

## 2. Sponsor's Analysis

For administrative reasons (slow accrual), the sponsor subsequently decided to combine the data from both protocols and analyze as one trial (S3AA3004/3007) with sample size of 364 patients.

A total of 373 patients were enrolled into this study (196 patients in S3AA3004 and 177 patients in S3AA3007). Two patients (numbers 7377 and 7416) were randomized to granisetron but did not receive active study drug. One hundred and eighty-four (184) patients received oral ondansetron 24mg and 187 patients received i.v. granisetron 10 mcg/kg. Of the 371 patients, there were 133 ondansetron patients and 121 granisetron patients who completed the 24.5-hour study period. There were 119 patients (51 ondansetron and 68 granisetron) withdrawn from the trial. The primary reason for subject withdrawal was lack of efficacy.

One subject (subject number 8817) received carboplatin instead of cisplatin. This subject was included with the cisplatin population for all efficacy analysis.

The 371 patients who were randomized and received study drug were included in the efficacy analysis.

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

Thirty of the ITT patients (13 ondansetron patients and 17 granisetron patients) were excluded from the Per-Protocol analysis because of major protocol violations. The majority of the violations were related to the use of prohibited concomitant medications.

The median dose of cisplatin was 70mg/m<sup>2</sup>. The dosing range was 31-100mg/m<sup>2</sup>.

The effectiveness of ondansetron was considered to be not inferior to granisetron if the lower limit of the 95% confidence interval for the difference in response rates is within 10% (stated post hoc).

Sites with fewer than 10 total patients were pooled together and all Mantel-Haenszel tests controlled for this strata variable.

### 2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline is given in attached Table 4. As seen from attached Table 4, there were no statistically significant

differences between treatment groups in terms of sex, ethnic origin, age, weight, height or alcohol consumption.

## 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 S3AA3004/3007 Sponsor's Complete Response (No vomiting and No rescue) (ITT Analysis)

Treatment	Rate	P-value vs. 10mcg/kg I.V.	95% C.I.
Ond 24mg QD PO	106/184 (58%)	0.202	(-4%, 17%)
Gran 10mcg/kg I.V.	95/187 (51%)		

### (Per-Protocol Analysis)

Treatment	Rate	P-value vs. 10mcg/kg I.V.	95% C.I.
Ond 24mg QD PO	99/171 (58%)	0.1891	(-3%, 18%)
Gran 10mcg/kg I.V.	86/170 (51%)		

P-values were from Mantel-Haenszel test.

Copied from Tables 10.1 and 10.3, pages 95 and 98, respectively, Vol. 10.

As seen from tables above, the difference between the two treatment groups was not statistically significant for both the ITT and Per-Protocol analyses.

### 2.2.1 Complete Response by Gender

Complete response rates by gender for both treatment groups were tabulated in attached Table 5. As seen from attached Table 5, females were less likely to respond to anti-emetic treatment. Complete responders were 46% (36/79) female versus 67% (70/105) males in the ondansetron treatment group and 41% (35/86) versus 59% (60/101) in the granisetron group, respectively. However, there does not appear to be a difference between the treatment groups for either the males or the females.

## 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 6.

As seen from attached Table 6, there were no statistically significant treatment difference among the treatment groups in terms of the percentage of patients with either a complete

or major response, the percentage of patients considered therapeutic failure, the percentage of patients receiving rescue medication and the percentage of patients with complete control of nausea.

### **3. Reviewer's Evaluation**

#### **3.1 Design Issues**

This study was designed as a superiority trial and was not designed as a non-inferiority trial. The sponsor's statement in the report "The effectiveness of ondansetron will be considered not inferior to granisetron if the lower limit of the 95% confidence interval for the difference in response rates is within 10%" was a post hoc and was not specified in the protocol.

A sample size of 364 was inadequate for either a non-inferiority or an equivalence trial. For example; for showing non-inferiority trial with a 10% delta, 594 patients (297 per group) would be required to provide 80% power to detect a 10% difference in response between the treatment groups, assuming an average response rate of 60%.

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

The study was designed as a superiority trial. The sample size was inadequate for a non-inferiority trial with a 10% delta. The sponsor's results were inconclusive to claim that ondansetron 24mg QD was at least as effective as, if not superior to granisetron i.v. 10mcg/kg.

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

#### **3.1.2 Reviewer's Analysis of Complete Responses by Treatment versus Historical Placebo Control**

This reviewer compared the results from study S3AA3004/3007 statistically to those of a historical placebo control using 22% as the placebo complete response rate. The results from the reviewer's analysis of complete response by treatment versus historical placebo control are given below.

**Protocol S3AA3004/3007**  
**Complete Response by Treatment vs. Historical Control**  
**(Intent-to-Treat Analysis)**

	Ond 24mg QD PO	Gran 10mcg/kg IV
Rate	106/184 (58%)	95/187 (51%)
P-value for comparison to Historical Placebo Control	<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 table above, each of the two treatment groups was statistically significantly superior to the historical placebo control.

#### D. Overall Summary and Recommendation

In study S3AA3012, the difference of complete response between the ondansetron 8mg BID and the ondansetron 24mg QD was not statistically significant in both the Intent-to-treat and the Per-Protocol analyses after adjustments for multiplicity. However, a numerical difference of about 12% in favor of the ondansetron 24mg QD was seen in both the ITT and the Per-Protocol analyses. Furthermore, each of the three treatment groups (ondansetron 8mg BID, 24mg QD, and 32mg QD) in the Study S3AA3012 was shown by this reviewer to be statistically significantly superior to an adequate historical placebo control. The emetogenic stimulus in this study consisted of cisplatin-based highly emetogenic regimens.

In study S3AA3004/3007, the difference of complete response between ondansetron 24mg QD and granisetron i.v. 10mcg/kg was not statistically significant. However, in this study, ondansetron 24mg QD treatment group was shown by this reviewer to be statistically significantly superior to an appropriate historical placebo.

In conclusion, a single, 24mg dose of ondansetron administered prior to cisplatin appeared to be statistically significantly superior to a relevant historical placebo control. However, the 24 mg dose was not statistically significantly different from the currently approved 10mcg/kg intravenous dose of granisetron for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy (cisplatin 50-75 mg/m<sup>2</sup>).

/s/

Milton C. Fan, Ph.D.  
 Mathematical Statistician

This review consists of 13 pages of text and 8 pages of tables.

Concur: Dr. Al-Osh /s/ 3/25/99

Dr. Welch /s/ 3/25/99

cc:

Archival NDA 20-103

HFD-180

HFD-180/Dr. Talarico

HFD-180/Dr. Gallo-Torres

HFD-180/Ms. McNeil

HFD-715/Dr. Nevius

HFD-715/Dr. Welch

HFD-715/Dr. Al-Osh

HFD-715/Dr. Fan

Dr. Fan/x73088/mcf/03/25/99

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Table 1

## Summary of Demographic and Baseline Characteristics --- Protocol S3AA3012

Characteristic	8mg BID (N=124)	Ondansetron 24mg QD (N= 116)	32mg QD (N=117)	Between Treatment p-value <sup>a</sup>
<b>Sex</b>				0.193
Male	79 (64%)	86 (74%)	77 (66%)	
Female	45 (36%)	30 (26%)	40 (34%)	
<b>Race</b>				0.120
Caucasian	85 (69%)	76 (66%)	78 (67%)	
African	14 (11%)	18 (16%)	10 (9%)	
Hispanic	24 (19%)	22 (19%)	25 (21%)	
Oriental	0 (0%)	0 (0%)	4 (3%)	
Other	1 (<1%)	0 (0%)	0 (0%)	
<b>Age (yr)</b>				0.995
Mean	60.9	61.1	60.1	
S.D.	12.7	13.5	14.4	
Min-Max	18-82	13-85	15-80	
<b>Height (cm)</b>				0.068
Mean	169.0	170.0	167.0	
S.D.	11.4	11.2	10.7	
Min-Max	142-196	143-191	132-196	
<b>Weight (kg)</b>				0.117
Mean	72.5	70.4	67.5	
S.D.	18.4	17.2	17.0	
Min-Max	39-144	31-106	33-151	
<b>Current Alcohol Use</b>				0.631
No current use	99 (80%)	86 (75%)	90 (79%)	
Current use	24 (20%)	28 (25%)	24 (21%)	
Missing	1	2	3	
<b>Prior Alcohol Use</b>				0.474
No prior use	52 (42%)	40 (34%)	43 (37%)	
Prior use	72 (58%)	76 (66%)	74 (63%)	
<b>Cisplatin Infusion Time (h)</b>				0.808
Mean	1.93	1.99	1.91	
S.D.	0.93	0.97	0.90	
Min-Max	0.33 -5.00	0.47- 4.00	0.45- 4.00	
Missing	0	1	0	

Copied from Tables 5 and 6, page 67-75, Vol. 5

P-values for age, height, weight, cisplatin infusion time, cisplatin were obtained by sponsor using van Elteren tests.

P-values for gender, race, current alcohol use, prior alcohol use, and cisplatin dose were obtained by sponsor using Mantel-Haenszel tests.

Table 1 (Continued)

## Summary of Demographic and Baseline Characteristics — Protocol S3AA3012

Characteristic	8mg BID (N=124)	Ondansetron 24mg QD (N= 116)	32mg QD (N=117)	Between Treatment p-valuea
Cisplatin ((mg/m <sup>2</sup> )				0.527
Mean	74.37	75.75	72.97	
S.D	19.68	19.23	19.53	
Min-Max	47.80- 112.5	48.00- 105	47.20- 110.0	
Missing	0	1	0	
Cisplatin ((mg/m <sup>2</sup> )				0.948
Dose < 50 mg	4 (3%)	2 (2%)	5 (4%)	
50 ≤ Dose < 70mg	47 (38%)	43 (37%)	47 (40%)	
70 ≤ Dose < 100mg	48 (39%)	46 (40%)	42 (36%)	
100 ≤ Dose	25 (20%)	24 (21%)	23 (20%)	
Missing	0	1	0	
Primary Neoplasm				
Lung	53 (43%)	62 (53%)	58 (50%)	
Head and Neck	27 (22%)	19 (16%)	21 (18%)	
Gynecologic	15 (12%)	10 (9%)	13 (11%)	
Gastrointestinal	7 (6%)	14 (12%)	6 (5%)	
Genito-urinary	9 (7%)	7 (6%)	6 (5%)	
Other	6 (5%)	1 (<1%)	6 (5%)	
Bone and Soft Tissue	2 (2%)	1 (<1%)	2 (2%)	
Skin	2 (2%)	2 (2%)	1 (<1%)	
Thorax	3 (2%)	0 (0%)	2 (2%)	
Hematopoietic/ Immunologic	0 (0%)	1 (<1%)	1 (<1%)	

Copied from Tables 5 and 6, page 67-75, Vol. 5

P-values for age, height, weight, cisplatin infusion time, cisplatin were obtained by sponsor using van Elteran tests.

P-values for gender, race, current alcohol use, prior alcohol use, and cisplatin dose were obtained by sponsor using Mantel-Haenszel tests.

Table 2

Sponsor's Complete Response by Gender --- Protocol S3AA3012  
(ITT Analysis)

Gender	Ondan 8mg BID	Ondan 24mg QD	Ondan 32mg QD
Males	49/79 (62%)	63/86 (73%)	45/77 (58%)
Females	19/45 (42%)	13/29 (45%)	19/40 (48%)

Copied from Table 10.4, page 105, Vol.5

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Table 3

Sponsor's Results of Secondary Efficacy Variable --- Protocol S3AA3012  
(ITT Analysis)

Efficacy Variable	Treatment	Rate	vs. 8 mg BID p-value	vs. 24 mg QD p-value
Complete plus major control	Ondan 32mg QD	78/117 (67%)	0.658	0.310
	Ondan 24mg QD	84/115 (73%)	0.125	
	Ondan 8mg BID	80/124 (65%)		
Therapeutic failure	Ondan 32mg QD	30/117 (26%)	0.844	0.190
	Ondan 24mg QD	21/115 (18%)	0.223	
	Ondan 8m BID	30/124 (24%)		
Rescue	Ondan 32mg QD	25/117 (21%)	0.854	0.372
	Ondan 24mg QD	19/115 (17%)	0.416	
	Ondan 8m BID	25/124 (20%)		
Complete control of nausea	Ondan 32mg QD	55/117 (50%)	0.019	0.396
	Ondan 24mg QD	64/115 (56%)	0.001	
	Ondan 8mg BID	43/124 (36%)		

Copied from Table 10.1 and 12, pages 101, 102, and 121, Vol. 5.

Table 4

Summary of Demographic and Baseline Characteristics ---  
Protocol S3AA3004/S3AA3007

Characteristic	Ondansetron 24mg QD (N=184)	Granisetron 10mcg/kg IV (N= 187)	Between Treatment p-valuea
Sex			0.599
Male	105 (57%)	101 (54%)	
Female	79 (43%)	86 (46%)	
Race			0.300
Caucasian	161 (88%)	172 (92%)	
African	18 (10%)	12 (6%)	
Hispanic	1 (<1%)	2 (1%)	
Oriental	2 (1%)	0 (0%)	
Other	2 (<1%)	0 (0%)	
Age (yr)			0.424
Mean	63.8	64.3	
S.D.	10.6	11.0	
Min-Max	32-86	38-86	
Height (cm)			0.812
Mean	169.4	169.4	
S.D.	10.6	10.3	
Min-Max	142-198	142-193	<b>BEST POSSIBLE</b>
Weight (kg)			0.907
Mean	72.5	70.4	67.5
S.D.	18.4	17.2	17.0
Min-Max	39-144	31-106	33-151
Current Alcohol Use			0.633
No current use	141 (77%)	138 (75%)	
Current use	43 (23%)	47 (25%)	24 (21%)
Missing	0	2	
Prior Alcohol Use			0.929
No prior use	92 (50%)	92 (34%)	
Prior use	92 (50%)	92 (34%)	
Missing	0	3	

Copied from Tables 5 and 6, page 62-70, Vol. 10

P-values for age, height, weight, cisplatin infusion time, cisplatin were obtained by sponsor using van Elteren tests.

P-values for gender, race, current alcohol use, prior alcohol use, and cisplatin dose were obtained by sponsor using Mantel-Haenszel tests.

Table 4 (Continued)

Summary of Demographic and Baseline Characteristics —  
Protocol S3AA3004/S3AA3007

Characteristic	Ondansetron 24mg QD (N=184)	Granisetron 10mcg/kg IV (N= 187)	Between Treatment p-value <sup>a</sup>
Cisplatin Infusion Time (h)			0.958
Mean	1.8	1.8	
S.D.	0.7	0.8	
Min-Max	0.3-3.5	0.3- 3.7	
Missing	4	3	
Cisplatin ((mg/m <sup>2</sup> ))			0.770
Mean	65.6	65.2	
S.D	8.5	9.5	
Min-Max	42.0- 76.0	31.0- 100.0	
Missing	4	3	
Cisplatin ((mg/m <sup>2</sup> ))			0.705
Dose < 50 mg	4 (2%)	5 (3%)	
51 ≤ Dose < 70mg	72 (39%)	76 (41%)	
71 ≤ Dose < 100mg	108 (59%)	104 (56%)	
101 ≤ Dose	0 (0%)	1 (<1%)	
Missing	0	1	
Primary Neoplasm			
Lung	111 (60%)	109 (58%)	
Gynecologic	18 (10%)	19 (10%)	
Head and Neck	15 (8%)	11 (6%)	
Gastrointestinal	15 (8%)	15 (8%)	
Genito-urinary	17 (9%)	16 (9%)	
Other	6 (3%)	6 (3%)	
Bone and Soft Tissue	1 (<1%)	2 (1%)	
Skin	1 (<1%)	6 (3%)	
Thorax	0 (2%)	3 (2%)	

Copied from Tables 5 and 6, page 62-70, Vol. 10

P-values for age, height, weight, cisplatin infusion time, cisplatin were obtained by sponsor using van Elteren tests.

P-values for gender, race, current alcohol use, prior alcohol use, and cisplatin dose were obtained by sponsor using Mantel-Haenszel tests.

Table 5

Sponsor's Complete Response by Gender --- Protocol S3AA3004/S3AA3007  
(ITT Analysis)

Gender	Ondan 24 mg QD	Gran 10mcg/kg IV
Males	70/105 (67%)	60/101 (59%)
Females	36/79 (46%)	35/86 (41%)

Copied from Table 10.4, page 99, vol. 10.

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Table 6

Sponsor's Results of Secondary Efficacy Variable --- Protocol S3AA3004/S3AA3007  
(ITT Analysis)

Efficacy Variable	Treatment	Rate	vs. Gran 10mcg/kg I.V. p-value
Complete plus major control	Ondan 24mg QD	126/184 (68%)	0.131
	Gran 10mcg/kg I.V.	114/187 (61%)	
Therapeutic failure	Ondan 24mg QD	50/184 (27%)	0.114
	Gran 10mcg/kg I.V.	122/187 (35%)	
Rescue	Ondan 24mg QD	49/184 (27%)	0.112
	Gran 10mcg/kg I.V.	64/187 (34%)	
Complete control of nausea	Ondan 24mg QD	79/184 (43%)	0.095
	Gran 10mcg/kg I.V.	64/185 (35%)	

Copied from Table 10.1 and 12, pages 95, 96, and 121, Vol. 10.

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