7. Concomitant Medications

All prescription and non-prescription medication[5] with known or potential antiemetic activity were excluded during the 24.5-h study period and during the 24 hours prior to the first dose of test medication. All concomitant medications taken during the study period were listed in the case report form along with their dose, time, indication, and route of administration.

8. Withdrawals/Assessment of Patient Compliance

My review of this subsection (p. 24 of the Clinical Report) indicates that these aspects of the protocol were adequate.

9. Study Evaluations

a. Primary Efficacy Parameters

- The primary efficacy variable for this trial was the number of subjects with zero emetic episodes who completed the trial without rescue over the 24-h study period.[6]
- The total number of emetic episodes was grouped to create a variable called treatment response, defined for the study period as follows:

Complete response:	No emetic episode over the 24-h period following cisplatin initiation.
Major response:	1 to 2 emetic episodes over the 24-h period following cisplatin initiation
Minor response:	3 to 5 emetic episodes over the 24-h period following cisplatin initiation
Therapeutic failure:	One or more of the following reasons: - >5 emetic episodes over the 24-h period following cisplatin initiation. - Requirement of rescue therapy due to severity of emesis during the 24-h period following cisplatin initiation. - Severity of N&V resulting in withdrawal from the study.
Withdrawal:	Withdrawal from study due to other reasons (e.g. AEs, administrative errors, etc.).

[5] This included but was not limited to phenothiazines, butyrophenones, hydroxyzine, lorazepam, cannabinoids, MCP, corticosteroids, and trimethobenzamide. Amendment 02 modified the exclusion criterion for concurrent therapy and allowed the use of selective serotonin re-uptake inhibitors and tricyclic antidepressants during the study period provided the subject had been on stable doses for at least 2 weeks prior to study entry and no increase in dosage occurred during the 24.5-h study period.

[6] 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 was 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.

b. Secondary Efficacy Parameters

- These measures included the number of subjects with a complete or major treatment response, number of subjects who were therapeutic failures, time to treatment failure (i.e., first emetic episode, withdrawal, or rescue), and subject assessments of nausea.

- Nausea was assessed using an 11-point, whole number, linear numerical scale from 0 to 10. Zero represented "No Nausea" while 10 represented nausea "as bad as it could be". Control of nausea was defined as a "No Nausea" response post-baseline with no rescue or premature withdrawal.

c. AE Monitoring/Laboratory Evaluations

These were adequate.

10. Data Collection/Data Management/Quality Assurance

My review of the evidence (p. 27-28 of Clinical Report) indicates that these aspects of the study were adequate.

11. Statistical Methodology

a. Sample Size

The sponsor notes that the sample size of 107 subjects in each treatment group was chosen so that the comparison of the percentage of subjects 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 8 mg BID and the other two treatments at a Type I error rate of 5%. This was based on a large-sample normal approximation to the binomial distribution. The true response rates were assumed to be:

40% for ondansetron 8 mg BID
60% for ondansetron 24 mg QD, and
65% for ondansetron 32 mg QD.

b. Generalities

All statistical tests and confidence intervals were two-sided and performed with a 0.05 Type 1 error rate. There was no formal adjustment for analyses of multiple endpoints. The primary assessment of efficacy was the comparison between the 8 mg BID and 24 mg QD treatment groups.[7]

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[7] The following windows were defined for all assessments:
- Baseline/Pre-treatment – to have been completed within 24h prior to start of test medication.
- 24-h – to have been completed within 24±2h after start of cisplatin chemotherapy.

The 24-h nausea assessment used in the analyses was any assessment performed post-baseline.

Sites with fewer than 15 total subjects were pooled together and all Mantel-Haenszel tests controlled for this strata variable. However, the results do not change appreciably if the sites are not pooled or if the analyses are not controlled for site differences. There was one site with two investigators (Investigator No. 9395 and Investigator No. 50012); these two investigators were pooled together into one site but were then pooled together with all the other sites with fewer than 15 subjects.

c. Populations

Three study populations[8] were considered in the analysis: Safety Population, Intent-to-Treat Population, and Per-Protocol Population.

d. Background Characteristics

- Baseline characteristics and demographic data (age, race, sex, height, weight, child-bearing potential, alcohol consumption) were summarized by treatment group using descriptive statistics and p-values based on Mantel-Haenszel methods, using van Elteren procedures for quantitative variables.

- The cisplatin dose (mg/m^2) and time of infusion were included as baseline characteristics and compared between treatment groups.

- Other baseline characteristics (primary neoplasm, chemotherapies, medical history) were summarized with descriptive statistics.

e. Efficacy

i) Emesis

The number of emetic episodes was classified into one of the 5 categories described under 9.a. above.

- To qualify as a complete, major, or minor response the subject had to have completed the entire post-treatment period without rescue. Subjects who withdrew

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[8]

- **Safety Population** – All subjects who received at least one dose of test medication.
- **Intent-to-Treat Population** – All subjects in the Safety population who received cisplatin chemotherapy. This was the primary population for efficacy analyses.
- **Per-Protocol Population** – All subjects in the intent-to-treat population without deviations from the protocol that could significantly affect the interpretation of efficacy endpoints (major protocol violations). Withdrawal or receipt of rescue medication did not constitute a protocol violation.

from the study for reasons other than lack of efficacy but would otherwise qualify as therapeutic failures were considered therapeutic failures. Subjects without a recorded number of emetic episodes and who did not otherwise qualify as a treatment failure were considered non-evaluable for efficacy.

- The primary analysis of efficacy compared the number of subjects in each treatment group with a complete response during the post-treatment period in the intent-to-treat population. A supporting analysis of the primary endpoint was performed in the per-protocol population. The number of subjects in each group with a complete or major response was compared.

- The treatment groups were compared using Mantel-Haenszel methods. A supporting analysis was performed using Fisher's exact test. A 95% confidence interval on the difference in response rates between the two treatment groups was computed using a large sample normal approximation.

- The primary endpoint was to have been analyzed controlling for any baseline characteristic found to be unbalanced between treatment groups using Mantel-Haenszel methods. The emetic response was summarized in each treatment group by sex, race, alcohol consumption, and site.

- The percentage of subjects requiring rescue medications and the percentage of therapeutic failures were summarized and compared between treatment groups.

- The time to treatment failure was calculated from the time of the start of chemotherapy until the first emetic episode, withdrawal, or rescue. For display purposes, the times were grouped as follows:

  - Oh <time to failure $\leq$3h
  - 3h < time to failure $\leq$6h
  - 6h < time to failure $\leq$12h
  - 12h < time to failure $\leq$18h
  - 18h < time to failure $\leq$24h
  - completed study without failure
  - Time to treatment failure not recorded/missing

- Time to treatment failure was analyzed using Kaplan-Meier methods and the treatment groups compared with log-rank tests. Subjects who completed the study without an emetic episode were considered censored observations at 24h. If the time of first emetic episode was missing then the time was imputed to be at midnight on the day of the event or, if they occurred on the same day, one minute after the start of cisplatin therapy. Only the intent-to-treat population was analyzed for this endpoint.

- Subjects who completed the trial but otherwise had no emetic episode data recorded were considered unevaluable.

ii) Nausea

- The subjects' nausea assessments were recorded at baseline and during the visit 24h after chemotherapy. Only the ITT population was analyzed for this endpoing.

- The percentage of subjects who completed the trial without any recorded nausea post-baseline, with no rescue or withdrawal were analyzed similarly to the emetic episode data. It was originally planned to use the baseline nausea score as a covariate in the analysis of post-baseline scores; however, as all but a couple of the baseline responses were "No nausea" this would not have been a useful covariate. Subjects who completed the trial but did not have a post-baseline nausea assessment were considered unevaluable.

- Nausea assessments made after the subject was withdrawn or rescued, or observations missing after the subject was withdrawn or rescued, were replaced by the worst possible score in the calculation of summary statistics. Missing baseline nausea was assumed to be "none". These nausea scores were compared using Mantel-Haenszel methods, controlling for site differences, using van Elteren statistics.

f. Safety

Handing of data on AEs and laboratory values were adequate.

12. Results

a. Participating Investigators/Number of Patients per Arm

From the information provided by the sponsor in the Clinical Report (vol. 5, p. 18), the following is noted:

- A total of 358 patients were recruited for participation in this study by 45 investigators[9] at 44 centers. Of these, 357 received test medication,[10] with the following distribution:

OND 8 mg BID	124
OND 24 mg QD	116
OND 32 mg QD	117

- The following 10 Investigators enrolled at least 5 patients per arm:

[9] An additional fifteen investigators were filed with the FDA but did not enroll any subjects into this trial (Patricia Adams-Graves, MD; Rafat Ansari, MD; Bharat H. Barai, MD; Lloyd Barron, MD; Pasquale Benedetto, MD; Barry Boston, MD; Hoo Chun, MD; Lawrence Cone, MD; LeRoy Essig, MD; Paul Jacquin, MD; Julie Kish, MD; Dustan Osborn, MD; Calvin Rosenfeld, MD; Douglas Trochelman, MD; and S. Donald Zaentz, MD).

[10] One patient consented but withdrew prior to receiving test medication.

Subject Recruitment by Site
Number (%) of subjects

	ONDANSETRON (PO)		
	8 mg BID	24 mg QD	32 mg QD
	n=124	n=117	n=117
Garcia-Rodriquez	12 (10%)	12 (10%)	12 (10%)
Baez	10 (8%)	10 (9%)	10 (9%)
Needles	9 (7%)	9 (8%)	9 (8%)
Miranda	8 (6%)	8 (7%)	8 (7%)
Spector	7 (6%)	7 (6%)	8 (7%)
Craig	6 (5%)	6 (5%)	6 (5%)
Krasnow	6 (5%)	6 (5%)	5 (4%)
Cohen	6 (5%)	5 (4%)	6 (5%)
Patel	5 (4%)	4 (3%)	5 (4%)
Velez-Garcia	4 (3%)	5 (4%)	4 (3%)
Listed in this Table are only those sites enrolling at least 5 patients in one of the three arms of the study.			

b. Patient Accounting/Primary Reasons for Withdrawal from the Study/Major Protocol Violations (table 5)

The information included in this Table can be summarized as follows:

- Of the 357 patients exposed to test medication, there were 98 OND 8 mg BID, 95 OND 24 mg QD, and 87 OND 32 mg QD who completed the 24.5-h study period without withdrawal due to lack of efficacy, adverse events, or other reasons.

- There were 78 patients (26 OND 8 mg BID, 20 OND 24 mg QD, and 30 OND 32 mg QD) withdrawn from the trial after exposure to cisplatin.

- The primary reason for patient withdrawal was lack of efficacy. This occurred in 25 of the OND 8 mg BID patients, 19 of the OND 24 mg QD, and 25 of the OND 32 mg QD patients who were withdrawn.

- Patients withdrawn from the study[11] due to an AE included one in the OND 8 mg BID arm and two in the 32 mg QD arm. There were no ondansetron 24 mg QD patients who were withdrawn from the study due to an AE.

- The mean number of hours[12] spent in the trial per treatment group was:

[11] The randomization codes were not broken for these three patients.
[12] Counted from the administration of test medication until withdrawal or study completion.

Group	Mean (SD) h
8 mg BID	22.3 (5.44)
24 mg QD	22.7 (4.91)
32 mg QD	22.3 (4.53)

NOTE: As the majority of subjects in each treatment group completed the trial, the median time spent in the trial was 24.5 h in all treatment groups.

- Patient No. 20815 received dose one of test medication but did not subsequently receive cisplatin chemotherapy. This subject was included in the safety population but not in the efficacy populations.

- There were 12 OND 8 mg BID patients, 13 24 mg QD (including one patient who did not receive test medication and one who did not receive cisplatin), and 13 32 mg QD patients with a major protocol ciolation. The majority of the violations were related to the use of prohibited concomitant medications.

- Patient No. 13763, randomized to 24 mg QD was consented and randomized but did not receive active test medication.

- The ITT opulation was used for all efficacy endpoints. The subset of per-protocol subjects was used in a supporting analysis of the primary endpoint of complete response.

TABLE 5

Study S3AA3012 (Report RM1998/00111/00)

PATIENT ACCOUNTING; NUMBER OF HOURS IN STUDY, PRIMARY REASON FOR WITHDRAWAL AND MAJOR PROTOCOL VIOLATIONS

Parameter of Evaluation	ONDANSETRON (PO) 8 mg BID [n=124]	ONDANSETRON (PO) 24 mg QD [n=117]	ONDANSETRON (PO) 32 mg QD [n=117]
I. PATIENT ACCOUNTING			
A. Subject Disposition			
Did not receive study drug	0	1 (<1%)	0
Did not receive cisplatin therapy	0	1 (<1%)	0
Withdrew after receiving cisplatin	26 (21%)	20 (17%)	30 (26%)
Completed study	98 (79%)	95 (81%)	87 (74%)
B. Protocol Compliance[a]			
Did not receive study drug	0	1 (<1%)	0
Did not receive cisplatin therapy	0	1 (<1%)	0
Major protocol violations	12 (10%)	11 (9%)	13 (11%)
No protocol violations	112 (90%)	104 (89%)	104 (89%)
C. Dosing Compliance			
Non-compliant	9 (7%)	7 (6%)	4 (3%)
Compliant	115 (93%)	110 (94%)	113 (97%)
II. NUMBER OF HOURS IN STUDY[b]			
Mean (STD)	22.3 (5.44)	22.7 (4.91)	22.3 (4.53)
Median	24.5	24.5	24.5
Min-Max	1.8-25.5	0.3-25.7	4.1-27.2
n	124	116	117
III. PRIMARY REASON FOR WITHDRAWAL			
AE	1/26 (4%)	0/22	2/30 (7%)
Lack of Efficacy	25/26 (96%)	19/22 (86%)	25/30 (83%)
Other	0/26	3/22 (14%)	3/30 (10%)
(Completed study)	98	95	87
IV. MAIN PROTOCOL VIOLATIONS			
NONE	112 (90%)	104 (89%)	104 (89%)
Major protocol violations	12 (10%)	11 (9%)	13 (11%)
Received excluded med within 24h prior to or during study	3 (2%)	4 (3%)	9 (8%)
Cisplatin infusion > 3.5h	2 (2%)	3 (3%)	3 (3%)
Cisplatin infusion began < 15 min or >60 min after Dose 1	4 (3%)	2 (2%)	0
Study drug Dose 2 administered < 6h or >10h after Dose 1	2 (2%)	0	1 (<1%)
Received an excluded chemotherapy regimen during study	0	1 (<1%)	0
Received radiation to the abdomen/pelvis within 48h prior to or during the study	0	1 (<1%)	0
Confounding current or past condition	0	1 (<1%)	0
Was not administered and/or did not take Dose 2 (no rescue involved)	1 (<1%)	0	0
Did not receive test medication	0	1 (<1%)	0
Did not receive cisplatin therapy	0	1 (<1%)	0

Reviewer's Table

This Table is a composite of sponsor's Tables 3, 4 and 5 in the Clinical Report (p. 62 through 66), with major modifications. The original Tables were produced with macros SIMSTAT and DTAB.

a) Dosing compliance refers to major protocol violations as associated with dosing of cisplatin or test medication.
b) Counted from start of test med. to withdrawal or 24h after cisplatin therapy.

c. Sandardization of Emetogenic Stimulus

Regarding cisplatin dosing, the three treatment arms were comparable to each other in average infusion time, dose per m^2 and dose level of cisplatin received (at the start of the trial). (See Table 6).

TABLE 6
Study S3AA3012 (Report RM 1998/00122/00)

CISPLATIN DOSING[a]

Variable	ONDANSETRON (PO)[b]		
	8 mg BID [n=124]	24 mg QD [n=116]	32 mg QD [n=117]
A. CISPLATIN INFUSION TIME (h)			
Mean (STD)	1.93 (0.93)	1.99 (0.97)	1.91 (0.90)
Median	2.0	2.0	2.0
Min-Max	0.33-5.00	0.47-4.00	0.45-4.00
n	124	115	117
B. AVERAGE CISPLATIN DOSE (mg/m^2)			
Mean (STD)	74.37 (19.68)	75.75 (19.23)	72.97 (19.53)
Median	73.5	74.9	70.7
Min-Max	47.80-112.5	48.00-105.0	47.20-110.0
n	124	115	117
C. CISPLATIN DOSE LEVEL (mg/m^2)			
Dose < 50 mg	4/124 (3%)	2/115 (2%)	5/117 (4%)
50< = Dose <70mg	47/124 (38%)	43/115 (37%)	47/117 (40%)
70< = Dose <100 mg	48/124 (39%)	46/115 (40%)	42/117 (36%)
100 mg< = Dose	25/124 (20%)	24/115 (21%)	23/117 (20%)
Missing	0	1	0

This Table is based on sponsor's Table 5 (p. 70 of the Clinical Report), with major modifications.

a) Based on p-values on Mantel-Haenszel tests, there were no statistically significant differences between the treatment groups on the variables listed in this Table.
b) Pt. No. 13803 who started on cisplatin, was dosed for 10 min., stopped and then continued 2.5h later. The second dosing record was used at the time and dose for cisplatin in these calculations.

d. Patient Demographic and Baseline Characteristics and Additional Data Demonstrating Comparability of Treatment Groups Pre-Treatment

1) Demographics (Table 7; upper panel)

There were no statistically significant differences between the three treatment groups with respect to any of the demographic variables listed in this Table (p-values calculated on van Elteran tests). Roughly, 2/3 of the patients were caucasian/white females, of average height 167-170 cm and average age 60.1 – 61.1 years. There were no statistically significant differences among the treatment groups in current or prior alcohol use, or child bearing potential variables among females.

TABLE 7
Study S3AA3012 (Report RM 1998/00122/00
PATIENT DEMOGRAPHICS AND DISEASE BASELINE CHARACTERISTICS

Variable	ONDANSETRON (PO) 8 mg BID [n=124]	24 mg QD [n=116]	32 mg QD [n-117]
I. DEMOGRAPHICS			
Age (y)			
Mean (STD)	60.9 (12.7)	61.1 (13.5)	60.4 (14.4)
Median	64	63	64
Min-Max	18-82	13-85	15-80
Height (cm)			
Mean (STD)	169.0 (11.4)	170.0 (11.2)	167.0 (10.7)
Weight (kg)			
Mean (STD)	72.5 (18.4)	70.4 (17.2)	67.5 (17.0)
Min-Max	39-144	31-106	33-151
Gender			
F	45/124 (36%)	30/116 (26%)	40/117 (34%)
M	79/124 (64%)	86/116 (74%)	77/117 (66%)
Race			
Black	14/124 (11%)	18/116 (16%)	10/117 (9%)
Hispanic	24/124 (19%)	22/116 (19%)	25/117 (21%)
Oriental	0/124	0/116	4/117 (3%)
Caucasian/White	85/124 (69%)	76/116 (66%)	78/117 (67%)
Other	1/124 (<1%)	0/116	0/117
II. PRIMARY NEOPLASMS			
Lung	53 (43%)	62 (53%)	58 (50%)
Adenocarcinoma of lung	20 (16%)	20 (17%)	14 (12%)
Small cell cancer of lung	15 (12%)	17 (15%)	20 (17%)
Squamous cell cancer of lung	8 (6%)	12 (10%)	10 (9%)
Head and Neck	27 (22%)	19 (16%)	21 (18%)
Gynecologic	15 (12%)	10 (9%)	13 (11%)
Gastrointestinal	7 (6%)	14 (12%)	6 (5%)
Cancer of esophagus	4 (1 %)	10 (9%)	5 (4%)
Cancer of stomach	1 (<1%)	1 (<1%)	1 (<1%)
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	2 (2%)
Hematopoietic/Immunologic	0	1 (<1%)	1 (<1%)
III. CURRENT MEDICAL CONDITIONS			
Number of subjects with current medical condition	112 (90%)	101 (87%)	104 (89%)
Respiratory	49 (40%)	50 (43%)	53 (45%)
Cardiovascular	52 (42%)	49 (42%)	40 (34%)
Musculoskeletal	39 (31%)	40 (34%)	45 (38%)
Gastrointestinal	34 (27%)	45 (39%)	40 (34%)
Non-site specific	27 (22%)	35 (30%)	47 (40%)
Ears, Nose and Throat	25 (20%)	24 (21%)	29 (25%)
Endocrine and metabolic	24 (19%)	26 (22%)	23 (20%)

2) Primary Neoplasm (Table 7, mid-panel)

As shown, the primary neoplasm reported with the highest incidence was lung cancer, occurring in 43% of OND 8 mg BID patients, 53% of 24 mg QD patients, and 50% of the 32 mg QD patients. Head and neck, and gynecologic were the next most frequently occurring primary neoplasma. Other types of tumors (see Table 7) were reported but at lower rates, with no other tumor type occurring in more than 10% of the subjects.

3) Concurrent Illnesses (Table 7, lower panel)

- 90% of the 8 mg BID patients, 87% of the 24 mg QD and 89% of the 32 mg QD patients had at least one concurrent medical condition other than their primary cancer.

- Respiratory conditions were the most frequent.

- As shown in Table 7, concurrent medical conditions were generally similar between the treatment groups, although the 32 mg patients had a higher percentage of musculoskeletal and non-site specific conditions than the other patients, and the 24 mg patients had a higher percentage of gastrointestinal conditions than the other patients. But these numerical imbalances are not expected to have significant impact on efficacy results.

4) Distribution of Chemotherapeutic Regimens (Table 8, upper panel)

In addition to cisplatin (see Table 6 on Cisplatin dosing above), patients in both treatment groups received concomitant chemotherapy. This consisted of at least one of the following agents:

etoposide	(28%)
Fluorouracil (5-FU)	(19%)
vinorelbine tartrate	(12%)
other compounds at a lower frequency	(≤3%)

The 8 mg BID patients had a higher incidence of exposure to 5-FU and a lower incidence of exposure to vinorelbine tartrate but these numerical differences are not expected to have a significant impact on efficacy results.

5) Concurrent Medications (Table 8, lower panel)

In this Table, concurrent medications are summarized into the traditional groups. There were no significant differences in concurrent medication use among the three treatment groups. As shown in this Table, medications most frequently used concurrently included mannitol, furosemide, magnesium sulfate, and potassium chloride. As noted, all of these medications are commonly used during treatment with cisplatin chemotherapy. The three experimental groups were well-balanced in the concomitant use of these medications.

TABLE 8
Study S3AA3012 (Report RM1998/00122/00)

CHEMOTHERAPEUTIC REGIMENS AND CONCURRENT MEDICATIONS

	ONDANSETRON (PO)		
	8 mg BID [n=124]	24 mg QD [n=116]	32 mg QD [n=117]
I. DISTRIBUTION OF CHEMOTHERAPEUTIC REGIMENS			
Number with chemotherapy medication	124 (100%)	115 (>99%)	117 (100%)
Cytotoxics & Anti-Neoplastics	124 (100%)	115 (>99%)	117 (100%)
Cisplatin	124 (100%)	115 (>99%)	117 (100%)
Etoposide	31 (25%)	35 (30%)	35 (30%)
Fluorouracil	30 (24%)	20 (17%)	18 (15%)
Vinorelbine tartrate	15 (12%)	15 (13%)	14 (12%)
Gemcitabine	4 (3%)	2 (2%)	4 (3%)
Doxorubicin hydrochloride	4 (3%)	2 (2%)	3 (3%)
Methotrexate	0 (0%)	4 (3%)	3 (3%)
Vinblastine suplhate	1 (<1%)	2 (2%)	2 (2%)
Vinblastine	1 (<1%)	1 (<1%)	2 (2%)
Paclitaxel	1 (<1%)	0 (0%)	2 (2%)
Mitomycin	1 (<1%)	1 (<1%)	0 (0%)
Bleomycin	2 (2%)	0 (0%)	0 (0%)
Cyclophosphamide	0 (0%)	1 (<1%)	0 (0%)
Vincristine	1 (<1%)	0 (0%)	0 (0%)
II. CONCURRENT MEDICATIONS			
Number with concurrent medication	122 (98%)	113 (97%)	115 (98%)
Cardiovascular System	115 (93)	110 (95%)	104 (89%)
Mannitol	96 (77%)	89 (77%)	87 (74%)
Frusemide	34 (27%)	46 (40%)	37 (32%)
Digoxin	8 (6%)	12 (10%)	1 (<1%)
Gastrointestinal System	84 (68%)	74 (64%)	82 (70%)
Magnesium sulfate	69 (56%)	60 (52%)	62 (53%)
Docusate sodium	7 (6%)	7 (6%)	10 (9%)
Ranitidine hydrochloride	7 (6%)	5 (4%)	5 (4%)
Drugs Acting Via the Nervous System	71 (57%)	75 (65%)	86 (74%)
Paracetamol	25 (20%)	16 (14%)	16 (14%)
Salbutamol sulphate	12 (10%)	7 (6%)	16 (14%)
Percocet	10 (8%)	14 (12%)	10 (9%)
Aspirin	6 (5%)	12 (10%)	12 (10%)
Ipratropium bromide	7 (6%)	6 (5%)	7 (6%)
Morphine sulphage	3 (2%)	7 (6%)	9 (8%)
Nutrition	72 (58%)	77 (66%)	75 (64%)
Potassium chloride	67 (54%)	67 (58%)	62 (53%)
Multivitamins	5 (4%)	7 (6%)	7 (6%)
Endocrine & Metabolic	42 (34%)	39 (34%)	39 (33%)
Anti-Infectives & Immunologicals	16 (13%)	16 (14%)	19 (16%)
Various Drugs	9 (7%)	5 (4%)	14 (12%)
Skin, Ear & Eye Preparations	2 (2%)	2 (2%)	0 (0%)
Cytotoxics & Anti-Neoplastics	0 (0%)	1 (<1%)	1 (<1%)
Oxygen	0 (0%)	0 (0%)	2 (2%)

e. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 9)

In this Table, results of analyses of both the ITT as well as the Per Protocol study populations are depicted.

- In ITT analysis (Fisher's exact test) the OND 24 mg QD dose level showed a therapeutic gain of 11% when compared to the OND 8 mg BID arm. This difference was nearly statistically significant (p=0.053). It is to be noted that a 95% CI on the difference in CR rates (OND 24 mg QD – (minus) OND 8 mg BID) was 0% to 23%.

  - OND 24 mg QD dose level showed a therapeutic gain of 11% when compared to the OND 32 mg QD arm. This difference was not statistically significant (p=0.073).

  - No therapeutic gain was seen when comparing the CR rate obtained with the OND 32 mg QD and the OND 8 mg BID dose level.

- In Per Protocol analyses, OND 24 mg QD dose level showed a therapeutic gain of 14% when compared to the OND 8 mg BID arm. This difference was statistically significant (p=0.027). It is to be noted, however, that the statistical significant difference was shown when using the Mantel-Haenszel test, but not when using the Fisher's exact test (p=0.086). The sponsor interprets these results as implying that the difference between the 24 mg QD and the 8 mg BID doses is not clearly statistically significant but that there is evidence of a treatment effect.

  - OND 24 mg QD does level showed a therapeutic gain of 11% when compared to the OND 32 mg QD arm. As in the ITT analysis, this difference was not statistically significant (p=0.073).

  - Once again, virtually no therapeutic gain (2%) was seen when comparing the CR rate obtained with the OND 32 mg QD and the OND 8 mg BID dose level.

b) Complete Response by Subgroups

The sponsor analyzed CR rates for each treatment group as a function of gender, alcohol consumption gender plus alcohol consumption and race. Although CR in these strata were examined for completeness, no consistent results were seen. Because of marked variability, no firm conclusions can be drawn, primarily because of the small number of patients per cell. According to these calculations, females were less likely to respond to antiemetic treatment. Regardless of the gender, response rates were higher among patients

reporting alcohol consumption. For these parameters, the difference between the 24 mg QD and the 8 mg BID dose groups was more consistent with the overall response rates. The responses for Caucasians were similar to those of the overall responses.

c) Complete Response by Site

Response by site was summarized in sponsor's Table 10.8 (data not presented in the present review). Participating investigators enrolled between 1 and 36 patients per site. No one site enrolled more than 10% of subjects so by-site analyses are not conclusive.[13]

2) Analyses of Secondary Efficacy Parameters

The secondary efficacy measures included the number of patients considered therapeutic failures, rescue, complete plus major response, time to onset of emesis or treatment failure and patient's assessments of nausea. Results are briefly summarized below.

- In terms of therapeutic failures, there were no statistically significant differences between the 24 mg QD and the 8 mg BID (p=0.416) treatment groups, or the 32 mg QD and the 8 mg BID (p=0.844) treatment groups.

- In terms of rescue medication, there were no statistically significant differences between 24 mg QD and the 8 mg BID (p=0.416) treatment groups, or the 32 mg QD and the 8 mg BID (p=0.854) treatment groups.

- The two main comparisons of interest (24 mg QD vs 8 mg BID and 24 QD vs 32 mg QD) did not show statistically significant differences.

- There was not a statistically significant difference between treatment groups in their time to treatment failure (p=0.083). Of those patients who did fail treatment, few did so within the first 3 h; most did so between 6 and 24 h after the start of chemotherapy.

- Nausea assessment data are summarized below:

  - Only 11 subjects reported any nausea at baseline.

  - 36% OND 8 mg BID patients, 56% 24 mg QD and 50% 32 mg QD patients completed the trial without nausea or rescue medication.

  - The difference between 24 mg QD and the 8 mg BID treatment groups was statistically significant (p=0.001).

[13] The one obvious difference was that at the Mexican site (Principal Investigator: Garcia-Rodriquez) most subjects were treatment failures. None were withdrawn or rescued; almost all had at least one emetic episode. Although this was the largest single site, it was not so much larger than any other site that the results would change considerably if the analysis was performed without it.

- A 95% confidence interval on the difference between the 24 mg QD and 8 mg BID control rates (24 mg minus 8 mg) is 33% fo 9%.

- There was a statistically significant difference between the 32 mg QD and the 8 mg BID treatment groups (p=0.019).

- There was not a statistically significant difference between the 24 mg QD and 32 mg QD treatment groups (p=0.396).[14]

- There was a statistically significant difference between the 24 mg QD and the 8 mg BID dose groups (p=0.007) in their post-baseline assessment scores.

- There was not a statistically significant difference between the 32 mg QD and the 8 mg BID treatment groups (p=0.175). The sponsor notes that the nausea score for the 32 mg patients was inflated by the imputation scheme of replacing missing observations with the worse possible score.

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[14] Patient No. 21038 completed the nausea assessment prior to withdrawing due to an AE; this patient received no nausea but was not considered a complete responder due to premature withdrawal. All other subjects who reported no nausea at their 24-h assessment completed the trial.