STATISTICAL REVIEW AND EVALUATION --- NDA
CLINICAL STUDIES --- PEDIATRIC

Medical Division: Gastrointestinal and Coagulant Drug Product (HFD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORDS:
NDA #: 20-007
SERIAL NUMBER: SE5-035
DATE RECEIVED BY CENTER: September 29, 2004
DRUG NAME: Zofran (ondansetron hydrochloride) injection
INDICATION: Prevention of postoperative emesis
SPONSOR: GlaxoSmithKline.
DOCUMENTS REVIEWED: Electronic submission Dated September 28, 2004
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A. Background

Zofran (ondansetron hydrochloride) was originally approved on January 4, 1991. The original Proposed Pediatric Study Request was submitted on September 28, 1999. The formal Written Request for Pediatric Study was submitted on June 26, 2001 and was amended on March 1, 2002, March 11, 2004, and September 7, 2004. In accordance with the Written Request, the sponsor has completed three clinical studies (Study S3A40319, S3A40320, and Study S3A4323) listed below.

Study S3A40319: A Phase IV, Multi-Center, Two-Arm, Single-Dose Pharmacokinetic Study of Intravenous ZOFRAN in Pediatric Surgical Patients from 1 Month to 24 Months of Age.

Study S3A40320: An Open-label, Multi-center, Study of the Safety and Antiemetic Effect of 0.15 mg/kg Intravenous Ondansetron Hydrochloride Administered for Three Doses to Pediatric Cancer Subjects from Age 6 Months to 48 Months Who Are Receiving Moderate to Highly Emetogenic Chemotherapy.

Study S3A40323: A Randomized, Double-Blind, Placebo-controlled, Multi-center Study of Intravenous Ondansetron Hydrochloride 0.1 mg/kg for the Prevention of Postoperative Emesis in Pediatric Surgical Subjects from 1 Month to 24 Months of Age Who Are Undergoing Routine Surgery Under General Anesthesia.

Only Study S3A40323 was a well controlled study, so it will be evaluated in this review.

B. Study S3A4032

1. Study Design

This was a randomized, double-blind, placebo-controlled, multicenter (28 sites), single-dose study with a 24-hour assessment period.

The primary objective of this study was to evaluate the efficacy of a single 0.1 mg/kg dose of intravenous ondansetron prophlylactically over at least 30 seconds to pediatric subjects age 1 month to 24 months who were undergoing routine surgical procedures under general anesthesia.

Male or female children 1 month to 24 months who were undergoing routine surgery under general anesthesia were eligible to be enrolled in the study.

Subjects were randomized in a 1:1 ratio and received either single intravenous dose of 0.1 mg/kg of ondansetron or placebo (normal saline). Treatment assignment was stratified according to anticipated opioid usage as part of the anesthetic technique or for postoperative analgesia.

Rescue antiemetic medication was defined as medication that was given specifically for the treatment of emesis during the 24 hour assessment phase. The first dose of rescue antiemetic medication was permitted to be administered when medically indicated, if three emetic episodes occurred within 15-minutes period, at physician discretion or at any time upon subject/parent/guardian request.

The primary efficacy endpoint was the proportion of subjects who experienced at least one emetic episode during the postoperative 24-hour assessment phase.

The secondary efficacy endpoints included time to first emetic episode, time to first rescue, incidence of emetic episodes, proportion of subjects receiving rescue medication, and proportion of subjects experiencing emetic episodes after the receipt of rescue medication.

The analysis of the primary efficacy endpoint was based on the Cochran-Mantel-Haenszel test. The overall treatment comparison was assessed by the common odds ratio, while controlling for the effect of the anticipated opioid use. The primary efficacy endpoint was also analyzed based on a logistic regression model, in order to adjust for potential prognostic factors. Adjusted odds and corresponding 95% confidence interval were obtained from the logistic regression model.

Secondary event-time endpoints were analyzed based on the hazard ratio. All other secondary endpoints were analyzed descriptively.

The primary population was the Intent-to-Treat (ITT) population. This population was defined as all subjects who were randomized to one of the two treatment regimens and who received study medication.

The per-protocol (PP) population was defined as those subjects who were randomized, who received study medication, and who met all important protocol requirements.

Subjects who were withdrawn from the trial without having experienced an emetic episode were considered to have had at least one emetic episode.

Subjects with missing emetic data were pooled with those who experienced one or more emetic episodes in the statistical calculations.

The incidence of emetic events was categorized as follows:

Complete response: subject did not experience emetic event, receive rescue antiemetic medications, or withdrawn from the study prematurely.

Partial response: subjects experienced 1-2 emetic episodes, but did not receive antiemetic medications or withdrawn from the study prematurely.

Therapeutic failure: subjects either experience at least 3 emetic episodes or received rescue medication, or withdrew from the trial.

Assuming an underlying emetic rate of 15% in the placebo group, and 7.5% in the ondansetron group, 300 patients per group were needed with 80% power at and two-sided type I error of α=0.05. In addition, a 15% dropout was assumed for a total sample of 345 patients per group.

2. Sponsor's Analysis

A total of 689 subjects were randomized (344 in ondansetron and 345 in placebo). A total of 19 subjects were randomized but not treated (9 in ondansetron 10 in placebo). A total of 670 subjects were in the intent-to-treat (ITT) population. (335 in ondansetron and 335 in placebo).

A total of 644 subjects completed study (323 in ondansetron 321 in placebo). A total of 26 subjects were prematurely withdrawn (12 in ondansetron and 14 in placebo). The main reason for premature withdrawal was lost to follow-up.

In the placebo group, there were 194 (58%) subjects in the opioid stratum and 141 (42%) in the non-opioid stratum. Similarly, in the ondansetron group, there were 196 (59%) subjects in the opioid stratum and 139 (41%) in the non-opioid stratum.

2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for safety population is given Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic characteristics.

2.2 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy endpoint was the proportion of subjects who experienced at least one episode of emesis during the 24-hour assessment phase.

The result of analysis of emetic episodes is given below.

Summary of Emetic Episodes --- ITT Population

	Treatment Group			
	Placebo (N = 335)		ZOFRAN (N = 335)	
	n	(%)	n	(%)
0 Emetic Episodes	242	(72)	297	(89)
> 0 Emetic Episodes[1]	93	(28)	38	(11)
Odds Ratio	0.33			
95% CI for Odds Ratio	(0.22, 0.5)			
p-value for Odds Ratio	<0.0001			

1. Includes 10 (3%) subjects in both the placebo group and **ZOFRAN** groups who had incomplete/missing data.

Source data: Section 12, Table 20.1

As seen from table above, the common odds ratio was 0.33, suggesting that the odds of emesis after ondansetron administration was roughly a third of that after placebo. The results were highly statistical significant.

2.3 Sponsor's Analysis of Secondary Efficacy Parameters

Secondary efficacy endpoints included time to first emetic episode, time to first rescue medication, incidence of emetic episodes, proportion of subjects receiving rescue medication, and proportion of subjects with emetic episodes after the receipt of rescue medication(s).

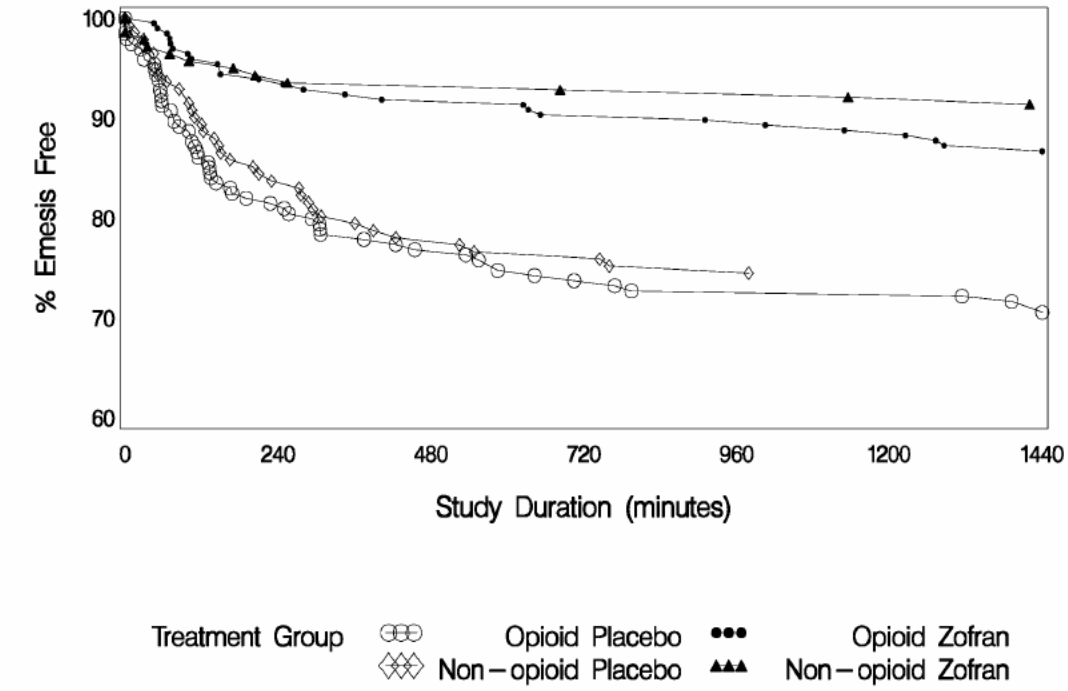
2.3.1 Time to First Emetic Episode

The time to first emetic episode was defined as the duration of time between the termination of anesthesia and the first emetic episode observed during the postoperative 24-hour assessment phase.

A total of 93 (28%) and 38 (11%) subjects experienced emesis in the placebo and ondansetron groups, respectively.

The Kaplan-Meier plot of time to first emetic event is given below.

Time to First Event



The median time to first event for ITT population is given below.

Median Time to First Emetic Event --- ITT Population

	Treatment Group					
	Opioid Stratum		Non-Opioid Stratum		Overall	
	Placebo (N=194)	ZOFRAN (N=196)	Placebo (N=141)	ZOFRAN (N=139)	Placebo (N=335)	ZOFRAN (N=335)
n (%)	57 (29)	26 (13)	36 (26)	12 (9)	93 (28)	38 (11)
Median Time (min)	132	264	149	135	135	207

Source data: Section 12, Table 20.5

The stratified log-rank test yielded p-value of <0.0001. It confirmed that the treatment comparison was highly significant even after adjusting for the effect of anticipated opioid use.

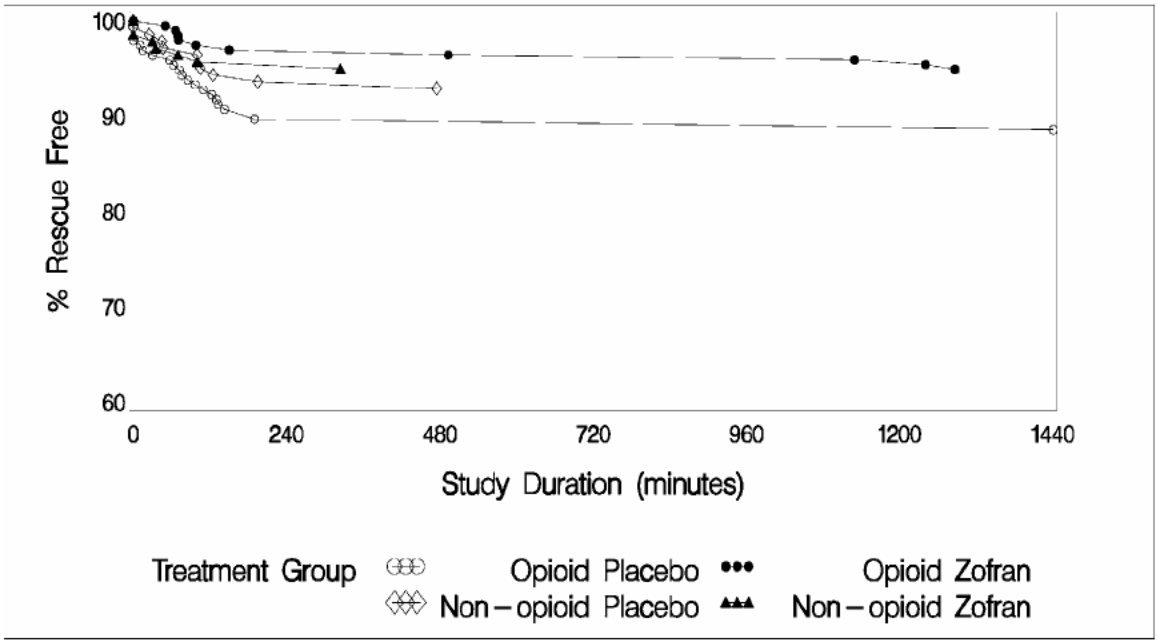
Within opioid and non-opioid strata, the hazard ratios were 0.39 and 0.31 respectively. The corresponding 95% confidence intervals respectively were (0.24 – 0.62) and (0.16 – 0.59). The p-values associated with the opioid and non-opioid strata were <0.0001 and 0.0004, respectively.

2.3.2 Time to First Rescue Medication (or Withdrawal)

Overall, 32 (10%) of placebo and 18 (5%) of ondansetron subjects received rescue antiemetic medication(s) or withdrew from the study prematurely.

A plot of time to first rescue data is given below.

Time to First Rescue Medication



As seen from the plot above, ondansetron appeared to be better than placebo within the opioid stratum.

The stratum-specific results for time to first rescue medication are given below.

Time to First Rescue Medication --- ITT Population

	Treatment Group					
	Opioid Stratum		Non-Opioid Stratum		Overall	
	Placebo (N=194)	Zofran (N=196)	Placebo (N=141)	Zofran (N=139)	Placebo (N=335)	ZOFRAN (N=335
n (%)	22 (11)	11 (6)	10 (7)	7 (5)	32 (10)	18 (5)
Median Time (Mins)	81	150	103	35	91	85

Source data: Section 12, Table 20.9

The treatment group comparison of the need for rescue medication/withdrawal within the non-opioid group was non-significant (p=0.489) while the opioid comparison was significant at p=0.0283. The overall treatment group comparison was significant at p=0.028. The stratum-adjusted treatment group comparison was significant at p=0.025.

Although fewer ondansetron subjects required rescue medication, they received rescue earlier than placebo subjects.

2.3.3 Incidence of Emetic Episodes during the 24-Hour Assessment Period

Complete response was defined as no emetic episodes and partial response was defined as 1 to 2 emetic episodes. Therapeutic failure was defined as greater than 2 emetic episodes, use of rescue medication, or withdrawal from the study.

Results of analysis of incidence of emetic episodes for ITT population are given blew.

Incidence of Emetic Episodes --- ITT Population

	Treatment Group			
	Placebo N=335		ZOFRAN N=335	
	n	(%)	n	(%)
Complete Response	242	(72)	297	(89)
Partial Response	57	(17)	19	(6)
Therapeutic Failure	26	(8)	9	(3)
Incomplete/Missing Data	10	(3)	10	(3)

Data source: Section 12, Table 20.13

As seen from table above, compared to the placebo group, the ondansetron group had more subjects who had a complete response and fewer therapeutic failures.

3. Safety

Overall, 18% of subjects in both the placebo and ondansetron groups experienced one or more adverse events (59/334 placebo, 62/336 ondansetron). Most AEs were reported in 1% or fewer subjects, with exceptions of pyrexia, bronchospasm, and post-procedural pain.

4. Reviewer's Comments and Evaluation

4.1 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable**

The sponsor's ITT analysis of primary efficacy endpoint did not include all randomized patients. It excluded 19 patients (9 in ondansetron and 10 in placebo) who were randomized but not treated. It was not a true ITT but modified ITT analysis.

The most clinically meaningful endpoint for prevention of postoperative emesis was "complete response." Complete response was defined as no emetic episodes, no use of rescue medication, and no withdrawn from the study.

This reviewer analyzed patients with "complete response" by stratum using Mantel-Haenszel method for the true ITT analysis. The results are given below.

Complete Response --- Reviewer's ITT Analysis

Stratum	Zofran	Placebo	Difference	P-value
Opioid	170/200 (85%)	137/203 (67%)	18%	<0.0001
Non-Opioid	127/144 (88%)	105/142 (74%)	14%	0.0024
Total	297/344 (86%)	242/345 (70%)	16%	<0.0001

Compiled by this reviewer.
P-values for opioid and non-opioid strata were obtained by Fisher's exact test.
P-value for total was obtained Mantel-Haenszel method adjusted for strata.

As seen from table above, the results from the reviewer's analysis was similar to those given by the sponsor. The odd ratios was 0.372 with 95% confidence interval (0.253, 0.546).

4.1.1 **Subgroup Analysis**

Subgroup analyses were performed on the number of subjects with complete response for the subgroups by country, age (aged 1 to 12 moths vs. ≥13 months), gender, race, ASA, and surgery type for ITT population.

The results of subgroup analysis of number of subjects with complete response are given below.

Number of Patients with Complete Response by Subgroup
Reviewer's ITT Population
Protocol S3A40323

Subgroup	Ondansetron	Placebo	Difference	95% C. I.
Country				
Canada	66/77 (86%)	56/77 (73%)	13%	(0.3%, 25.6%)
US	231/267 (87%)	186/268 (69%)	18%	(10.2%, 24.0%)
Race				
White	195/226 (86%)	152/217 (70%)	16%	(8.7%, 23.8%)
Black	38/46 (83%)	40/56 (71%)	12%	(-4.9%, 27.3%)
Asian	7/8 (88%)	6/9 (67%)	21%	(-17.6%, 59.2%)
Hispanic	38/42 (90%)	30/42 (71%)	19%	(2.8%, 35.3%)
Other	19/22 (86%)	14/21 (67%)	19%	(-5.0%, 44.4%)
Gender				
Male	224/263 (85%)	179/259 (69%)	16%	(9.0%, 23.1%)
Female	73/81 (90%)	63 /86 (73%)	17%	(5.5%, 28.3%)
Age				
1 to 12 months	149/168 (89%)	123/174 (71%)	18%	(9.7%, 26.3%)
13 to 24 months	147/175 (84%)	119/171 (70%)	14%	(5.6%, 23.2%)
>24 months	1/1 (100%)			
ASA				
1	219/256 (86%)	173/245 (71%)	15%	(7.8%, 22.1%)
2	77/83 (93%)	66/92 (72%)	21%	(10.3%, 31.8%)
3	1/3 (33%)	3/5 (60%)	-27%	(-95.2%, 41.8%)
Surgery Type				
Adenoidectomy	19/24 (79%)	13/20 (65%)	14%	(-12.3%, 40.6%)
Dental procedure	4/6 (67%)	3/3 (100%)	-33%	(-71.1%, 4.4%)
Hernia repair	42/44 (95%)	30/40 (75%)	20%	(5.7%, 35.2%)
Hydrocelectomy	5/6 (83%)	4/4 (100%)	-17%	(-46.5%, 13.2%)
Myringotomy	30/36 (83%)	25/37 (68%)	15%	(-3.6%, 35.2%)
Orchidopexy	35/40 (88%)	26/40 (65%)	23%	(4.5%, 40.5%)
Orthopaedic	10/10 (100%)	9/15 (60%)	40%	(15.2%, 64.8%)
Other	165/190 (87%)	140/192 (73%)	14%	(6.0%, 21.8%)
Plastic surgery	39/42 (93%)	26/38 (68%)	25%	(7.7%, 41.1%)
Strabismus surgery	10/13 (77%)	10/11 (91%)	-14%	(-42.5%, 14.5%)
Tonsillectomy	2/4 (50%)	3/4 (75%)	-25%	(-89.8%, 39.8%)

Compiled by this reviewer.

As seen from table above, the statistically significant results in favor of ondansetron on "complete response" were consistent among countries, race, gender, age, ASA, and most of surgery types.

C. Overall Summary and Recommendation

The sponsor submitted a single double-blind, placebo-controlled, multicenter study (S3A40323) for the prevention of postoperative emesis in pediatric subjects from 1 month to 24 months of age who are undergoing routine surgery under general anesthesia.

Study S3A40323 showed for pediatric patients ages 1 month to 24 months who were undergoing routine surgery under general anesthesia, ondansetron was statistically better than placebo for the primary efficacy endpoint, the proportion of patients who experienced at least one episode of emesis during the 24-hour assessment phase.

Furthermore, this study also show that the statistically significant results in favor of ondansetron on "complete response" were consistent among countries, race, gender, age, ASA, and most of surgery types.

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol S3A40323

Characteristics	Ondansetron (N=344)	Placebo (N=345)	Between Treatment p-value
Stratum			0.8519
Opioid	200 (58.1%)	203 (58.8%)	
Non-Opioid	144 (41.9%)	142 (41.2%)	
Sex			0.4915
Male	263 (76.5%)	259 (75.1%)	
Female	81 (23.6%)	86 (24.9%)	
Race			0.8657
White	226 (65.7%)	217 (62.9%)	
Black	46 (13.4%)	56 (16.2%)	
Asian	8 (2.3%)	9 (2.6%)	
Hispanic	42 (12.2%)	42 (12.2%)	
Other Races	22 (6.4%)	21 (6.1%)	
Age (months)			0.3522
Mean (SD)	12.6 (6.3)	12.2 (6.0)	
Age			0.5582
1 to 12 months	168 (48.8%)	174 (50.4%)	
13 to 24 months	175 (50.9%)	171 (49.6%)	
>24 months	1 (0.3%)	0 (0.0%)	
Height (cm)			0.9036
N	317	314	
Mean (SD)	73.5 (11.9)	73.6 (9.6)	
Weight (kg)			0.3380
N	344	342	
Mean (SD)	9.9 (2.4)	9.8 (2.3)	
ASA			0.5476
1	256 (74.9%)	245 (71.6%)	
2	83 (24.3%)	92 (26.9%)	
3	3 (0.9%)	5 (1.5%)	
Surgical Procedure			
Adenoidectomy	24 (7.0%)	20 (5.8%)	
Dental procedure	6 (1.7%)	3 (0.9%)	
Hernia repair	44 (12.8%)	40 (11.6%)	
Hydrocelectomy	6 (1.7%)	4 (1.2%)	
Myringotomy	36 (10.5%)	37 (10.7%)	
Orchidopexy	40 (11.6%)	40 (11.6%)	
Orthopaedic	10 (2.9%)	15 (4.3%)	
Other	190 (55.2%)	192 (55.7%)	
Plastic surgery	42 (12.2%)	38 (11.0%)	
Strabismus surgery	13 (3.8%)	11 (3.2%)	
Tonsillectomy	4 (1.2%)	4 (1.1%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight.

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/s/

Milton Fan
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