TABLE 9

Study S3AA3012 (Report RM1998/00122/00

CLINICAL RESPONSE: ANALYSIS OF PRIMARY EFFICACY PARAMETER
COMPLETE RESPONSE

RESPONSE BY TREATMENT GROUP (OND PO)				THERAPEUTIC GAIN (%)/95% CI [p-value][a]		
I. INTENT-TO-TREAT ANALYSIS [n=356]						
8 mg BID [n=124]	**24 mg QD** [n=116]	**32 mg QD** [n=117]		**24 mg vs 8 mg**	**24 mg vs 32 mg**	**32 mg vs 8 mg**
68 (55%)	76 (66%)	64 (55%)		11% (23%, 0%) [0.053]	11% (1, 23%) [0.073]	0% [N.S.]
II. PER PROTOCOL ANALYSIS [n=320]						
[n=112]	[n=104]	[n=104]				
62 (55%)	72 (69%)	59 (57%)		(14%) (26%, 2%) [0.027]	(12%) (1%,-24) [n=0.073]	(2%) [n=N.S.]

Reviewer's Table

a) p-values and estimates from Mantel-Haenszel test

f. Safety Results (Table 10)

The main conclusion from these evaluations is that a single, 24 mg oral OND dose is well-tolerated. The safety profile of this dose level of the drug was similar to that of 8 mg BID and 32 mg QD. All 357 patients who received test medication were included in the safety analyses. There were no obvious dose response relationships for any AE, including headache, the most commonly reported AE. Withdrawals due to AEs [n=3], serious AEs [n=5] and deaths reported during the 24-h study period [n=3], were not considered related to test medication. The three treatment groups were similar with respect to transitions in laboratory parameters. The majority of transitions in hematology and chemistry laboratory values were within the normal range at pre-treatment and remained in the normal range at post-treatment for all treatment groups.

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TABLE 10
Study S3AA3012 (Report RM1998/00122/00)

SUMMARY RESULTS OF SAFETY EVALUATIONS

	ONDANSETRON (PO)		
	8 mg BID	**24 mg QD**	**32 mg QD**
Extent of Exposure (n=)	124	116	117
Median Dose of Cisplatin (mg/m^2)	73.5	74.9	70.7
Median Time of Cisplatin Infusion (h)	2	2	2
Number of Deaths (cause)	1 #21006 (massive pulmonary embolism)	0	2 #13800 (probable organ shutdown, respiratory arrest). #14079 (acute respiratory distress= extensive metastatic small cell lung cancer)
Serious AEs	1 #21006 (pulmonary embolism)	2 #13776 (pleural effusion and shortness of breath.) #20965 (fever)	2 #13800 1 BP, oliguria, multiple organ failure and respiratory arrest. #14079 acute respiratory distress syndrome and rapid tumor growth
Withdrawals due to AEs	1	0	2
Proportion Reporting One or More AE	44 (35%)	37 (32%)	41 (35%)
Most common AE reported: headache[a]	16 (13%)	20 (17%)	17 (18%)
Proportion with treatment-related AE - Tx-related Headache	15 (12%) 9%	18 (16%) 13%	17 (15%) 13%

Reviewer's Table

a) All but 2 of the reported headaches were of mild to moderate severity; 2 subjects reported severe headaches
- 8 mg BID, n=1 (#13893, judged by the investigator as possibly related to test medication)
- 24 mg QD, n=1 (#13787)

Transitions in laboratory values and changes in hepatic enzymes over the 24-h study period were similar among the three treatment groups. The majority of outlier values occurred within lymphocytes and neutrophils. There were no patients withdrawn due to laboratory abnormalities. All in all, the transitions in laboratory values were consistent with what is expected in the patient population treated in this trial. In all instances, no mean change in laboratory values from baseline was smaller than the standard deviation of the change.

13. Sponsor's Conclusions

"A single, 24mg oral ondansetron dose is more effective than oral ondansetron 8mg BID in the prevention of acute nausea and vomiting following treatment with high-dose ($\geq$50mg/m^2) cisplatin-based chemotherapy.

"A single, 24mg oral ondansetron dose is numerically superior and clinically comparable to oral ondansetron 32mg QD in the prevention of acute nausea and vomiting following treatment with high-dose ($\geq$50mg/m^2) cisplatin-based chemotherapy.

"Adverse events and transitions in laboratory values were similar among the three treatment groups. The oral 24mg dose of ondansetron is safe and well tolerated."

14. Reviewer's Additional Comments

The sponsor of NDA 20-103, Ref. N. 015, SE1, has submitted results from two clinical trials in support of the approval of the marketing of ZOFRAN® (ondansetron hydro chloride = OND) tablets, at the oral dose of 24 mg once-a-day, for the prevention of N&V associated with highly emetogenic cancer chemotherapy, including cisplatin. Both trials (-3012 and –3004/3007) are pivotal. Assessed here is the adequacy of the design and execution of Study –3012.

Study S3AA3012 (-3012) employed a useful design. The trial was carried out with appropriate methodology. Specific general factors contributing to the proper methodology used in this trial include: standardization of the study population (chemotherapy-naive patients that had histologically confirmed diagnosis of cancer and were scheduled to receive cisplatin-based highly emetogenic regimens), adequate procedures for double-blind observations to minimize bias; randomization schemes resulting in comparable test groups; standardization of the emetogenic stimulus [median cisplatin dose (mg/m^2): 8 mg BID = 73.5, 24 mg QD = 74.9 and 32 mg QD = 70.7, all administered in a median infusion time of 2h]; standardization of the clinical evaluation endpoints to gather data to assess efficacy and safety; and utilization of appropriate statistical methodology to evaluate results and draw valid, meaningful conclusions.

This active-active-active trial was set to test the efficacy during the acute phase (first 24h after chemotherapy) of three dose levels of OND. The test group consisted of an orally administered single dose of OND, 24 mg/day. One of the control groups was oral OND. 8 mg BID, a regimen approved not for the same indication being tested here, but for use with moderately emetogenic (cyclophosphamide-based) chemotherapy. Efficacy was to be

demonstrated by showing superiority of the 24 mg/day over the 8 mg BID dose. As noted in Section III. 11. a. (sample size) of this review, a therapeutic gain of 20% (Complete Response, OND 24 mg = 60%, OND 8 mg BID = 40%) was expected between the experimental (24 mg QD) and this control group.

The other control group (third arm) in this trial consisted of oral OND 32 mg QD. Strictly speaking this is also an experimental group, because this dose of OND is not approved for any indication when administered orally. The 32 mg OND once-a-day is an intravenous regimen approved for the prevention of N&V induced by highly emetogenic regimens, including cisplatin. The protocol is not very clear about this, but based on the information summarized in Section III. 11. a. (sample size) of this review, no therapeutic gain was expected when comparing the effects of 24 mg (expected CR=60%) to 32 mg (expected CR=65%) of the drug and this seems to be a more logical approach. So, the protocol actually predicted a 5% lower CR rate with the 24 mg when compared to the 32 mg OND oral dose.

In study –3012, the study population (ITT=357) consisted of platinum-naive, median age of 64y, mostly caucasian, 68% male, 32% female, in general, without evidence of significant cardiovascular/hepatic disease. The site for primary neoplasm that occurred with the highest frequency was the lung, followed by head and neck. The randomization procedures used in this trial were apparently well executed and resulted in three treatment populations of patients (124, 116 and 117, respectively) that were comparable to each other with respect to variables that may influence outcome. For the three test groups, the demographics, primary disease state, other significant medical conditions, Karnosky status and prior medications were similar. The treatment groups were also balanced with respect to concomitant medications in general and concomitant medications that may be confounding, such as concomitant chemotherapy (etoposide=28%; 5-FU=19%; vinorelbine tartrate=12%).

In this trial, the three treatment groups were well matched with regard to the standardization of the emetic stimulus. This consisted primarily of cisplatin, with a median dose of 74, 75 and 71 mg/m^2 infused over a median time of 2h. This regimen is best characterized as being of high emetogenic potential. Also adequate were the clinical procedures and the statistical methodology used to assess efficacy. The primary endpoint of efficacy was Complete Response (CR) which was derived by adequate and previously validated approaches. Only CR is considered for the purpose of the reviewer's presentation and discussions.

As summarized in Table 9, ITT analyses showed a therapeutic gain of 11% of the 24 mg OD over the control (8 mg BID). This 11% fell short from the projected 20%. The difference between the two groups was barely statistically significant (p=0.053) and this cannot be taken as strong evidence of efficacy. When one turns to the other comparison for proof of efficacy, one finds a surprising finding. Instead of the expected 5% less therapeutic gain, an 11% gain of the 24 over the 32 mg OND was demonstrated. The difference between these two treatment groups was not statistically significant (p=0.073); again, this cannot be taken as strong evidence of efficacy. It seems that a reasonable

conclusion from these comparisons is that the OND 24 mg/day dose is at least as effective as the 32 mg/day dose and likely superior to 8 mg BID.

In summary, results of ITT analysis suggest but do not strongly prove that the 24 mg oral OND dose is most likely efficacious but that something in the design/execution of the trial prevents a clear-cut demonstration of superiority of the 24 mg dose over the other two groups. On the other hand, the 24 mg oral OND dose is as effective as the 32 mg/day dose.

The Per-Protocol analyses, with a 3% higher therapeutic gain of the 24 mg/day over the 8 mg BID dose, the difference between these two groups was statistically significant ($p=0.027$) and this was expected as the 14% therapeutic gain of one group over the other is now closer to the projected 20% based on sample size. Analysis of results in this population confirmed the results in the ITT group with regard to the comparison between the OND 24 mg/day group and the 32 mg/day group: both levels of the drug appear to be similarly effective.

An additional conclusion from the above-discussed findings in study –3012 is that a confirmatory trial is needed to convincingly demonstrate that OND 24 mg/day is efficacious.

In study –3012, graded oral doses of ondansetron, whether 8 mg BID, 24 mg once-a-day or 32 mg/day were safe and well tolerated.

IV. STUDY S3AA3004/3007 (REPORT RM1997/04252/00)

1. Title

"A Randomized, Double-Blind Comparison of Oral Ondansetron and Intravenous Granisetron in the Prevention of Nausea and Vomiting Associated with Moderately-High Emetogenic Chemotherapy"

NOTE The description of the Protocol that follows includes three amendments.

Amendment #01 (origination date, 05 April 1995) for Protocol S3AA3004 modified the inclusion criteria to allow the inclusion of subjects that had previously received OND for PONV. The amendment was provided and approved for one select investigator (Howard Homesley, M.D.; Winston-Salem, NC).

Amendment #02 (origination date, 05 May 1995) for Protocol S3AA3004 and Amendment #01 for S3AA3007 (origination date, 03 May 1995) modified the maximum allowable dose of cisplatin from 70 to 75 mg/m^2.

Amendment #03 (origination date 26 March 1997) for Protocol S3AA3004 and Amendment #02 for S3AA3007 (origination date, 26 March 1997) modified the inclusion criteria to include the use of carboplatin ≥200 mg/m^2 and allowed subjects to receive **selective serotonin re-uptake inhibitors** during the study period provided the subject had been on stable doses for at least 2 weeks and no increase in dosage occurred during the 24.5-h study period.

2. Objectives

1) To compare the antiemetic efficacy of a single 24 mg ondansetron tablet with a single 10 μg/Kg granisetron infusion in patients receiving highly emetogenic cisplatin-based (50-75 mg/m^2) chemotherapy regimens.

2) To compare the safety profile of a single 24 mg ondansetron tablet with a single 10 μg/Kg granisetron infusion in patients receiving cisplatin-based chemotherapy regimens.

3. Study Population

The inclusion-exclusion criteria were very similar to those listed in Table 4 of this review for study –3012. The patients were scheduled to receive cisplatin 50 to 75 mg/m^2 or carboplatin ≥200 mg/m^2, administered over a period of ≤3h.

4. Study Design

From the review of the evidence, studies S3AA3004 and S3AA3007 were identical, parallel, randomized, double-blind, comparative, multicenter trials. The use of corticosteroids (such as dexamethasone=DEX) was not allowed as DEX is not approved as an antiemetic and the intent was to demonstrate activity of OND alone. The sponsor noted that the use of this antiemetic regimen (no DEX) severely limited patient accrual. Therefore, for administrative reasons, it was subsequently decided to combine the data from both Protocols and analyze as one trial (S3AA3004/3007) with a sample size of 364 patients.

- All subjects were to receive chemotherapy regimens containing 50 to 75 mg/m^2 cisplatin (or carboplatin ≥200 mg/m^2) administered over a period of ≤3 h. Thirty minutes prior to the initiation of cisplatin (or carboplatin) subjects were randomized (1:1) to receive:

  - A single 10 μg/Kg GRAN infusion and a PL tablet

    or

  - A single 24 mg OND tablet and a PL infusion.

  The intravenous dose of test medication was infused over a period of 5 min.

- During a screening visit that could occur up to 7 days before receipt of study drug, patients provided a complete medical Hx and had a P.E. Blood samples for clinical laboratory tests were obtained. Urine pregnancy tests (in female subjects of childbearing potential) were obtained within 48 h prior to receipt of test medication. Written IC was obtained from each patient.

- Baseline assessments of nausea and appetite were obtained within the 30 min. before test drug administration. Patients were instructed to assess their nausea and satisfaction with the antiemetic therapy at 3-h and 6-h following the initiation of cisplatin (or carboplatin) chemotherapy. Throughout the 24.5-h study period patients were requested to document the occurrence of emesis.

- At the end of the 24-h study period or immediately prior to withdrawal, assessments of nausea, appetite, satisfaction with antiemetic therapy were obtained, as well as blood samples for laboratory safety studies.

- **Control Group**

  The labeled dosage regimen of intravenous GRAN (10 μg/Kg) served as the control group for this trial. The efficacy results provided in the FDA approved labeling for GRAN report CR rates of 56% in subjects receiving chemotherapy regimens containing cisplatin (mean cisplatin dose 64 mg/m^2). A CR was defined in the GRAN trials as no vomiting and no use of rescue medication during the first 24 h following cisplatin.

5. Randomization/Blinding/Anti-emetic Treatment/Chemotherapy

These aspects of the trial were adequate.

- The patients were randomized (1:1 ratio) to receive either a single 10 μg/Kg GRAN infusion and a PL tablet or a single 24 mg OND tablet and a PL infusion.[15]

  The randomization schedule was provided in sponsor's Appendix 3 and a patient listing of treatment allocation was provided in sponsor's Appendix 5. Sponsor's Table 23 listed the disposition of treatment numbers allocated per investigational site.

- This was a double-blind trial. Patients were randomized within blocks of 6 to treatment according to a randomization schedule generated by the Medical Data Sciences Department at Glaxo Wellcome Inc. The schedule was furnished to the designated pharmacist at each institution. Investigators received complete randomization blocks.

[15] The randomization schedule was generated by the Medical Data Sciences Department at Glaxo Wellcome Inc. As subjects were identified for participation in the study, the principal investigator's designee (research pharmacist) assigned the next consecutive treatment number according to the random code.

- The methods used to preserve the double-blind character of the trial were adequate. Patients randomized to receive a 24 mg OND tablet were given a 50 ml infusion of either normal saline or D_5W PL, concurrently. The investigational sites could substitute D_5W for normal saline provided that all patients received the same 50 ml infusion. The infusion for all patients was to be administered over 5 min. Subjects randomized to receive a single 10 μg/Kg GRAN infusion (50 ml) also received a PL tablet.

- **Anti-emetic Treatment**

  Each patient was given one tablet of test medication and a 50 ml intravenous infusion, simultaneously. The infusion for all subjects was to be administered over 5 min.

6. Emetogenic Stimulus (Chemotherapy)

Cisplatin (or carboplatin) was administered beginning 30 min. after the ingestion of oral test medication and initiation of intravenous test medication. Other chemotherapy agents of low emetogenicity could also be co-administered.

7. Concomitant Medications

All prescription and non-prescription medication with known or potential antiemetic activity were excluded during the 24.5-h study period and during the 24 h prior to the first dose of trial medication. Among the proscribed medications were phenothiazines, butyrophenones, hydroxyzine, lorazepam, cannabinoids, MCP, corticosteroids, and trimethobenzamide. All concomitant medications were listed in the CRF.

8. Withdrawals/Assessment of Patient Compliance

My review of this subsection (p. 24-25 of the Clinical Report) indicates that these aspects of the trial were adequate.

9. Study Evaluations

a. Primary Efficacy Parameters

As in study –3012, the **primary efficacy variable** for this trial was the number of patients with zero emetic episodes who completed the trial without rescue over the 24-h study period. The definitions used to assess emetic episodes were adequate (see Section III.9., of this review).

b. Secondary Efficacy Parameters

The secondary efficacy parameters were as those used in study –3012 (see Section III. 9., of this review).

c. AE Monitoring/Laboratory Evaluations

These were adequate.

10. Data Collection/Data Management/Quality Assurance

My review of the evidence (p. 28-29 of the Clinical Report) indicates that these aspects of the study were adequate.

11. Statistical Methodology

a. Sample Size

The sponsor noted that the sample size of 182 subjects in each treatment group was chosen so that the comparison of the percentage of patients in each treatment group who completed the trial without emetic episodes or rescue would have at least 80% power to detect **a difference of 15%** at a Type I error rate of 5%. This was based on a large-sample normal approximation to the binomial distribution.

NOTE: The expected difference of 15% between treatment arms is testing the hypothesis that OND 24 mg QD is **superior** to GRAN 10 μg/Kg I.V.

b. Generalities

All statistical tests and confidence intervals were two-sided and performed with a 0.05 Type I error rate. There was no formal adjustment for analyses of multiple endpoints. The sponsor noted that the effectiveness of ondansetron was to be considered not inferior to granisetron if the lower limit of the 95% confidence interval for the difference in response rates was within 10%. Historically, "this difference has been considered of no clinical importance".[16]

Nausea and appetite assessments were assumed to have occurred at their scheduled times unless there was documented information to the contrary. In order to account for assessments made outside the study window the 3-h assessment was the last assessment made in the interval 0-4 h, the 6-h assessment the last assessment made in the internal 4-7 h and the 24-h assessment the last assessment made after 7 h post-dose.

Sites with fewer than 10 total subjects were pooled together and all Mantel-Haenszel tests controlled for this strata variable. However, the results did not change appreciably if the sites were not pooled or if the analyses were not controlled for site differences.

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[16] The following windows were defined for all assessments:

- Baseline/Pre-treatment – to have been completed <24h prior to start of test medication.
- 3-h – to have been completed within 3 $\pm$ 1h after start of cisplatin (or carboplatin) chemotherapy.
- 6-h – to have been completed within 6 $\pm$ 1h after start of cisplatin (or carboplatin) chemotherapy.
- 24-h – to have been completed within 24 $\pm$ 2h after start of cisplatin (or carboplatin) chemotherapy.

c. Populations

Three study populations, with the same definitions as per study –3012 (see III. c., above) were considered in the analysis:

- Safety Population
- ITT Population
- Per Protocol Population

Because, in this trial, all subjects who received test medication went on to receive chemotherapy the Safety and ITT populations were the same.

d. Background Characteristics

In an approach like the one used in Study –3012, 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. Patient No. 8817 received carboplatin instead of cisplatin. This subject was not included in this summary.

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 III., 9. a., above.

- To qualify as a complete, major, or minor response the patient had to have completed the entire post-Tx period without rescue. Patients who withdrew from the trial for reasons other than lack of efficacy, but would otherwise qualify as therapeutic failures were considered therapeutic failures. Patients 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 patients in each Tx group with a CR during the post-Tx period in the Intent-to-Treat population. A supporting analysis of the primary endpoint was performed in the Per-Protocol population. The number of patients in each group with a complete or major response was compared.

- The Tx 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 Tx groups using Mantel-Haenszel methods. The emetic response was summarized in each treatment group for males and females, separately, and at each site.

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

- The time to Tx 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:

  - 0h <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
  - Complete study without failure
  - Time to Tx failure not recorded/missing

- Time to Tx failure was analyzed using Kaplan-Meier methods and the Tx groups compared with log-rank tests. Patients who completed the trial 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 00:00:01 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.

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

ii) Nausea

- The patients' nausea assessments were recorded at baseline and during the visits at 3h, 6h, and 24h after chemotherapy. Only the Intent-to-Treat population was analyzed for this endpoint.

- The percentage of patients who completed the trial without any recorded nausea or withdrawal was analyzed similarly to the emetic episode data. Subjects without a post-baseline nausea assessment but who were not withdrawn or rescued were considered unevaluable for this endpoint.

- The over-all nausea scores were compared between Tx groups using the Mantel-Haenszel methods outlined in sponsor's Appendix 6. It was originally planned to use the baseline nausea score as a covariate in the analysis; however, as all but a couple of the baseline responses were "No nausea" this would not have been a useful covariate. Observations made after the patient was withdrawn or rescued, or observations missing after the patient was withdrawn or rescued, were replaced by the worst possible score. Missing baseline nausea was assumed to be "none", and all other missing values were imputed using the last non-missing value carried forward.

f. Safety

Handling of data on AEs and laboratory values was adequate.

12. Results

a. Participating Investigators/Number of Patients per Arm

From the information provided by the sponsor in the Clinical Report (vol. 10, p. 36.) the following is noted:

- A total of 373 patients were recruited for participation in this trial by 38 investigators[17] at 37 centers. Of these, 371 received test medication[18], with the following distribution:

OND 24 mg QD	184
GRAN 10 μg/Kg I.V.	187

The following 12 investigators enrolled at least 6 patients per arm.

Patient Recruitment by Site
Number (%) of Patients

Investigator	OND 24 mg QD PO [n=184]	GRAN 10 μg/Kg I.V. [n=189]
Spector	30 (16%)	30 (16%)
Lester	20 (11%)	20 (11%)
Harvey	16 (9%)	16 (8%)
Chevlen	14 (8%)	16 (8%)
Sciortino	13 (7%)	12 (6%)
Whaley	9 (5%)	9 (5%)
Madajewicz	8 (4%)	8 (4%)
Isaacs	8 (4%)	8 (4%)
Homesley	7 (4%)	8 (4%)
Yee	6 (3%)	8 (4%)
Beck	6 (3%)	6 (3%)
Tchekmedyian	5 (3%)	6 (3%)
Listed in this Table are only those sites enrolling at least 6 patients in one of the two arms of the trial.		

[17] Eight investigators did not enroll any patients into these trials (Willard Barnes, M.D., William John, M.D., Raul Mena, M.D., Howard Gross, M.D., William Mitchell, M.D., Bancroft Lesesne, M.D., Michael Messino, M.D., James Beardon, M.D.).

[18] Two subjects did not receive test medication.

b. Patient Accounting/Primary Reasons for Withdrawal From the Study/Major Protocol Violations (Table 11)

- 2 patients did not receive test medication; 184 patients received oral OND 24 mg and 187 received i.v. GRAN 10 μg/Kg.

- Of the 371 patients exposed to test medication, there were 133 OND and 121 GRAN patients who completed the 24.5-h study period without withdrawal due to lack of efficacy, AEs, or other reasons.

- There were 119 patients (51 OND and 68 GRAN) withdrawn from the trial.

- The primary reason for patient withdrawal was lack of efficacy, which occurred in 46 of the 51 OND and 63 of the 68 GRAN patients who were withdrawn. There were 2 ondansetron patients and zero GRAN patients who were withdrawn from the study due to an AE.

- The mean number of hours spent in the trial per Tx group was:

Group	Mean (S.D.) h
OND	21.9 (5.4)
GRAN	20.9 (6.5)

- There were 13 OND and 19 GRAN patients with a major protocol violation.[19] The majority of the violations were related to the use of prohibited concomitant medications. The Intent-to-Treat population was used for all endpoints. The subset of Per-Protocol patients was used in a supporting analysis of the primary endpoint of CR. As the percentage of protocol violations in each Tx group was small and about equal, there should not be any major difference between the two populations.

- There were 7 OND and 4 GRAN patients who had major protocol violations associated with dosing procedures, either related to cisplatin or study drug. These violations were primarily related to the length of cisplatin dosing or the time of cisplatin dosing relative to test medication, or the dose of cisplatin.

[19] Two patients (numbers 7377 and 7416, both randomized to GRAN in protocol S3AA3004) were consented and randomized but, due to a pharmacy error, did not receive test medication.

TABLE 11

Study S3AA3004/3007 (Report RM1997/04252/00)

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

	OND 24 mg QD PO [n=184]	GRAN 10 μg/KG I.V. [n=189]
I. PATIENT ACCOUNTING		
A. Subject Disposition		
Did not receive test medication	0	2 (1%)
Withdrew after receiving cisplatin	51 (28%)	66 (35%)
Completed study	133 (72%)	121 (64%)
B. Protocol Compliance[a]		
Did not receive test medication	0	2 (1%)
Major protocol violations	13 (7%)	17 (9%)
No protocol violations	171 (93%)	170 (90%)
C. Dosing Compliance		
Non-compliant	7 (4%)	4 (2%)
Compliant	177 (96%)	183 (97%)
II. NUMBER OF HOURS IN STUDY[b]		
Mean (STD)	21.9 (5.38)	20.9 (6.45)
Median	24.5	24.5
Min-Max	4.9-27.3	0.7-25.0
n	184	186
III. PRIMARY REASON FOR WITHDRAWAL		
Adverse event	2/51 (4%)	0/68
Lack of efficacy	46/51 (90%)	63/68 (93%)
Other	3/51 (6%)	5/68 (7%)
(Completed study)	133	121
IV. MAJOR PROTOCOL VIOLATIONS		
NONE	171 (93%)	170 (90%)
Major protocol violations	13 (7%)	17 (9%)
Received excluded med within 24h prior to or during study	6 (3%)	10 (5%)
Study personnel unblinded to test med. randomization	2 (1%)	4 (2%)
Cisplatin infusion began at incorrect time	4 (2%)	1 (<1%)
Received <45 mg per m^2 or >80 mg per m^2 cisplatin	1 (<1%)	2 (1%)
Cisplatin infusion >3.5h	1 (<1%)	2 (1%)
Test medication infusion <3 min or >45 min	2 (1%)	0
Experienced vomiting or retching or uncontrolled nausea within 24h prior to the study	0	1 (<1%)
Failure to collect data regarding emetic episodes	0	1 (<1%)
Did not receive study drug	0	2 (1%)
Did not receive test med.	0	2 (1%)
Received excluded med within 24h prior to or during study	0	1 (<1%)
Was misrandomized	0	1 (<1%)
Cannot be confirmed patient received test med.	0	1 (<1%)
Cisplatin infusion began at incorrect time	0	1 (<1%)

Reviewer's Table

This Table is a composite of sponsor's Tables 2, 3 and 4 in the Clinical Report (p. 57 through 61) with major modifications. The original Tables were produced with macros SIMSTAT and DTAB.

a,b) As in Footnote to Table 5.

c. Standardization of the Emetogenic Stimulus (Table 12)

Results of variables investigated are summarized in this Table. The median dose of cisplatin was 70 mg/m^2. The dosing range was 31 to 100 mg/m^2. The median time of infusion was 2 h for both OND patients and GRAN patients. There was not a statistically significant difference between the Tx groups on either of these variables.

TABLE 12
Study S3AA3004/3007 (Report RM1997/04252/00)

CISPLATIN DOSING

Variable	OND 24 mg QD PO [n=184]	GRAN 10 μg/Kg I.V. [n=187]
A. Cisplatin Infusion Time (h)		
Mean (STD)	1.8 (0.7)	1.8 (0.8)
Median	2.0	2.0
Min-Max	0.3-3.5	0.3-3.7
n	180	184
B. Average Cisplatin Dose (mg/m^2)		
Mean (STD)	65.6 (8.5)	65.2 (9.5)
Median	70.0	70.0
Min-Max	42.0-76.0	31.0-100.0
n	184	186
C. Cisplatin Dose Level (mg/m^2)		
Dose <50 mg	4/184 (2%)	5/186 (3%)
50< = Dose <70 mg	72/184 (39%)	76/186 (41%)
70< = Dose <100 mg	108/184 (59%)	104/186 (56%)
100 mg< = Dose	0/184	1/186 (<1%)
Missing	0	1

This Table is based on sponsor's Table 5 (p. 65 of the Clinical Report) with major modifications. There were no statistically significant differences between the Tx groups in the variables listed in this Table.

The p-values based on Mantel-Haenszel tests.

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

1) Demographics (Table 13, upper panel)

In both treatment groups, subjects receiving test medication were mostly males (56%), ranging in age between 32 to 86 y. The large majority (90%) were white. Of the females, the majority were either post-menopausal or sterile. There were no statistically significant differences between the two Tx groups with respect to any of the demographic characteristics summarized in this Table.