.2.1 (Reviewer's) Exact two-sided 95% confidence interval on proportion difference of zero emesis

Study	Ondansetron 8 mg n/N (%)	Ondansetron 32 mg n/N (%)	Exact two-sided 95% CI for 8 mg – 32 mg
Ruff	97/164 (59)	82/160 (51)	(-0.03, 0.19)
Beck [†]	94/222 (42)	117/195 (60)	(-0.27, -0.08)

[†]: proportions of zero emesis were combined from high- and low-dose cisplatin reported by the applicant.

Table 3.2.1 indicates that for Study Ruff, the lower and upper bounds for the two sided 95% confidence interval on the proportion difference of no-emesis for ondansetron 8 mg minus 32

mg are -3% and 19%, respectively while for Study Beck, the lower and upper bounds are -27% and -8%, respectively. If equivalence margin 10% was pre-specified in the protocol before conducting the two studies Ruff and Beck, then, since the two Ruff and Beck confidence intervals (-0.03, 0.19) and (-0.27, -0.08) are not included in the interval of (-0.10, 0.10) formulated by the pre-specified margin of 10%, the equivalence of the two treatments is not supported by the two studies.

However, if no margin was pre-specified in the protocol, then, after inspecting data for the two active-control studies (Studies Ruff and Beck), in order to show the equivalence of the two treatments (ondansetron 8 mg versus 32 mg), it is very possible that the equivalence margin of 28% which has no statistical-sound support from the historical placebo control trials conducted under the conditions similar to those of the two studies (Ruff and Beck) would be selected. Although the equivalence of the two treatments is achieved, using this margin to perform the equivalence analysis not only loses the credibility on the selection of equivalence margin but also inflates the significance level of equivalence analysis. In addition, as commented in the sub-section of **“Loss of credibility on the selection of non-inferiority margin”**, it is always possible to choose an equivalence margin (for example 28%) leading to an erroneous conclusion of equivalence if it is chosen after the data have been inspected, as shown by this hypothetical example.

3) Issue on the quality of the three studies

As indicated by E10, assay sensitivity is an essential attribute of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment. Assay sensitivity is important in any trial but has different implications for trials intended to show differences between treatments (superiority trials) and trials intended to show equivalence. Unlike a superiority trial being able to fail to lead to a conclusion of efficacy for the test treatment, an equivalence trial which is intended to demonstrate efficacy by showing a test treatment to be equivalent to an active control, but lacks assay sensitivity, may find a treatment to be equivalent to an ineffective control and lead to an erroneous conclusion of efficacy.

ICH E10 further emphasizes that in order to deduce the presence of assay sensitivity in a non-inferiority or equivalence trial, not only should the design of the new equivalence trial be similar (e.g., entry criteria, allowable concomitant therapy) to that of historical trials used to determine historical evidence of sensitivity to control drug effects; but, in addition, the actual study population entered, the concomitant therapies actually used, etc., should be assessed to ensure that conduct of the study was, in fact, similar to the historical trials, i.e., the new trial conduct should also adhere closely to that of the historical trials. Finally, the new trial should also be conducted with high quality (e.g. good compliance, few losses to follow-up). Together with historical evidence of sensitivity to drug effects, appropriate trial conduct provides assurance of assay sensitivity in the new active control trial.

However, the literature submitted by the applicant only provided information on the summary data for the two treatment groups, ondansetron 32 mg versus ondansetron 8 mg, on demographics,

baseline characteristics, and efficacy comparisons. **As indicated in section 2.2 “Data Sources”,** the applicant did not submit raw data on the three studies (Seynaeve, Ruff, and Beck/Hainsworth) for the Agency to review. Without detailed information (raw data) for individual patients enrolled by the three studies, the Agency can not assess the quality and credibility of the data collected and the analyzed results reported by the three studies by performing imperative efficacy analyses (for example, treatment by center interaction, treatment efficacy by center, prognostic analysis to identify baseline variable affected the primary endpoint, etc). If the three trials were improperly conducted, the reference drug ondansetron 32 mg may not be effective in the three trials reported by the literature. In addition, due to no placebo arm included in any of the three studies, the concern of the lack of effectiveness of ondansetron 32 mg can not be ruled out.

Finally, since these three trials were designed for superiority analysis, no equivalence margin was selected by authors or by the applicant based upon the principle recommended by ICH E10. Accordingly, the concern of lack of assay sensitivity for ondansetron 32 mg embedded in the three trials (Seynaeve, Ruff, and Beck/Hainsworth) and no equivalence margin pre-selected before conducting the three trials result in the equivalence claim made by the applicant for ondansetron 8 mg versus ondansetron 32 mg being not statistically meaningful.

4) Issue on incomplete literature search

It was possible that there were more reports (published or unpublished) which compared the efficacy between ondansetron 8 mg versus ondansetron 32 mg that were not selected by the applicant, since the three trials were conducted more than 10 years ago. The efficacy differences on the primary endpoint for the two treatments (ondansetron 8 mg and ondansetron 32 mg) studied by those published/unselected literatures not selected by the applicant may be worse than the three trials selected by the applicant. As a consequence, the true efficacy difference on the primary endpoint (complete or major response) may not be represented by the three trails submitted by the applicant.

3.2 Evaluation of Safety

Safety reports from individual studies are presented in 3.1, Part A.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS – Not Applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As indicated by this reviewer in the beginning of **section 3.2 “Evaluation of Efficacy”, the issues** of equivalence claim for ondansetron 8 mg versus granisetron 3 mg and ondansetron 8 mg versus ondansetron 0.15 mg/kg x 3 are similar to those of ondansetron 8 mg versus ondansetron 32 mg. In this section, the statistical issues and collective evidence are discussed for the efficacy

comparison between ondansetron 8 mg and ondansetron 32 mg.

- The applicant claimed the efficacy equivalence/similarity of ondansetron 8 mg to ondansetron 32 mg based upon the non-significant result shown in the superiority analysis reported by the three selected trials (Ruff, Beck/Hainsworth, and Seynaeve). However, it is well known to the statistician that the inability to reject the null hypothesis of no efficacy difference between ondansetron 8 mg and 32 mg dose does not mean we accept the null hypothesis and assert that the efficacy of the two treatments are equivalent. It only indicates that there is not sufficient data to reject the null hypothesis of no treatment difference and to support the alternative hypothesis of treatment difference. Therefore, this result does not support the equivalence of the two drugs.

In order to demonstrate the equivalence of the two drugs ondansetron 8 mg and ondansetron 32 mg, the applicant should have selected an adequate margin (Δ) and shown that the 95% two-sided confidence interval on the difference of probabilities for patients with 0 to 3 emeses and no rescue therapy between ondansetron 8 mg and 32 mg was included in the interval, $(-\Delta, \Delta)$, formulated by the margin of Δ . It follows that the equivalence claim based upon the non-significant result shown in the superiority analysis made by the applicant was not based upon a valid equivalence analysis and is not acceptable.

- After examining data for the three trials (Studies Ruff, Beck, and Seynaeve), the applicant had lost the opportunity to identify a just equivalence margin and is no longer able to perform a valid equivalence analysis.
- The applicant mainly employed complete response plus major control (i.e., 0 to 2 emeses) and no rescue therapy as the primary endpoint to assess the efficacy of ondansetron 8 mg for the submitted three trials (Studies Ruff, Beck, and Seynaeve). However, the medical reviewer, Dr. Lolita Lopez, deems that the primary endpoint should be no emesis and no rescue therapy. Accordingly, the equivalence claim of ondansetron 8 mg to ondansetron 32 mg made by the applicant based on the efficacy results assessed by the proportions of 0 to 2 emeses shown by the three submitted trials may not fully characterize the proposed indication.
- Only the summary data reported in the literature on demographics, baseline characteristics, and efficacy comparisons for treatment groups were provided. Without detail information (raw data) for individual patients enrolled by the three studies (Seynaeve, Ruff, and Beck/Hainsworth), the Agency can not assess the quality and credibility of the data collected and the analyzed results reported by the three studies by performing imperative efficacy analyses (for example, treatment by center interaction, treatment efficacy by center, prognostic analysis to identify baseline variable affected the primary endpoint, etc). If any of the three trials were improperly conducted, the reference drug ondansetron 32 mg may not be effective in that trial. In addition, due to lack of placebo arm in any of the three studies, the concern about the lack of effectiveness of ondansetron 32 mg can not be ruled out.

Finally, since these three trials were designed for superiority analysis, no equivalence margin was selected by authors or by the applicant based upon the principle recommended by ICH E10. Accordingly, the concern of lack of assay sensitivity for

ondansetron 32 mg embedded in the three trials (Seynaeve, Ruff, and Beck/Hainsworth) and no equivalence margin pre-selected before conducting the three trials result in the equivalence claim made by the applicant for ondansetron 8 mg versus ondansetron 32 mg being not statistically meaningful.

- It was possible that there may be more literature (published or un-published) which compared the efficacy between ondansetron 8 mg versus ondansetron 32 mg which were not selected by the applicant. The efficacy differences on the primary endpoint for the two treatments studied by those published/unselected literatures may be worse than the three trials selected by the applicant. As a consequence, the true efficacy difference on the primary endpoint (complete + major responses) may not be represented by the three trails (Studies Ruff, Beck, and Seynave) submitted by the applicant.

5.2 Conclusions and Recommendations

From the statistical perspective, based upon the **remarks stated in the section of "Statistical Issues and Collective Evidence"**, **the literature submitted by the applicant does not provide** substantial evidence to support that the efficacy of ondansetron 8 mg is equivalent to that of an approved drug for the prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy.

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6.0 APPENDIX A

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3. Ruff P, Paska W, Goedhals L, Pouillart P, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: A multicentre double-blind, randomised, parallel-group study. *Oncology* 1994;51:113-8.
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