

S3AA1002

(SEI/015, 8/27/99)

serum Ondansetron AUC((0-inf)) Values (ng-hr/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OND 24MG TAB (Test)
Treatment B = OND 1X8MG TAB (Reference)

Subject No.	Sequence	Treatment A		Treatment B		Difference A-B	Ratio A/B	Log Ratio ln A/B
		AUC((0-inf))	Flag	AUC((0-inf))	Flag			
18957	BA					18.72	1.02	0.019
18958	AB					-87.72	0.86	-0.146
18959	AB					-252.68	0.79	-0.240
18960	BA					28.84	1.06	0.055
18961	BA					-82.41	0.92	-0.081
18962	AB					99.38	1.17	0.159
18963	BA					22.63	1.02	0.023
18964	AB					133.81	1.46	0.375
18965	AB					432.39	1.33	0.285
18966	BA					-64.22	0.95	-0.055
18967	BA					89.68	1.05	0.053
18968	AB					115.67	1.08	0.082
18969	AB					-26.26	0.96	-0.045
18970	BA					50.21	1.05	0.046
18971	BA					-32.37	0.97	-0.033
18972	AB					235.24	1.25	0.226

Flag: * = 3 points used in Lambda-z determination
+ = Different Lambda-z intervals used for each treatment

Statistic	Treatment A		Treatment B		Difference A-B	Ratio A/B	Log Ratio ln A/B
	AUC((0-inf))		AUC((0-inf))				
Geometric LMean	999.47		956.91				
95% CI (lower)	941.52		898.97				
95% CI (upper)	1057.41		1014.86				
Median	980.47		989.57		25.73	1.04	0.035
Minimum	427.47		293.66		-252.68	0.79	-0.240
Maximum	1741.75		1641.28		432.39	1.46	0.375
Arithmetic Mean	999.47		956.91				
SD	399.98		356.08				
CV	40.02		37.21				
Geometric Mean	921.79		882.89				
Mean of logs	955.47		956.91				
SD of logs	399.98		356.08				
Comparison LSM	999.47		956.91			1.04	
90% CI (lower)						0.97	
90% CI (upper)						1.11	
p-value						0.28	

LMean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LMean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ***)
90% CI = 90% confidence interval of ratio of comparison LSMs
p-value = p-value of test for difference between treatments

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(SE1/015, 8/27/99)

Serum Ondansetron AUC(0-t) Values (ng·hr/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OTC 24MG TAB (Test)
Treatment B = OTC 1X8MG TAB (Reference)

Subject No.	Sequence	-- Treatment A --		-- Treatment B --		Log		
		AUC(0-t)	AUC(0-t)	A-B	A/B	Ln A/B	Ratio	
18957	BA			-10.02	0.99	-0.011		
18958	AB			-82.63	0.87	-0.144		
18959	AB			-219.95	0.80	-0.221		
18960	BA			28.68	1.06	0.056		
18961	BA			-71.52	0.93	-0.073		
18962	AB			102.13	1.18	0.166		
18963	BA			55.01	1.06	0.062		
18964	AB			133.12	1.46	0.378		
18965	AB			232.81	1.20	0.180		
18966	BA			-39.49	0.97	-0.036		
18967	BA			78.09	1.05	0.049		
18968	AB			98.74	1.08	0.072		
18969	AB			-25.07	0.96	-0.044		
18970	BA			25.31	1.02	0.025		
18971	BA			-14.72	0.98	-0.015		
18972	AB			211.61	1.23	0.208		

Statistic	-- Treatment A --		-- Treatment B --		Log		
	AUC(0-t)	AUC(0-t)	A-B	A/B	Ln A/B	Ratio	
Geometric LSmean	940.79	909.40					
95% CI (lower)	897.25	865.87					
95% CI (upper)	984.32	952.94					
Median	932.23	945.89	27.00	1.04	0.037		
Minimum	422.60	289.48	-219.95	0.80	-0.221		
Maximum	1635.09	1557.00	232.81	1.46	0.378		
Arithmetic Mean	940.79	909.40					
SD	348.92	330.40					
CV	37.09	36.32					
Geometric Mean	878.11	842.99					
Mean of logs	940.79	909.40					
SD of logs	348.92	330.40					
Comparison LSM	940.79	909.40				1.03	
90% CI (lower)						0.98	
90% CI (upper)						1.09	
p-value						0.29	

LSmean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LSmean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ***)
90% CI = 90% confidence interval of ratio of comparison LSMs
p-value = p-value of test for difference between treatments

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(SE1/015, 8/27/99)

Serum Ondansetron Cmax Values (ng/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OND 24MG TAB (Test)
Treatment B = OND 1X8MG TAB (Reference)

Subject No.	Sequence	--- Treatment ---		Difference A-B	Log Ratio	
		Treatment A Cmax	Treatment B Cmax		A/B	Ln A/B
18957	BA			36.67	1.11	0.268
18958	AB			13.28	1.25	0.136
18959	AB			1.35	1.01	0.010
18960	BA			13.17	1.14	0.132
18961	BA			9.20	1.07	0.065
18962	AB			-15.28	0.88	-0.128
18963	BA			67.06	1.82	0.599
18964	AB			-0.38	1.00	-0.004
18965	AB			46.24	1.25	0.227
18966	BA			16.15	1.11	0.108
18967	BA			-10.79	0.96	-0.043
18968	AB			-25.74	0.91	-0.098
18969	AB			5.63	1.05	0.050
18970	BA			-26.97	0.84	-0.177
18971	BA			19.72	1.10	0.099
18972	AB			21.10	1.12	0.110

Statistic	--- Treatment ---		Difference A-B	Log Ratio	
	Treatment A Cmax	Treatment B Cmax		A/B	Ln A/B
Geometric LSmean	160.05	149.52			
95% CI (lower)	150.30	139.77			
95% CI (upper)	169.60	159.27			
Median	149.27	139.20	11.18	1.09	0.082
Minimum	89.54	81.76	-28.97	0.84	-0.177
Maximum	249.35	275.09	67.06	1.82	0.599
Arithmetic Mean	160.05	149.52			
SD	51.45	57.24			
CV	32.14	38.25			
Geometric Mean	152.54	140.18			
Mean of logs	160.05	149.52			
SD of logs	51.45	57.24			
Comparison LSM	160.05	149.52		1.07	
90% CI (lower)				0.99	
90% CI (upper)				1.15	
p-value				0.12	

LSmean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LSmean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ***)
90% CI = 90% confidence interval of ratio of comparison LSMs
P-value = p-value of test for difference between treatments

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Individual Serum Ondansetron Concentrations (ng/mL)

OND 24MG TAB (Test)

Time(h)	Subject	Subject	Subject	Subject	Subject	Subject	Subject	Subject
	18957	18958	18959	18960	18961	18962	18963	18964
0.00	[REDACTED]							
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

OND 1X8MG TAB (Reference)

Time(h)	Subject	Subject	Subject	Subject	Subject	Subject	Subject	Subject
	18957	18958	18959	18960	18961	18962	18963	18964
0.00	[REDACTED]							
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

NR = sample value not reportable or missing
BQL = Below quantitation limit (1.00ng/mL)

BEST POSSIBLE

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(SE1/015, 8/27/99)

Individual Serum Ondansetron Concentrations (ng/mL)

OND 24MG TAB (Test)

Time(h)	Subject 18965	Subject 18966	Subject 18967	Subject 18968	Subject 18969	Subject 18970	Subject 18971	Subject 18972
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

BEST POSSIBLE

OND 128MG TAB (Reference)

Time(h)	Subject 18965	Subject 18966	Subject 18967	Subject 18968	Subject 18969	Subject 18970	Subject 18971	Subject 18972
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

NR = sample value not reportable or missing
BQL = Below quantitation limit (1.00ng/mL)

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Serum Ondansetron AUC((0-inf)) values (ng·hr/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OND 24MG TAB (Test)
Treatment B = OND 1X8MG TAB (Reference)

Subject No.	Sequence	Treatment A		Treatment B		Difference A-B	Ratio A/B	Log Ratio Ln A/B
		AUC((0-inf))	Flag	AUC((0-inf))	Flag			
18957	BA					18.72	1.02	0.019
18958	AB					-87.72	0.86	-0.146
18959	AB					-252.68	0.79	-0.240
18960	BA					28.84	1.06	0.055
18961	BA					-82.41	0.92	-0.081
18962	AB					99.38	1.17	0.159
18963	BA					22.63	1.02	0.023
18964	AB					133.81	1.46	0.375
18965	AB					432.39	1.33	0.285
18966	BA					-64.22	0.95	-0.055
18967	BA					89.68	1.05	0.053
18968	AB					115.67	1.08	0.082
18969	AB					-26.26	0.96	-0.045
18970	BA					50.21	1.05	0.046
18971	BA					-32.37	0.97	-0.033
18972	AB					235.24	1.25	0.226

Flag: * = 3 points used in Lambda-z determination
+ = Different Lambda-z intervals used for each treatment

BEST POSSIBLE

Statistic	Treatment A		Treatment B		Difference A-B	Ratio A/B	Log Ratio Ln A/B
	AUC((0-inf))	Flag	AUC((0-inf))	Flag			
Geometric LSmean	999.47		956.91				
95% CI (lower)	941.52		898.97				
95% CI (upper)	1057.41		1014.86				
Median	980.47		989.57		25.73	1.04	0.035
Minimum	427.47		293.66		-252.68	0.79	-0.240
Maximum	1741.75		1641.28		432.39	1.46	0.375
Arithmetic Mean	999.47		956.91				
SD	399.98		356.08				
CV	40.02		37.21				
Geometric Mean	923.79		882.89				
Mean of logs	959.47		956.91				
SD of logs	399.98		356.08				
Comparison LSM	999.47		956.91				
90% CI (lower)						1.04	
90% CI (upper)						0.97	
p-value						1.11	
						0.28	

LSmean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LSmean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ...)
90% CI = 90% confidence interval of ratio of comparison LSMs
p-value = p-value of test for difference between treatments

S 3 AA 1002

(SE1/015, 8/27/99)

Serum Ondansetron AUC(0-t) Values (ng*hr/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OND 24MG TAB (Test)
Treatment B = OND 3X8MG TAB (Reference)

Subject No.	Sequence	-- Treatment A --- -- Treatment B ---		Difference A-B	Log Ratio	
		AUC(0-t)	AUC(0-t)		A/B	Ln A/B
18957	BA			-10.02	0.99	-0.011
18958	AB			-82.63	0.87	-0.144
18959	AB			-219.95	0.80	-0.221
18960	BA			28.68	1.06	0.056
18961	BA			-71.52	0.93	-0.073
18962	AB			102.13	1.18	0.166
18963	BA			55.01	1.06	0.062
18964	AB			133.12	1.46	0.378
18965	AB			232.81	1.20	0.180
18966	BA			-39.49	0.97	-0.036
18967	BA			78.09	1.05	0.049
18968	AB			98.74	1.08	0.072
18969	AB			-25.07	0.96	-0.044
18970	BA			25.31	1.02	0.025
18971	BA			-14.72	0.98	-0.015
18972	AB			211.61	1.23	0.208

Statistic	--- Treatment A --- --- Treatment B ---		Difference A-B	Log Ratio	
	AUC(0-t)	AUC(0-t)		A/B	Ln A/B
Geometric LSmean	940.79	909.40			
95% CI (lower)	897.25	865.87			
95% CI (upper)	984.32	952.94			
Median	932.23	945.89	27.00	1.04	0.037
Minimum	422.60	289.48	-219.95	0.80	-0.221
Maximum	1635.09	1557.00	232.81	1.46	0.378
Arithmetic Mean	940.79	909.40			
SD	348.92	330.40			
CV	37.09	36.33			
Geometric Mean	878.11	842.99			
Mean of logs	940.79	909.40			
SD of logs	348.92	330.40			
Comparison LSM	940.79	909.40		1.03	
90% CI (lower)				0.98	
90% CI (upper)				1.09	
p-value				0.29	

LSmean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LSmean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ***)
90% CI = 90% confidence interval of ratio of comparison LSMs
P-value = p-value of test for difference between treatments

S 3 A A 1 0 0 2

(SE1/015, 8/27/99)

Sertraline Ondansetron C_{max} Values (ng/mL) and Summary Statistics
(8 Males, 8 Females)

Treatment A = OND 24MG TAB (Test)
Treatment B = OND 1X8MG TAB (Reference)

Subject No.	Sequence	--- Treatment ---		Difference A-B	Log Ratio	
		A C _{max}	B C _{max}		A/B	Ln A/B
18957	BA			36.67	1.31	0.268
18958	AB			13.28	1.15	0.136
18959	AB			1.35	1.01	0.010
18960	BA			13.17	1.14	0.132
18961	BA			9.20	1.07	0.065
18962	AB			-15.28	0.88	-0.128
18963	BA			67.06	1.82	0.599
18964	AB			-0.38	1.00	-0.004
18965	AB			46.24	1.25	0.227
18966	BA			16.15	1.11	0.108
18967	BA			-10.79	0.96	-0.043
18968	AB			-25.74	0.91	-0.098
18969	AB			5.63	1.05	0.050
18970	BA			-26.97	0.84	-0.177
18971	BA			19.72	1.10	0.099
18972	AB			21.10	1.12	0.110

Statistic	--- Treatment ---		Difference A-B	Log Ratio	
	A C _{max}	B C _{max}		A/B	Ln A/B
Geometric LSmean	160.05	149.52			
95% CI (lower)	150.30	139.77			
95% CI (upper)	169.80	159.27			
Median	149.27	139.20	11.18	1.09	0.082
Minimum	89.54	81.76	-28.97	0.84	-0.177
Maximum	249.35	275.09	67.06	1.82	0.599
Arithmetic Mean	160.05	149.52			
SD	51.45	57.24			
CV	32.14	38.29			
Geometric Mean	152.54	140.18			
Mean of logs	160.05	149.52			
SD of logs	51.45	57.24			
Comparison LSM	160.05	149.52		1.07	
90% CI (lower)				0.99	
90% CI (upper)				1.15	
p-value				0.12	

LSmean = least square mean, adjusted for design imbalance if present (includes all subjects)
CI = confidence interval for LSmean
SD = standard deviation; CV = coefficient of variation.

Comparison LSM = least square mean used for comparative analysis (excludes subjects with ***)
90% CI = 90% confidence interval of ratio of comparison LSMs
p-value = p-value of test for difference between treatments

3. OVERALL SUMMARY

VIII. Clinical Data Summary and Results of Statistical Analysis

F. Safety Summary – General Safety Conclusions

1. Introduction

NDA 20-103 for Zofran® Tablets presented safety data from 2133 subjects who received orally administered ondansetron for the prevention of chemotherapy-induced emesis in clinical trials worldwide. The safety update submitted 21 February 1991 included 1652 subjects who received orally administered ondansetron. A submission for radiation-induced nausea and vomiting (231 ondansetron-treated subjects) was filed on 21 October 1993 and a submission for twice daily dosing in the prevention of chemotherapy-induced emesis (442 ondansetron-treated subjects) was filed on 30 June 1994. A submission for prevention of postoperative nausea and vomiting (2798 ondansetron-treated subjects) was filed on 08 March 1994.

This document presents safety data for 728 subjects enrolled in two US primary efficacy studies (S3AA3012 and S3AA3004/3007) that investigated a single oral dose of ondansetron 24mg and 538 subjects enrolled in one international (non-US) supporting clinical efficacy study (S3AB3008). All subjects enrolled in clinical efficacy studies were cancer patients undergoing treatment with highly emetogenic cisplatin-containing chemotherapy regimens (cisplatin \geq 50mg/m²). Safety data are also presented for 16 healthy volunteers enrolled in clinical pharmacology study S3AA1002 conducted in the US. For this submission, the two US clinical efficacy studies are referred to as the 'primary efficacy studies' and the international study is referred to as the 'supporting study.' Together these studies are referred to as 'treatment studies.' The design of all studies is described in Table 3.9.

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Table 3.9
Table of Studies
Safety Summary

Report Number Protocol Number Investigators	Completion Status (Start Date)	Country	Location (Vol/Page)	Study Design	Treatment Doses	Duration of Treatment	Number Treated	Age Range (Median)	% Male/Female (% Black/White/Other)
Primary Efficacy RM1998/00122/00 S3AA3012 60 investigators ¹	Completed (26Jul96)	Mexico, Puerto Rico, USA	5/1	Randomized, double-blind, parallel, cisplatin ($>50\text{mg}/\text{m}^2$) in chemotherapy-naïve patients	Zofran: 8mg BID po 24mg QD po 32mg QD po	24 hour study period	357	13-85 (64)	68/32 (12/67/21)
RM1997/04252/00 S3AA3004/3007 38 investigators ²	Completed (02Nov94)	USA	10/1	Randomized, double-blind, parallel, cisplatin ($50\text{mg}/\text{m}^2$ - $75\text{mg}/\text{m}^2$) or carboplatin ($>200\text{mg}/\text{m}^2$) in chemotherapy-naïve patients	Zofran: 24mg QD po Kytril: 10mcg/kg iv	Single dose, 24 hour study period	371	32-86 (66)	56/44 (8/90/2)
Supporting GM1997/00089/00 S3AB3008 31 investigators ³	Completed (08Feb96)	Canada, France, Germany, Iceland, Italy, Poland, South Africa, UK	15/1	Randomized, double-blind, parallel, cisplatin ($>50\text{mg}/\text{m}^2$) in cisplatin chemotherapy-naïve patients	Zofran: 24mg QD po + dexamethasone 12mg po Zofran: 8mg QD iv + dexamethasone 20mg iv	Single dose, 24 hour study period	530 (+ 8 subjects who received both treatments)	19-86 (55)	61/39 (9/86/5)
Clinical Pharmacology RM1997/00392/00 S3AA1002 Moeller	Completed (15Oct96)	USA	2/75	Randomized, single-dose, open-label, 2 period, cross- over in healthy volunteers	Zofran: 24mgx1 po 8mgx3 po	Single dose PK evaluated from pre-dose to 24 hours post-dose	16	18-43 (28)	50/50 (25/69/6)

¹ Abramowitz, Adams-Graves, Alden, Amin, Ansari, Bank, Baral, Barreras, Barron, Beauty, Benedetto, Boston, Burton, Byrne, Chowhan, Chun, Cohen, Cone, Craig, Decker, Deutsch, Diaz, DiBenedetto, Dobbs, Eisenberg, Essig, Fesen, Fiskin, Goldberg, Grapski, Harrer, Jacquin, Keiback, Kish, Kosmo, Krasnow, Lester, McLaren, Meza, Miletello, Mintzer, Miranda, Needles, Osborn, R Patci, Perry, Rainey, Reeves, Rodriguez, Rosenfeld, Shandas, Sher, Spector, Stella, Sylvester, Trochelmann, Velez-Garcia, Wiznitzer, Zaentz, Zarabi

² Al-Saraf, Amsden, Anderson, Barnes, Bearden, Beck, Caldwell, Chawla, Chevlen, Felgert, Garewal, Gross, Hainsworth, J Harvey, Homesley, Isaacs, John, Kalman, Lesscne, Lester, Madajewicz, McLeod, Mena, Messino, Mitchell, Modiano, H Patci, Petrus, Post, Schiller, Scintorno, Spector, Teckmedyan, Thant, Whaley, Winokur, Yee

³ Bessette, Brunet, Chang, Cognetti, Cristimann, Cronje, Cunningham, Duckworth, Giovannini, Goedhals, Gozdz, Hrafnkelsson, Jordaen, Krzakouski, Madej, Maksymiuk, Maxwell, Pawlicki, Raats, Rapoport, Riviere, Roberts, Roszak, Ruff, Schneider-Waterberg, Selby, Tomiak, Tujakowski, Vorobiof, Yelle, Zaluzki

2. Treatment Exposure

A total of 1282 subjects, 1095 of which received ondansetron, were treated with study drug. The extent of exposure to study drug for the studies included in this submission is presented in Table 3.10:

**Table 3.10
Treatment Exposure**

Treatment Groups	Number of Subjects				
	S3AA3012	S3AA3004/ 3007	S3AB3008	S3AA1002	Total
Ondansetron 24mg p.o.	116	184	--	--	300
Ondansetron 8mg BID p.o. (total dose 16mg)	124	--	--	--	124
Ondansetron 32mg p.o.	117	--	--	--	117
Ondansetron 24mg + dexamethasone 12mg p.o.	--	--	262	--	262
Ondansetron 8mg + dexamethasone 20mg IV	--	--	268	--	268
Ondansetron 8mg IV/24mg p.o.+ dexamethasone 20mgIV/12mg p.o.*	--	--	8	--	8
Ondansetron 24mg x2 doses p.o. (total dose 48mg)	--	--	--	16	16
Granisetron 10 mcg IV	--	187	--	--	187

* Not a protocol specified treatment group

3. Demographics

The demographics of age, gender, and ethnic origin are summarized in Table 3.4.

The combined data from both primary efficacy studies (S3AA3012 and S3AA3004/3007) revealed that the 300 subjects in the oral ondansetron 24mg QD group had a mean age of 62.8 years, a mean height of 169.6cm, and a mean weight of 71.5kg. Of these subjects, most were male (64%), Caucasian/White (79%), were not current alcohol users (76%), had previously used alcohol (56%), and, if female, were postmenopausal (58%). For the 299 oral ondansetron 24mg QD-treated subjects who received cisplatin, the mean cisplatin dose was 69.49mg/m², with 52% of subjects receiving cisplatin doses of $\geq 70\text{mg/m}^2$ to $< 100\text{mg/m}^2$ and 8% of subjects receiving cisplatin doses of $\geq 100\text{mg/m}^2$.

For the individual primary efficacy studies, the treatment groups were similar with respect to age (means: 60.1-64.3 years), height (means: 167.0-170.0cm), weight (means: 67.5-72.8kg), and current alcohol use (75-80% not current users; 20-25% current users). Differences in subject characteristics were noted in terms of gender (higher proportions of males in the S3AA3012 ondansetron 24mg group), ethnic origin (lower proportion of Caucasian/White subjects and a higher proportion of Hispanic subjects in S3AA3012),

prior alcohol use (higher incidence in S3AA3012), and subjects receiving cisplatin doses of $\geq 100\text{mg/m}^2$ (higher proportion in S3AA3012 due to design of study).

In the supporting study (S3AB3008) treatment groups were generally well balanced with respect to age (means: 52.7-53.9 years), height (means: 166.8-167.8 cm), weight (means: 61.0-68.7kg), and gender (38-39% female, 61-63% male). Most subjects in the two protocol-specified treatment groups were Caucasian/White (86-87%) and did not report current alcohol use (69-71%) or prior alcohol use (53-56%). Mean cisplatin dose for the two protocol-specified treatment groups was $74.71\text{-}75.45\text{mg/m}^2$, with 34-38% of subjects in each group receiving cisplatin doses of $\geq 70\text{mg/m}^2$ to $< 100\text{mg/m}^2$ and 24-27% of subjects receiving cisplatin doses of $\geq 100\text{mg/m}^2$.

For the 16 subjects enrolled in the clinical pharmacology study (S3AA1002), the mean age was 29.9 years, mean height was 170.2 cm, and mean weight was 77.9 kg. Fifty percent of subjects reported current alcohol use, 50% were female, and 69% were Caucasian/White.

4. Adverse Events

All adverse events, regardless of potential relationship to study drug, were recorded in the case report form. Information recorded included the type of event or signs and symptoms, date and time of occurrence, severity, and duration. Investigators were also asked to assess the relationship of all adverse events to study drug.

Complete summary listings of all adverse events for all subjects are provided in the Integrated Summary of Safety Table 5 (Vol. 17, p.29) and Table 6 (Vol. 17, p. 38) for primary efficacy studies S3AA3012 and S3AA3004/3007, in Table 7 (Vol. 17, p. 42) and Table 8 (Vol. 17, p. 50) for supporting study S3AB3008, and in Table 9 (Vol. 17, p.55) for clinical pharmacology study S3AA1002.

Overall adverse events. For the primary efficacy studies, the overall incidence of adverse events was 27% (81/300) in ondansetron 24mg-treated subjects, with headache (11%, 33/300) being the only event that occurred in $\geq 5\%$ of these subjects.

In general, the overall incidence of adverse events was higher for subjects enrolled in S3AA3012 (32-35%) than for those enrolled in S3AA3004/3007 (24-28%). Within each of the primary efficacy studies, the proportion of subjects with one or more adverse events was similar across treatment groups. Only headache and diarrhea had incidences of $\geq 5\%$ in any treatment group. The incidence of headache was generally similar for the ondansetron 24mg group (17%) and the other treatment groups (13-15%) enrolled in the S3AA3012 study, and was lower for the ondansetron 24mg group (7%) than for the granisetron $10\mu\text{/kg}$ group (12%) enrolled in the S3AA3004/3007 study. The incidence of diarrhea was similar for the ondansetron 24mg group (6%) and the other treatment groups (3-7%) enrolled in the S3AA3012 study, and was lower for the ondansetron 24mg group (3%) and the granisetron $10\mu\text{/kg}$ group ($< 1\%$) enrolled in the S3AA3004/3007 study. The incidence of other commonly occurring events was low ($< 5\%$ per group) and generally similar among treatment groups.

For supporting study S3AB3008, the proportion of subjects who experienced at least one adverse event was similar for those who received oral ondansetron 24mg plus dexamethasone 12mg (26%, 69/262) and those who received IV ondansetron 8mg and dexamethasone 20mg (27%, 73/268). Headache and constipation were the only events that occurred in $\geq 5\%$ of subjects in any treatment group. Headache occurred in 9% (23/262) of subjects in the oral treatment group and in 8% (22/268) of subjects in the IV treatment group. Constipation occurred in 7% (19/262) of in the oral treatment group and in 5% (14/268) of subjects in the IV treatment group.

For the 16 subjects who were enrolled in the clinical pharmacology study, 38% experienced adverse events. The events that occurred were as follows: headache (38%), dizziness (6%), and nausea and vomiting (6%).

There was no clear evidence of age-related or ethnic origin-related differences in the incidence of adverse events in any primary efficacy study treatment group. Across treatment groups within each of the primary efficacy studies, the overall incidence of subjects with one or more adverse events was higher for female subjects than for male subjects as is consistent with previous studies.

Deaths. Four deaths were reported. A list of the fatalities is provided in Table 3.11 below. Listings of these deaths are also provided in the Integrated Summary of Safety Table 16, (Vol. 17, p. 147). Of these, one subject (<1%) received ondansetron 8mg BID, two (<1%) received ondansetron 24mg, and two (2%) received ondansetron 32mg. All deaths occurred in the primary efficacy studies (S3AA3004/3007 and S3AA3012) and were considered to be unrelated or unlikely related to study drug administration. Case narratives for these subjects are provided in Appendix 2 of the Integrated Summary of Safety (Vol. 17, p. 216) and case report forms are provided in Section 12 (Vol. 18, p. 1) of this application.

Table 3.11
Listing of Deaths

Treatment	Study	Subject Number	Adverse Events	Study Drug Relationship
OND8 BID p.o.	S3AA3012	21006	massive pulmonary embolism	unrelated
OND24 qd p.o.	S3AA3007	9051	unable to arouse cerebrovascular accident	unlikely unrelated
OND32 qd p.o.	S3AA3012	13800	probable organ shutdown, respiratory arrest drop in blood pressure, decreased urinary output	unrelated unlikely
		14079	rapid tumor growth, acute respiratory distress	unrelated

OND8 BID p.o.: ondansetron 8mg p.o., twice daily
 OND24 qd p.o.: ondansetron 24mg p.o., once daily
 OND32 qd p.o.: ondansetron 32mg p.o., once daily

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Withdrawals due to adverse events. Subjects who were withdrawn from the clinical trials because of an adverse event are listed in Table 3.12 below and in the Integrated Summary of Safety Table 17 (Vol. 17, p. 154). Seven subjects, all of whom were enrolled in primary efficacy studies, were withdrawn due to adverse events. Of these, one subject (<1%) received ondansetron 8mg BID, two (<1%) received ondansetron 24mg, two (2%) received ondansetron 32mg, and two (<1%) received oral ondansetron 24mg plus dexamethasone 12mg. With the exception of Subject 8628 (ondansetron 24mg plus dexamethasone 12mg) who was withdrawn due to headache and neck ache considered to be possibly related to study drug, none of the events associated with withdrawal were considered by the investigators to be study drug related. Case report forms for subjects who were withdrawn due to adverse events are provided in Section 12 (Vol. 18, p. 1) of this application.

**Table 3.12
Subjects Withdrawn from Studies Due to Adverse Events**

Treatment	Study	Subject Number	Reason for Withdrawal	Fatal?	Study Drug Relationship
OND8 BID p.o.	S3AA3012	21006	massive pulmonary embolism	Yes	unrelated
OND24 qd p.o.	S3AA3007	9011	shaking chills, fever, possible urinary tract infection, bladder spasms, intractable bladder pain	No	all unrelated
		9051	unable to arouse cerebrovascular accident	Yes Yes	unlikely unrelated
OND32 qd p.o.	S3AA3012	13800	probable organ shutdown, respiratory arrest drop in blood pressure, decreased urinary output	Yes Yes	unrelated unlikely
		14017	mental status changes, back pain	No	unrelated
OND24 qd+dex p.o.	S3AB3008	8585	nausea, retching, diarrhea	No	unrelated
		8628	headache and neck ache nausea, vomiting	No No	possible unlikely

OND8 BID p.o.: ondansetron 8mg p.o., twice daily

OND24 qd p.o.: ondansetron 24mg p.o., once daily

OND32 qd p.o.: ondansetron 32mg p.o., once daily

OND24 qd+dex p.o.: ondansetron 24mg p.o. plus dexamethasone 12mg p.o., once daily

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Serious adverse events. Subjects who experienced a serious adverse event are listed in Table 3.13 below and in the Integrated Summary of Safety Table 18 (Vol. 17, p. 156) and Table 19 (Vol. 17, p.159) for the primary efficacy and supporting studies, respectively. Sixteen subjects, all of whom were enrolled in treatment studies, experienced serious adverse events. Of these 16 subjects, one (<1%) received ondansetron 8mg BID, four (1%) received ondansetron 24mg, two (2%) received ondansetron 32mg, four (2%) received oral ondansetron 24mg plus dexamethasone 12mg, four (1%) received IV ondansetron 8mg plus dexamethasone 20mg, and one (<1%) received IV granisetron 10µ/kg. All serious adverse events were considered to be either unrelated or unlikely related to study drug administration by the investigators.

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**Table 3.13
Subjects With Serious Adverse Events**

Treatment	Study	Subject Number	Reason for Withdrawal	Fatal ?	Study Drug Relationship
OND8 BID p.o.	S3AA3012	21006	massive pulmonary embolism	Yes	unrelated
OND24 QD p.o.	S3AA3004	7168	no appetite, nausea, vomiting	No	unrelated
		9051	unable to arouse cerebrovascular accident	Yes Yes	unlikely unrelated
	S3AA3012	20965	fever (temperature 104.4°F)	No	unlikely
OND32 QD p.o.	S3AA3012	13776	shortness of breath, pleural effusion	No	unrelated
		14079	rapid tumor growth, acute respiratory distress	Yes	unrelated
		13800	probable organ shutdown, respiratory arrest drop in blood pressure, decreased urinary output	Yes Yes	unrelated unlikely
OND8 QD+dex IV	S3AB3008	8259	precordialgia	No	unrelated
		8815	lethargy, unable to eat or drink (due to thrush)	No	unrelated
		8737	hospitalized due to pleuritic right chest pain of pneumothorax ? infection	No	unrelated
		8089	febrile neutropenia, gastroenteritis	No	unrelated
OND24 QD+dex p.o.	S3AB3008	8339	dehydration status, hyperuricacidemia, hypercreatinemia, hyper urea	No	unrelated
		8793	dysphagia, nausea and retching severe epigastric pain	No No	unlikely unrelated
		8135	dehydration, urinary retention	No	unrelated
		8626	anorexia leading to hospitalization	No	unlikely
GRAN10 QD IV	S3AA3007	8876	acute myocardial infarct	No	unrelated

OND8 BID p.o.: ondansetron 8mg p.o., twice daily
 OND24 QD p.o.: ondansetron 24mg p.o., once daily
 OND32 QD p.o.: ondansetron 32mg p.o., once daily
 OND 8 QD+dex IV: ondansetron 8mg IV plus dexamethasone 20mg IV, once daily
 OND24 QD+dex p.o.: ondansetron 24mg p.o. plus dexamethasone 12mg p.o., once daily
 GRAN10 QD IV: granisetron 10µg/kg IV, once daily

5. Clinical Laboratory Evaluations

Clinical laboratory test data are presented in the Integrated Summary of Safety for the subjects enrolled in primary efficacy studies S3AA3012 and S3AA3004/3007, and for the subjects enrolled in clinical pharmacology study S3AA1002. Laboratory tests were not performed in supporting study S3AB3008. Clinical laboratory test changes were either consistent with those observed in subjects undergoing myelosuppressive chemotherapy or were similar for the ondansetron 24mg treatment group as compared with the other treatment groups.

6. Vital Sign Data

Vital sign data were collected for the 16 subjects enrolled in clinical pharmacology study S3AA1002. All of these subjects received ondansetron (cumulative dose 48mg p.o.). No

clinically meaningful changes in vital signs were observed in any subject after study drug administration.

7. ECG Data

ECGs were performed for the 16 subjects enrolled in clinical pharmacology study S3AA1002. All of these subjects received ondansetron (cumulative dose 48mg p.o.). No clinically notable changes were noted for any ECGs.

8. Drug Abuse and Overdose Information

Drug Abuse

As concluded in NDA 20-007 for Zofran® Injection (Vol. 107, p. 347 of the original application), actual or relative potential for abuse has not been demonstrated with ondansetron in either preclinical or clinical studies. Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

Overdose

Based on longer market exposure, most experience with Zofran® overdose has been observed with Zofran® Injection. The overdose section of the package insert for Zofran® Injection states:

- There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 145mg and total daily dosages (three doses) as large as 252mg have been administered intravenously without significant adverse events. These doses are more than 10 times the recommended daily dose.
- "Sudden blindness" (amaurosis) of 2-3 minutes' duration plus severe constipation occurred in one patient that was administered 72mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48mg of oral ondansetron. Following infusion of 32mg over only a 4-minute period, a vasovagal episode with transient second degree heart block was observed. In all instances, the events resolved completely.

9. Conclusions

The data presented in this document demonstrate that a single oral dose of ondansetron 24mg is safe and well-tolerated when administered to cancer subjects receiving highly emetogenic chemotherapy (including cisplatin $\geq 50\text{mg/m}^2$).

The most commonly occurring adverse events noted with administration of one dose of ondansetron 24mg p.o. were headache (11%, 33/300) and diarrhea (4%, 13/300). When one dose each of ondansetron 24mg p.o. and dexamethasone 12mg p.o. were administered, the most common adverse events were headache (9%, 23/262) and

constipation (7%, 19/262). Although lower in frequency, these events are similar to events observed for the orally administered three-day dosing regimens currently approved for the treatment of chemotherapy-induced nausea and vomiting (ondansetron 8mg BID p.o. and ondansetron 8mg TID p.o.). As reported in the package insert for Zofran® Tablets, for subjects who received moderately emetogenic cyclophosphamide-based chemotherapy the following events were observed in $\geq 5\%$ of the 242 subjects who received ondansetron 8mg BID p.o. and the 415 subjects who received ondansetron 8mg TID p.o.: headache (24-27%), malaise/fatigue (9-13%), constipation (6-9%), diarrhea (4-6%), and dizziness (4-5%). The incidence of these events in placebo-treated subjects (n=262) who received cyclophosphamide-based chemotherapy was as follows: headache (13%), malaise/fatigue (2%), constipation (<1%), diarrhea (4%), and dizziness (5%).

Changes in clinical laboratory tests were consistent with those that might be expected for subjects undergoing myelosuppressive chemotherapy and/or were of little or no clinical concern. As reported in the package insert for Zofran® Tablets, AST and/or ALT elevations exceeded twice the upper limit of normal in approximately 1-2% of subjects who received ondansetron tablets (ondansetron 8mg BID p.o. or ondansetron 8mg TID p.o.; both regimens for 3 days).

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