CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020103, S015

STATISTICAL REVIEW(S)

CSO/Medical

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 20-103/015

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Drug Class: 1S

Applicant: Glaxo Wellcome Inc.

Name of Drug: Zofran (Ondansetron hydrochloride) Tablets

Indication: Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin

Documents Reviewed: NDA Vol. 1, 4-17 Dated August 28, 1998

User Fee Date: 8/28/99 (12 mos), 6/28/99 (10 mos)

Statistical Reviewer: Milton C. Fan, Ph.D.

Medical Reviewer: This review has been discussed with medical officer, Hugo Gallo-Torres, MD, Ph.D.

Key Words: Intent-to-treat, placebo historical control

A. Background

FDA has approved 32mg ondansetron injection for prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy. Oral ondansetron 8mg TID was approved in 1992 for prevention of nausea and vomiting in patients receiving moderately emetogenic cancer chemotherapy. Subsequently to the 8mg TID approval, oral ondansetron 8mg BID was shown to be effective in moderately emetogenic chemotherapy (NDA 20-103, Supplement 008).

There are no oral antiemetics that provide a single dose regimen for adequate control in preventing nausea and vomiting associated with moderately to highly emetogenic cisplatin-based (≥ 50 mg/m^2) chemotherapy.

In the current NDA, the sponsor seeks approval of a single dose of ondansetron 24mg for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy (cisplatin ≥ 50 mg/m^2).

The sponsor has submitted three controlled efficacy studies in support of the proposed claim. Two primary efficacy studies (S3AA3012, S3AA3004/3007) and one supporting study (S3AB3008) were conducted in cancer patients receiving highly emetogenic chemotherapy (i.e., cisplatin ≥ 50 mg/m^2).

This review will address only the two primary efficacy studies (S3AA3012, S3AA3004/3007).

B. Protocol S3AA3012 (U.S. Active Controlled Study)

1. Description of Study

This study was a randomized, double-blind, parallel, multicenter trial to evaluate the efficacy and safety of oral ondansetron, 8mg administered twice daily, 24mg administered once daily, and 32mg administered once daily, in the prevention of nausea and vomiting associated with cisplatin (≥ 50 mg/m^2) chemotherapy.

The objective was to show oral ondansetron either 24mg or 32 mg administered once daily was superior to oral ondansetron 8mg administered twice daily

The treatment periods began at the time of study drug administration (30 minutes prior to cisplatin infusion initiation) and ended 24 hours after the initiation of the cisplatin infusion.

Eligible patients had histologically confirmed diagnosis of cancer and were scheduled to receive their first course of cisplatin chemotherapy. All patients received chemotherapy regimens containing cisplatin ≥ 50 mg/m^2 administered over a period of ≤ 3 hours.

Efficacy data were collected for each subject for the 24 hours after initiation of cisplatin. The primary efficacy variable was the number of patients with zero emetic episodes who completed the trial without rescue over the 24-hour study period. The following adequate definitions were used to assess emetic episodes:

Vomiting: The expulsion of stomach contents through the mouth.

Retching: An attempt to vomit that is not productive of stomach contents.

Emetic Episode: A single vomit or retch or any number of continuous vomits or retches. Continuous vomits or retches were defined as two or more vomits or retches with a gap of less than one minute between the individual vomits or retches.

The number of emetic episodes was classified into one of following response categories:

Complete response: No emetic episode over the 24-hour period following cisplatin initiation and at the most mild nausea

Major response: One to two emetic episodes over the 24-hour period following cisplatin initiation

Minor response: Three to five emetic episodes over the 24-hour period following

cisplatin initiation

Therapeutic failure: One or more of the following:
More than five emetic episodes over the 24-hour period following cisplatin initiation
Requirement of rescue therapy due to severity of emesis during the 24-hour period following cisplatin initiation
Severity of nausea or vomiting resulting in withdrawal from the study

Withdrawal: Withdrawal from study due to other reasons (e.g., adverse events, administrative errors, etc.).

To qualify as a complete, major, or minor response, the subject had to have completed the entire post-treatment period without rescue. Patients without a recorded number of emetic episodes and who did not otherwise qualify as treatment failures were considered non-evaluable for efficacy.

The secondary efficacy variables included the number of patients with complete plus major treatment response, the number of patients with therapeutic failure, time to treatment failure (i.e., first emetic episode, withdrawal, or rescue), and subject assessment of nausea.

Nausea was measured by utilizing 11-point, whole number, linear numerical scale from 0-10. Zero represents "No Nausea" while 10 represents nausea "as bad as it could be."

Safety evaluation included clinical adverse events and laboratory safety data. Patients were monitored for adverse events occurring from the time of study drug administration until 24.5 hours post study drug administration. Only adverse events related to study drug were reported during the post-treatment period (immediately following the 24.5 hour treatment period or up to 8 days after the administration of study drug).

Patients were randomized (1:1:1 ratio) within blocks of six to receive one of the three treatment arms: 8mg BID, 24mg QD or 32mg QD

The 24mg and 32mg treatment groups were compared against the 8mg treatment group using the Cochran-Mantel-Haenszel test, controlling for center. There was no formal adjustment for analyses of multiple endpoints.

The discrete demographic variables sex, race, and alcohol consumption were evaluated using the Chi-square test for the between treatment group comparability. The continuous variables age and weight were evaluated using ANOVA.

Sites with fewer than 15 total patients were pooled together and all Mantel-Haenszel tests controlled for this strata variable.

Three hundred and twenty-one (321) evaluable patients were planned to be enrolled in this trial. The sample size of 107 patients in each treatment group was chosen so that the comparison of the percentage of patients in each treatment group who completed the trial without emetic episodes or rescue would have at least 80% power to detect a difference between ondansetron 8mg BID and the other two treatments at Type I error rate of 5%. The true response rates were assumed to be: 40% for ondansetron 8mg BID, 60% for ondansetron 24mg QD, and 65% for ondansetron 32mg QD.

2. **Sponsor's Analysis**

A total of 358 patients were enrolled into the study. One subject (ondansetron 24mg QD) consented but withdrew prior to receiving study drug. One hundred twenty-four (124) patients received oral ondansetron 8mg BID, 116 patients received oral ondansetron 24mg QD, and 117 patients received oral ondansetron 32mg QD.

Of the 357 patients exposed to study drug, one subject (ondansetron 24 mg QD) received study drug but subsequently did not receive cisplatin chemotherapy. There were 98 ondansetron 8mg BID patients, 95 ondansetron 24mg QD patients, and 87 ondansetron 32mg QD patients who completed the 24.5-hour study period. There were 76 patients (26 ondansetron 8mg BID patients, 20 ondansetron 24mg QD patients, and 30 ondansetron 32mg QD patients) withdrawn from the trial after exposure to cisplatin. The primary reason for subject withdrawal was lack of efficacy.

Efficacy analyses were performed on both the Intent-to-Treat (ITT) population and the Per-Protocol population. Intent-to-Treat population consisted of all patients who received at least one dose of study medication. Per-Protocol population consisted of all patients who were included in ITT analysis without major protocol violations. Deviation from the protocol could significantly affect the interpretation of efficacy endpoint. The ITT analysis was used as the primary analysis. The Per-Protocol analysis was used as a supporting analysis.

Thirty-six of ITT patients (12 in 8mg BID, 11 in the 24mg QD, and 13 in the 32mg QD) were excluded from the Per-Protocol analysis because of major protocol violations.

The Mexican site (investigator Garcia-Rodriquez) enrolled most patients (12 patients per arm). Patients at the Mexican site had a large number of emetic episodes but were not rescued because of differences in clinical practice. Patients treated at the Mexican site received higher doses of cisplatin (the median cisplatin dose in Mexico was about 99mg/m^2 compared to the median cisplatin dose of 73.5 mg/m^2 for the 8mg BID group, 74.9mg/m^2 for the 24mg QD group, and 70.7mg/m^2 for the 32mg QD group).

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in attached Table 1. As seen from attached Table 1, there were imbalances, although not statistically significant, in height, weight, gender, and race. There were higher

percentages of males and blacks in the 24mg QD dose group. The sponsor assumes that these imbalances are not expected to impact efficacy and we agree with this assumption.

2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary variable was the percentage of patients with a complete response (defined as zero emetic episodes and no withdrawal or rescue and at the most mild nausea). The results for the ITT and Per-Protocol analyses are shown in the table below.

Protocol S3AA3012
Sponsor's Complete Response (No vomiting and No rescue)
(ITT Analysis)

Treatment	Rate	P-value Vs. 8mg BID	P-value vs. 24mg QD
32mg QD	64/117 (55%)	0.943	0.073
24mg QD	76/115 (66%)	0.053	
8mg BID	68/124 (55%)		

(Per-Protocol Analysis)

Treatment	Rate	P-value Vs. 8mg BID	P-value vs. 24mg QD
32mg QD	59/104 (57%)	0.723	0.073
24mg QD	72/104 (69%)	0.027	
8mg BID	62/112 (55%)		

P-values were from Mantel-Haenszel test.
Copied from Tables 10.1 and 10.3, pages 101 and 104, respectively, Vol. 5.

As seen from the tables above, in the ITT analysis, the difference between the 8mg BID and the 24mg QD doses approached statistical significance. However, the difference was not statistically significant by Fisher's exact test (p=0.086). There was not a statistically significant difference between the 8mg BID dose and the 32mg QD dose. There also was not a statistically significant difference between the 24mg QD dose and the 32mg QD dose. The difference between 8mg BID and 24mg QD was statistically significant in the Per-Protocol analysis (with no adjustment for multiple comparison). Together these results imply that the difference between the 8mg BID and 24mg QD doses is not clearly statistically significant but that there is evidence of a treatment effect.

2.2.1 Complete Response by Gender

Complete response rates for all treatment groups by gender were tabulated in attached Table 2.

As seen from attached Table 2, females were less likely to respond to antiemetic treatment. Among the females the complete response rates in the 8mg BID, 24mg QD, and 32mg QD dose groups were 42%, 45%, and 48%, respectively. Among the males, the

complete response rates in the 8mg BID, 24mg QD, and 32mg QD dose groups were 62%, 73%, and 58%, respectively.

2.3 Sponsor's Analysis of Secondary Efficacy Variables

The secondary efficacy variables were the number of patients with a complete or major treatment response, number of patients who were therapeutic failures, number of patients with rescue, and number of patients with complete control of nausea. The results are given in attached Table 3.

As seen from attached Table 3, there were no statistically significant treatment difference among treatment groups in terms of the percentage of patients with either a complete or major response, the percentage of patients considered therapeutic failure, and the percentage of patients receiving rescue medication. Both ondansetron 24mg QD and 32mg QD were significantly better than ondansetron 8mg BID in terms of complete control of nausea.

3. Reviewer's Evaluation

3.1 Study Design Issues

This study was designed as a superiority trial to show that ondansetron 24mg QD was more effective than the 8mg BID for prevention of nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy. But, the comparator, the 8mg BID, had shown to be effective only in moderately emetogenic chemotherapy. Furthermore, it has not established that the ondansetron 8mg BID is efficacious for prevention of nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy.

The study did not consider the multiplicity issues. For these reasons, this study was not optimally designed to demonstrate the effectiveness of oral ondansetron 24mg QD.

3.2 Multiple Comparison Issue

In the protocol, it was clearly stated that "the 24mg and 32mg treatment groups will be compared against the 8 mg treatment group using the Cochran-Mantel-Haenszel test, controlling for center." However, the protocol did not state which comparison is the primary assessment of efficacy. This reviewer believes that it was assumed that both comparisons would be primary assessments of efficacy.

Furthermore, "The primary assessment of efficacy was the comparison between the 8mg BID and 24mg QD treatment groups" was stated post hoc in the sponsor's report.

For preserving Type I error rate, the p-values should be adjusted for multiple comparisons using either Bonferroni procedure or the more powerful Hochberg procedure. The experimentwise Type I error needs to be maintained at 0.05 level.

3.3 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

Two ondansetron 24mg QD patients were not included in the sponsor's ITT analysis. One subject consented but withdrew prior to receiving study drug. The other subject received study drug but subsequently did not receive cisplatin chemotherapy.

If these two patients were included the ITT analysis as "not complete response", the p-value obtained from the Fisher's Exact test for comparing ondansetron 8mg BID versus ondansetron 24mg QD would be 0.117 instead of the reported 0.086. Thus, the sponsor's results favoring 24mg QD against 8mg BID might be biased and were not robust.

3.3.1 Adjustment for Multiple Comparison

With applying Hochberg method for adjustment for multiple comparison, all pairwise comparisons were statistically non-significant for both the ITT and Per-Protocol analyses. There was no statistically significant difference between the 8mg BID dose and the 24mg QD dose.

3.3.2 Reviewer's Analysis of Complete Responses

Due to ethical concerns, most controlled comparative trials in emesis do not include a placebo arm. To show the effectiveness of the drug, a historical placebo control is commonly used in comparison with the drug. The highly significant difference will provide compelling evidence of efficacy for the drug.

The sponsor did not perform an analysis of complete response by treatment versus historical placebo control.

3.3.2.1 Historical Control Data

This reviewer had identified four cisplatin-based published trials involving highly emetogenic chemotherapy (cisplatin 70-80 mg/m^2) The four studies were L.X. Cubeddu (1990), D.R. Cupissol, J.R. D'Olimpio, and SB 43694A/012.

The main study characteristics of L.X. Cubeddu, D.R. Cupissol, and J.R. D'Olimpio are given in Statistical Review and Evaluation, dated January 12, 1998, for IND 50,413.

The placebo response data of the four trials including 95%-confidence intervals for complete response rate are summarized in the table below. The confidence intervals were calculated using the Pearson-Clopper limits.

Summary of Placebo Response Data in Cisplatin Trials (cisplatin 70-80 mg/m^2)

Reference	Cisplatin mg/m^2	No of Patients	No. of Complete Response (N)	CRR (%)	Complete Response 95%-CI (%)
[redacted]	Mean 72.9	14	0	0	0 – 23
	Mean 80.5	14	1	7	0 – 34
	Median 75.0	32	7	22	9 – 40
	Mean 81	14	1	7	0 - 34

CRR=Complete response rate

As seen from the table above, the complete response rates ranged from zero to 22%. In those trials listed above, a comparable average cisplatin dose of approximately 75 mg/m^2 was used. Complete response in those trials was reported in 9 of 74 patients (12%, 95%-CI: 6-22%).

3.3.2.2 Reviewer's Analysis of Complete Responses by Treatment versus Historical Placebo Control

This reviewer statistically compared the results from study S3AA3012 to those of a historical placebo control using 22% as the placebo complete response rate. The results from this reviewer's analysis of complete response by treatment versus historical placebo control are given below.

Protocol S3AA3012
Complete Response by Treatment vs. Historical Control
(Intent-to-Treat Analysis)

	Ondansetron 8mg BID	Ondansetron 24mg QD	Ondansetron 32mg QD
Rate	68/124 (55%)	76/115 (66%)	64/117 (55%)
P-value for comparison to Historical Placebo Control	<0.001	<0.001	<0.001

P-values were obtained by this reviewer using Fisher's Exact test.
The historical placebo response rate was the upper endpoint of a 95% confidence interval based on the results of the published studies (LX Cubeddu, DR Cupissol, and JR Gralla) and SB 43694A/012 (NDA 20-305).

As seen from the above table, each of the three treatment groups was statistically significantly superior to the historical placebo comparator.

C. Protocol S3AA3004/3007

1. Description of Study

S3AA3004 and S3AA3007 were identical trials with same protocol.

This study was a randomized, double-blind, parallel, multicenter trial to evaluate the efficacy and safety of a single 24mg oral ondansetron tablet with a single 10mcg/kg granisetron injection in the prevention of nausea and vomiting associated with moderately-highly emetogenic (50-75 mg/m^2 cisplatin or ≥ 200mg//m^2 carboplatin) chemotherapy.

The treatment periods began at the time of study drug administration (30 minutes prior to cisplatin infusion initiation) and ended 24 hours after the initiation of the cisplatin or carboplatin infusion.

Eligible patients were chemotherapy-naïve, had a histologically confirmed diagnosis of cancer and were scheduled to receive their first course of cisplatin chemotherapy. All patients received chemotherapy regimens containing cisplatin 50-75 mg/m^2 or ≥ 200mg/m^2 carboplatin administered over a period of ≤ 3 hours.

The definitions for vomiting, retching, and emetic episode for this study were same as defined in Study S3AA3012. The response categories of complete response, major response, minor response, therapeutic failure, and withdrawal were also same as those defined in Study S3AA3012.

Appetite was assessed and recorded in the subject diary, using a three-point scale (usual, better than usual, or worse than usual). Subject satisfaction with antiemetic therapy (at 3 hours, 6 hours, and 24 hours following cisplatin initiation) was rated by each subject using the 5-point scale (1=very satisfied, 2=somewhat satisfied, 3=neither satisfied nor dissatisfied, 4=somewhat dissatisfied, and 5=very dissatisfied).

The primary efficacy variable was the number of patients with no emetic episodes. The secondary efficacy variables were the number of patients with therapeutic failure, the number of patients with complete plus major treatment response, time to first emetic episode, and subject assessments of nausea and appetite.

The discrete demographic variables sex, race, and alcohol consumption were evaluated using the Chi-square test for the between treatment group comparability. The continuous variables age and weight were be evaluated using the Wilcoxon rank sum test.

A sample size of 364 evaluable patients was sufficient to detect a +/-15% between group difference at the nominal 0.05 level of significance and 80% power.