Reviewer's Comment: This observation in Table 8 regarding gender-specific times to first episode of emesis suggests, along with certain other observations, that there may be a pattern of greater female susceptibility to emesis in placebo treated groups. Two lines of evidence suggest the possibility that females may be comparatively more susceptible to nausea and vomiting. The first is found in the PDR (1998) labeling for the analogous drug, ondansetron (Zofran®), when used intravenously for further postoperative therapy. Here, it is reported that the clinical response between genders has not been established because sufficient data have not been available in men. Clearance of the drug, however, has been shown to be more rapid in men. A second point is in reference to the same drug, ondansetron, that a more recent labeling modification has been reviewed (date: January 21, 1999) and approved. This revised labeling now states that "In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a single 4 mg IV ondansetron dose prevented postoperative vomiting over a 24-hour study period in 79% of males receiving drug compared to 63% of males receiving placebo ($p<0.001$)". This is an indication of possibly greater comparative efficacy of ondansetron in males, and suggests that it is at least as efficacious in males as in females despite its more rapid clearance after IV injection. In the present study, there is also a suggestion in the data of Table 8 regarding gender-specific times to first episode of emesis that the same pattern of greater female susceptibility to emesis in placebo-treated groups is seen. This recent information suggests that there may be gender-specific issues in this interaction, some of which await further clarification.

An analysis of the results for complete emetic control is shown in Table 9. These results show a striking difference between the treatment and placebo groups.

Table 9

Proportion of Patients with Emesis at 24 Hours, 10 Fractions, and 20 Fractions of Radiation- All Patients in the Intent-to-Treat (ITT) Population (260 patients)

Time	Granisetron		Placebo			
	n/N*	%	n/N*	%	Therapeutic Gain	p=Value
24 Hours	10/134	7.5%	48/126	38.1%	+30.6%	<0.0001
10 Fractions	15/104	14.4%	23/74	31.1%	+16.9%	0.0012
20 Fractions	12/52	23.1%	13/36	36.1%	+13%	NS
Overall	57/134	42.5%	73/126	57.9%	+15.4%	0.0047

(Table modified from table provided by sponsor in Vol. 4, p.9)(*n=number of patients affected; whereas. N=total number of patients at risk)

The results in Table 9 show statistically significant differences between treatment groups. indicating superiority for granisetron in the patients who did not experience emesis at 24 hours ($p<0.0001$) and after 10 fractions ($p=0.0012$). Statistical significance was not shown between treatment groups after 20 fractions for reasons to be discussed below.

Reviewer's Comment: As more fractions of radiation were received, the two treatment groups differed less. The most probable explanation for this is the fact that many more patients in the placebo group withdrew early in the study, primarily for lack of efficacy, thus resulting in a smaller treatment difference. The number of withdrawals for lack of efficacy in the placebo group compared to treated patients was strongly significant statistically (data given in table 3). Despite this, however, 52 patients given granisetron and 36 patients given placebo were available for assessment after 20 fractions. The magnitude of the effect after 20 fractions, though not statistically significant, is still probably of clinical importance. An evaluation of the overall comparative effect was obtained by using the last observation from every patient prior to his or her withdrawal from the study. This revealed a statistically significant intragroup difference (p= 0.0047) in Table 9.

The sponsor states that the time to the first episode of emesis (a primary efficacy endpoint) was analyzed and as shown in Table 10 revealed a strikingly significant difference between the granisetron and placebo treated groups.

Table 10

Statistical Analysis of Time to First Episode of Emesis-All patients in the ITT Population

Median time (Days)				
Granisetron (n=134)	**Placebo (n=126)**	**Hazard (Risk) Rate****	**p=Value for Relative Risk**	**95% Confidence Intervals for Risk ratio Granisetron vs Placebo**
35	**9**	**1.89***	**<0.001**	**(1.33, 2.67)**

(*Indicates that the chance of emesis occurring in the untreated group is about double that for the treated group)
(**Based on the Cox Proportional Hazard Regression Model)(Modified from table 17b provided by the sponsor in Vol 5, p 67)

2-Nausea Control

Data on efficacy of control of nausea-control-the second important Primary efficacy endpoint were collected and are now summarized. An analysis of time to first episode of nausea is given in Table 11. The results show that the findings for this endpoint are similar between the ITT and PDA-defined groups.

Table 11

Time to First Episode of Nausea-All Patients in ITT population Versus All Patients in the Protocol Defined Analysis (PDA)

Median Time (Days)-ITT				
Granisetron (n=134)	Placebo (n=126)	Hazard (Risk) Rate**	p=Value for Relative risk	95% Confidence Interval for Risk Ratio-Granisetron vs Placebo
11	1	1.78*	< 0.001	(1.34, 2.36)
Median Time (Days)-PDA				
Granisetron- (n=96)	Placebo (n=90)			
12	1	1.99*	<0.001	(1.41, 2.80)

Time to nausea is defined as the time to first nausea or rescue medication, whichever is first.
(*Indicates that the chance of emesis occurring in the untreated group is about double that for the treated group)(**Based on the Cox Proportional Hazard Model)(Modified from data provided by the sponsor in Tables 19(a) and (b) in Vol. 5, pp.71-72).

An analysis of the results of complete nausea control is shown in Table 12.

Table 12

Proportion of Patients with Nausea at 24 hours, 10 Fractions, and 20 Fractions of Radiation- All Patients in the Intent-to-Treat Population (ITT) (260 patients)

	n/N*	%	n/N	%	Therapeutic Gain	p=Value
24 Hours	28/134	20.8	69/126	54.7	+33.7%	<0.0001
10 Fractions	49/104	47.1	50/74	67.6	+20.5%	0.0064
20 Fractions	34/52	65.4	25/36	69.4	+4.0%	NS
Overall	93/134	69.4	105/126	83.3%	+13.9%	0.0042

(Table modified from sponsors table in Vol. 4, p.11)(*n=number of patients affected; whereas, N=total number of patients at risk)

The table shows that while there were statistically significant differences between treatment groups favoring granisetron in the proportion of patients who experienced nausea at 24 hours and after 10 fractions, after this point the effect was not significant.

The magnitude of the therapeutic effect diminished as more fractions of radiation were received, in a manner similar to that previously shown for proportions of patients with emesis. The magnitude of the effect on nausea after 20 fractions of radiation in patients given granisetron was small.

Because the comparison at 20 fractions fails to include information from the majority of patients, a further analysis was conducted using the last observation from every patient prior to his or her withdrawal from the study. In the overall endpoint analysis (see bottom row of Table 10), 69.4% of patients who received granisetron tablets, and 83.3% of placebo-treated patients had nausea. This difference was statistically significant, showing superiority of granisetron over placebo.

(f) **Results of Safety Evaluations** (provided by the sponsor)

Most Frequently Reported Adverse Experiences

Most of the randomized patients (75.8%) reported adverse experiences (AEs). Of these, 110 (82.1%) patients randomized to receive granisetron, and 90 (69.2%) patients randomized to receive placebo reported at least one adverse experience. A summary of most frequently reported AEs is given below in Table 13.

Table 13

Number and Percent of Patients with most Frequently (>5%) reported Adverse Experiences (AEs) Regardless of treatment attribution, in Descending Order for Granisetron

AEs by Preferred Term in Descending Order	Granisetron n=134	Placebo n=130
Patients with any AE	**110 (82.1)**	**90 (69.2)**
Diarrhea	37 (27.6)	44 (33.8)
Asthenia	34 (25.4)	25 (19.2)
Constipation**	26 (19.4)**	6 (4.6)**
Abdominal Pain	15 (11.2)	11 (8.5)
Nausea (after 20 fractions*)	15 (11.2)	12 (9.2)
Decreased Appetite	14 (10.4)	9 (6.9)
Pain	10 (7.5)	5 (3.8)
Dyspepsia	7 (5.2)	6 (4.6)
Headache	7 (5.2)	15 (11.5)
Rash	7 (5.2)	6 (4.6)

Two patients given granisetron and two placebo patients reported nausea before they received 20 fractions of radiation.(table taken and modified from sponsor's presentation in Vol 4, p 13)
(** The strikingly different incidence of constipation in the treatment versus the placebo group was analyzed using a two-sided test with a 2 x 2 contingency table and the application of Fisher's Exact Test. This resulted in a significance for this difference of p=0.0002).

The most notable differences between treatment groups were in the higher proportion of patients given granisetron compared to placebo who reported constipation (19.4% vs 4.6%, or 4.2 times greater)(see Table 13 footnote for further analysis); asthenia (25.4% vs 19.2%, or 1.3 times greater); abdominal pain (11.2% vs 8.5%, or 1.3 times greater), and decreased appetite (10.4% vs 6.9%, or 1.5 times greater). On the other hand, a higher proportion of patients in the placebo group reported diarrhea (33.8% vs 27.6%, or 1.2 times) and headache (11.5% vs 5.2%,

or 2.2 times greater). Otherwise, the difference between treatment groups in reports of any other event was no greater than 2.7%.

The adverse experiences reported in each treatment group were most commonly of mild or moderate intensity. Twenty patients in each treatment group (14.9% granisetron; 15.4% placebo) reported severe AEs. There were no notable differences between treatment groups in the types of severe AEs reported.

Reviewer's Comment: The comparatively low incidence of headache as an adverse event in this study of about 5% is remarkable (Table 13). It stands in contrast to a much higher greater occurrence of about 20% among over 100 patients in the initial approved study of granisetron for prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including high-dose Cisplatin. This adverse event also occurred with much higher frequency in the second pivotal study of this submission (i.e., about 28%) in a much-smaller group of patients. These two studies were similar in that both had a high incidence of headache as an adverse event and by design both had a greater intensity granisetron dosage, i.e., a few days. Perhaps this greater intensity of granisetron dosage accounts for the higher incidence of headache as an adverse event in these studies. In the present study (#259), by contrast, the lesser intensity of granisetron dosage occurred over a span of several weeks.

The sponsor states that approximately half of the patients in each treatment group reported adverse experiences that were considered by the investigators unrelated to treatment with study medication. Two patients who received granisetron reported three events (constipation, thinking abnormal and rash) that the investigator considered to be related to treatment with study medication. Three patients in the placebo group reported three events (abdominal pain, moniliasis, and nausea) that the investigator considered to be related to treatment with study medication. One report of constipation in a patient given granisetron who presented with a history of constipation was reported as both severe and related.

Reviewer's Comment: Decreased gastrointestinal motility is a known pharmacological effect of 5-HT_3 receptor antagonists. Thus, it is not surprising that among the granisetron-treated group there is marginally decreased diarrhea and greater constipation.

Serious Adverse Experiences (sponsor's description)

A total of 33 patients in both treatment groups reported serious AEs during the study or within 30 days of the last dose of study medication. Fifteen (11.2%) patient who received granisetron reported 27 serious adverse experiences, and 18 (13.8%) patients in the placebo group reported 37 serious AEs. The number and percent of patients reporting Severe Adverse Experiences is outlined in Table 14.

Table 14

Number and Percent of All Patients Reporting Severe Adverse Experiences by PreferredTerm

Preferred Term	Granisetron (n=134)	Placebo (n=130)
	n(%)	n(%)
Carcinoma**	5(3.7)	3 (2.3)
Dehydration	3 (2.2)	2 (1.5)
Constipation	2 (1.5)	0
Intestinal Obstruction	2 (1.5)	0
Anemia	1 (0.7)	3 (2.3)
Gastrointestinal Hemorrhage	1 (0.7)	2 (1.5)
Respiratory Disorder	1 (0.7)	2 (1.5)
Back Pain	0	2 (1.5)
Hypoventilation	0	2 (1.5)
Pneumonia	0	2 (1.5)
Thrombocytopenia	0	2 (1.5)

(** all carcinoma AE listings were due to progressive disease with metastatic lesions to such vital target organs as brain, progressive biliary tract cancer,etc.
(Source: appendix 23, Vol 4R)(Table taken from sponsor's table 33, Vol 4, p 83)

There were no clinically important differences between the treatment groups in the number or types of serious events reported. All but five events were considered "unrelated" to treatment with study medication. The five events (reported by two patients who received granisetron, and one placebo patient) were considered to be "probably unrelated" to treatment with study medication. None of the serious AEs were reported as "possibly related" or "related" to treatment with study medication.

Three patients who received granisetron experienced four serious AEs that resulted in withdrawal from the study and six placebo patients experienced ten serious AEs that resulted in withdrawal.

Deaths (information from the sponsor)

A total of 11 deaths occurred within 30 days of the last dose of study medication. Four deaths were reported in patients who received granisetron, and seven were reported in placebo patients. All of the deaths were considered to be unrelated to treatment with study medication.

Four additional deaths were reported in patients who died more than 30 days after the last dose of study medication. Two patients who received granisetron (003.057, 027.090) and two placebo patients (043.045, 050.189) died as a result of progression of their primary cancer, or of complications related to their primary disease. None of these deaths were considered related

to treatment with study medication. Table 15 provides a listing of all 15 patients in each treatment group who died, with cause of death in days after the first and last dose of study medication.

One additional (unlisted) patient (259.052.8586), who was randomized to receive placebo, died of complications from metastatic colon cancer before receiving study medication. This patient is not listed in Table 15.

Table 15

Patient Deaths

Patient ID	Granisetron	Placebo	Cause of Death	Days after First and (after Last) Dose of Study Medication
003.057	x		Progressive Lymphoma	67 (45)
016.139	x		Progression of Disease (Colon CA)	20 (3)
027.090*	x		Progression of Disease (Prostate CA)	121 (104)*
036.026	x		Progression of Biliary Tract CA	32 (6)
038.022	x		Respiratory Failure-Progression of Disease (Metastatic AdenoCA)	20 (9)
049.344	x		Progression of Disease-CA	61 (29)
014.013		x	Metastatic CA	36 (14)
014.014		x	Respiratory Failure-Progression of Disease (CA)	29 (8)
026.029		x	Respiratory Failure-Progression of Disease (CA)	36 (22)
032.142		x	Cardiopulmonary Failure	48 (1)
037.163		x	Respiratory Arrest-Progression of Disease (CA)	28 (7)
037.045*		x	Progression of Disease (Esophageal CA)	54 (38)
043.111		x	Respiratory Arrest-Progression of Disease (Lymphoma)	20 (20)
050.189*		x	Gastrointestinal Bleed	68 (42)
056.333		x	Probable Sepsis	24 (3)

(Modified from sponsor's table 35, Vol. 4, P 86)
* Death occurred >30 days after the last dose of study medication.

Withdrawals Due to Adverse Experiences (from the sponsor)

There were 11 (18.2%) patients given granisetron who reported 16 AEs that resulted in withdrawal from the study. Two reports each of intestinal obstruction, leukopenia, and rash resulted in withdrawal for a total of six patients who received granisetron; six placebo patients were withdrawn for reasons including two reports each of asthenia, back pain, and progressive complications of carcinoma. Table 16 provides a listing of patients who were withdrawn by treatment group, adverse experience(s) resulting in withdrawal, investigator-determined relationship to study drug for each event, and designation of seriousness.

One patient given granisetron reported "rash" that was considered to be "related" to treatment with study medication, and another patient given granisetron reported four events (dizzyness, anxiety, dyspnea, and rash) that were considered to be "possibly related" to study medication. One placebo patient reported "sepsis" that was considered to be "probably unrelated" to study medication. All other adverse conditions leading to withdrawal were considered to be unrelated to treatment.

Table 16

Listing of Patients Withdrawn due to adverse Events by Treatment Group

Patient ID	Treatment	AE Leading to Withdrawal Preferred Term	Relationship	Serious/ Non-Serious
259.001.0185	Kytril®	Decreased Appetite	Unrelated	Non-Serious
		Flatulence	Unrelated	Non-Serious
259.005.0082	Kytril®	Dizziness	Possibly Related	Non-Serious
		Anxiety	Possibly Related	Non-Serious
		Dyspnea	Possibly Related	Non-Serious
		Rash	Possibly Related	Non-Serious
259.006.0253	Kytril®	Intestinal Obstruction	Unrelated	Serious
259.012.0033	Kytril®	Rash	Related	Non-Serious
259.017.0125	Kytril®	Intestinal Obstruction	Unrelated	Serious
259.024.0119	Kytril®	Peritonitis	Unrelated	Serious
		Leukopenia	Unrelated	Serious
259.036.0026	Kytril®	Dysphagia	Unrelated	Non-Serious
259.036.0210	Kytril®	Leukopenia	Unrelated	Non-Serious
259.043.0047	Kytril®	Pain	Unrelated	Non Serious
259.043.0287	Kytril®	Sarcoma	Unrelated	Non-Serious
259.045.0105	Kytril®	Arthralgia	Unrelated	Non-Serious
259.014.0014	Placebo	Abdominal Pain	Unrelated	Non-Serious
		Asthenia	Unrelated	Non-Serious
		Postural Hypotension	Unrelated	Non-Serious
		Hemorrhagic Gastritis	Unrelated	Serious
		Hypovolemia	Unrelated	Non-Serious
259.029.0237	Placebo	Carcinoma	Unrelated	Serious
259.037.0163	Placebo	Back Pain	Unrelated	Serious
		Neoplasm	Unrelated	Serious
		Anemia	Unrelated	Serious
		Thrombocytopenia	Unrelated	Serious
		Pneumonia	Unrelated	Serious
259.038.0023	Placebo	Carcinoma	Unrelated	Serious
259.039.0293	Placebo	Back Pain	Unrelated	Serious
259.043.0048	Placebo	Asthenia	Unrelated	Non-Serious
259.056.0333	Placebo	Sepsis	Probably Unrelated	Serious

(From sponsors table 38, Vol. 4, p 91)

Sponsor's Conclusion(s) (Study 259)(Vol. 4, p 14)

Two mg of granisetron tablets (two 1 mg tablets), taken as a single dose once daily, is significantly more effective than placebo in the prevention of nausea and emesis induced by fractionated upper abdominal radiation. Patients given granisetron tablets significantly longer

times to first emesis and nausea, and fewer patients significantly had nausea and emesis at 24 hours and after 10 fractions of radiation. The treatment effect appeared to diminish after 10 fractions of radiotherapy, but for emesis, a therapeutic effect was still seen. Reviewer's note: There exists precedent for these findings with another 5-HT_3 receptor antagonist, ondansetron (1,2).

Granisetron tablets were well tolerated, and no unexpected or clinically significant differences between treatment groups in adverse experiences were observed.

Reviewer's Comments: The present study protocol represents a clinical trial for this class of drug of comparatively long duration, i.e., several weeks of fractionated abdominal irradiation (except weekends) with concomitant granisetron treatment. Along with this, a concomitant change in the conventional primary endpoint, namely, time (days) to first emesis and time to first nausea. This endpoint, i.e., number of days without emesis and nausea differs from that used in previous studies of granisetron and of a comparable agent, ondansetron, for chemotherapy and for short-term (4 days) intensive irradiation (total body irradiation [TBI]) employed prior to bone marrow transplantation. This may be the justification for the present departure from the previous primary efficacy endpoint of "complete response" that has characterized these earlier shorter duration studies. Possibly the change was because of the occurrence with this treatment protocol of emesis and nausea over a prolonged period and repeated changes.

As noted previously, the sponsor has elected to employ a "modified" ITT population that so far does not appear to have had an unfavorable impact on the comparison between the treated and the placebo group results. From a clinical standpoint, the ITT population employed seems acceptable. As has been the previous pattern with studies involving 5-HT_3 receptor antagonists, the most striking effect has been in the earliest time periods. There is more than one reason for this phenomenon as discussed earlier, part of which is the excess in numbers of withdrawals in the placebo comparator group. Of undoubted impact on all treated patients with this regimen is the effect of prolonged radiotherapy on the gastrointestinal tract. Regarding granisetron's general safety and adverse effect (AE) profile, the most common AE in this study was diarrhea. This occurred in both the treated and untreated (placebo) groups. It thus seems reasonable that this effect is the outcome of abdominal radiation exposure rather than of treatment with granisetron.

III. Study #448 (November 1996-November 1997)

" A Double-blind, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Kytril (granisetron hydrochloride) Tablets 2 mg Once Daily and Ondansetron Tablets 8 mg Three Times Daily in the Prophylaxis of Nausea and Vomiting in Patients Receiving Hyperfractionated Total Body Irradiation"

1. **Objectives** (as listed by the sponsor)

(1) To assess the efficacy of granisetron tablets (2 mg once daily) and overencapsulated ondansetron tablets (8 mg three times daily) in patients receiving fractionated total body irradiation prior to bone marrow transplantation as measured by the proportion of patients with no emetic episodes.

(2) To assess the safety of granisetron tablets (2 mg once daily) and over-encapsulated ondansetron tablets (8 mg three time daily) in patients receiving fractionated total body irradiation prior to bone marrow transplantation.

2. **Study Design** (as outlined by the sponsor)

This was a two-arm, double blind, double dummy, active-active study to evaluate the effectiveness of granisetron tablets (2 mg once daily) and overencapsulated ondansetron tablets (8 mg prior to each fraction of radiation). The treatment was for hospitalized patients with malignant disease or aplastic anemia who were scheduled to receive total body irradiation prior to bone marrow transplantation.

Patients were screened within one week of receiving the first dose of study medication. All eligible patients were randomly assigned, at a ratio of 1:1, to receive either granisetron 2-mg tablets once daily or overencapsulated ondansetron tablets 8 mg three times daily for 4 days. Granisetron tablets were administered one hour prior to receiving the first fraction of radiation, while overencapsulated ondansetron tablets were administered 1.5 hours prior to each fraction of radiation. Patients received 3 fractions of radiation on Day 0 (first treatment day) to Day 2 followed by 2 fractions of radiation on Day 3. Each fraction consisted of 120 cGy for a total of 11 fractions and 1320 cGy radiation exposure during the 4-day study.

A Karnofsky (functional activity classification) performance status score was obtained immediately prior to the administration of study medication on Day 0. Several observations were made over the entire 4-day study period and over the 24-hour period of Day 0. These included: proportion of patients with no emetic episodes; proportion of patients who had complete emetic control (no emetic episodes and no rescue medication); number of emetic episodes; and time to first emesis. Other observations included the proportion of patients who had complete nausea control (no nausea and no rescue medication); maximum severity of nausea observed during the study; and time to first nausea. These observations were made by the coordinator and recorded at 24(±1) hour intervals, beginning at the time radiotherapy was initiated (time = 0). Safety was assessed by monitoring adverse experiences at the end of each 24 hour period. All patients that included those who withdrew for use of "rescue" antiemetics received a follow-up evaluation one day after the last day of the treatment period.

A historical negative control group was prospectively identified to serve in place of a placebo or negative (inactive) control group in the study. This group included patients who were identified through a patient chart review conducted at the City of Hope National Medical Center, Duarte, CA.

3. **Study Population** (as outlined by the sponsor)
The criteria for inclusion were conventional for this type of study.

Table 17

Characteristics of the Study Population

INCLUSION CRITERIA	REASON FOR EXCLUSION
• Adults (≥18y) of both genders with diagnosis of malignant disease or aplastic anemia who have been scheduled to receive the indicated course of radiotherapy; • Signed Informed Consent; willingness and ability to comply with protocol requirements; • Females of childbearing potential had to have a negative pregnancy test (urine or serum hCG) prior to entering the study, and agree to practice adequate contraceptive precautions during the study; • Males had to be surgically sterilized or agree to practice adequate contraceptive precautions during the study.	• Use of an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the screening phase of the study; • Karnofsky performance status score of > 60; • Any unstable medical disorder; • Patients receiving conditioning or intrathecal chemotherapy within 24 hours of the administration of the first fraction of total body irradiation on Day 0 or emetogenic systemic or intrathecal chemotherapy during the study; • Patients receiving treatment with agents known to have significant antiemetogenic activity within 24 hours of receiving study medication on Day 0; • Primary or secondary (from metastatic disease) brain neoplasm with signs or symptoms of increased intracranial pressure; • Patients who had any episodes of nausea within 1 hour or any emesis (vomiting and/or retching) within 24 hours of receiving study medication on Day 0; Patients known to be hypersensitive to any 5-HT_3 -receptor antagonist.

(Table prepared by Reviewer)

PATIENT SELECTION FOR THE HISTORICAL CONTROL GROUP

According to the sponsor, this group was identified prospectively to serve as a negative control group in place of a placebo or inactive control. The included patients were available through a chart review conducted at the City of Hope National Medical Center. Patients were considered qualified for the historical group if they received the same emetogenic stimulus (four day hyperfractionated total body irradiation) (TBI) as the randomized patients in the remainder of the study. The following eligibility requirements were applied to selected patients from chart review:

(1) Adults (≥18y) or older with a diagnosis of malignant disease or aplastic anemia;
(2) Received a 4-day regimen of hyperfractionated TBI (11 fractions total, 120 cGy per fraction with a total exposure of 1320 cGy);
(3) Patients who had not received treatment with 5-HT_3 receptor antagonists within 24 hours of receiving the first fraction of radiation.

4. **Highlights of Study Execution; Efficacy Assessment** (sponsor's description)

The sponsor states that patients were randomly assigned at a ratio of 1:1 to receive either granisetron tablets (2 mg once daily) or overencapsulated ondansetron tablets (8 mg three time daily). Patients randomized to granisetron tablets were administered two 1 mg tablets one hour prior to receiving the first daily fraction on Day 0 through Day 3. Patients randomized to receive overencapsulated ondansetron Tablets were administered one 8-mg capsule 1.5 hours prior to each fraction of radiation on Day 0 through Day 3 (i.e.,TID).

- **Efficacy Parameters**: The protocol-defined **Primary efficacy endpoint** consisted of the proportion of patients who had complete emetic control, i.e., (0 emetic episodes and no rescue medication over the 4-day study period).

- **Secondary Efficacy Endpoints**: These consisted of the number of emetic episodes on Day 0 (24 hours) and over the entire 4-day study period; the proportion of patients with no emetic episode on Day 0 (24 hours); and time to first emesis.

Other Efficacy Endpoints included: the proportion of patients who had complete nausea control (no nausea and no rescue medication over the 4-day study period), maximum severity of nausea observed during the study, and time to first nausea.

5. **Test Medication/Maintenance of Blinding**

- As indicated by the sponsor, to maintain the double-blind throughout the study, patients receiving granisetron tablets were administered placebo capsules to match overencapsulated ondansetron tablets, and patients randomized to receive overencapsulated ondansetron tablets were administered placebo tablets to match granisetron tablets. A summary of the dosing schedule for this study is presented in Table 18.

Table 18

Study Medication Dosing Schedule in Minutes Before Receiving TBI Fraction

Fraction of Radiation	Medication	Day 0	Day 1	Day 2	Day 3
First Fraction	capsules (ondansetron)	90 min	90 min	90 min	90 min
	tablets (granisetron)	60 min	60 min	60 min	60 min
Second Fraction	capsules (ondansetron)	90 min	90 min	90 min	90 min
Third Fraction	capsules (ondansetron)	90 min	90 min	90 min	

(modified from sponsor's table in Vol. 8, p. 6)

6. **Statistical Methodology** (as represented by the sponsor)

- Assuming a ≥70% granisetron and ondansetron event rate, and a 100% event rate over a 4-day period for the historical negative control group, it was estimated that 36 randomized patients (18 patients per treatment group) and 91 patients in the historical control group (approximately 4:1 ratio) would be needed to detect a treatment difference with an adjusted $\alpha = 0.01$ and a 92% power test.

- The protocol-based primary efficacy analysis was to be a comparison of the proportion of patients with no emetic episodes over the entire 4-day study period. This was to be done by presenting proportions and 99% exact confidence intervals for the difference between patients who received granisetron tablets and the historical control and between patients who received overencapsulated ondansetron tablets and the historical control.

- The following secondary efficacy endpoints were to be analyzed as follows:

  a) The number of emetic episodes for patients with granisetron tablets versus historical control and patients treated with overencapsulated ondansetron tablets versus historical controls were to be analyzed over the entire 4-day study period by presenting the 99% exact confidence intervals of the differences.

  b) The proportion of patients with no emetic episodes over 24 hours and number of emetic episodes over 24 hours were to be analyzed as above.

  c) Point estimates for median time to event were to be presented for each treatment group. Patients who do not experience the event were to be censored.

  d) Time to first emesis was to be defined as time to first emetic episode or rescue medication, whichever occurred first. Time to first nausea was to be defined in a similar way.

  Tests of hypothesis concerning the efficacy of granisetron tablets versus the historical negative group was to be two-tailed at an $\alpha=0.01$. The hypothesis testing was to be done in the context of the 99% confidence interval of the difference and whether or not the interval included zero. The overall α level of 0.02 will be adjusted since there are two comparisons of interest.

  The inclusion of the ondansetron treatment group: 1) allowed for randomization into one of two active treatment groups; 2) allowed for double-blinding to eliminate bias; and 3) created a basis for comparing results of this study with a previous placebo-controlled study of ondansetron efficacy utilizing the same TBI regimen. The study was designed with adequate power to compare each active treatment group to the prospectively defined historical control group.

7. **Results** (according to the sponsor)

(a) **Participating Investigators/ Patient Accounting**

- Three principal investigators at three centers within the USA conducted this study. These include:

  Stanley Frankel, M.D., Georgetown University-Bone Marrow Transplantation Unit, Washington, DC

  Stephen Forman, M.D., City of Hope National Medical Center, Duarte, CA

and

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- Of 36 current patients screened for entry, 2 patients failed screening and a total of 33 patients were included in the intent-to treat (ITT) population

- Ninety of the 262 patients identified from the Bone Marrow Transplant Registry were included from the previously indicated criteria into the historical negative control group. Eighty-eight of the 90 patients in the historical control group were included in the protocol-defined population.

A summary of the key elements of patient distribution is given in Table 19.

Table 19

Patient Disposition and Key Demographic Data

	Granisetron		Ondansetron		Historical Control	
Total Number Screened	36*					
Randomized/ reviewed Charts*	18*		16*		90**	
Completed study	7	38.9%	6	37.5%		
Withdrawn from 4-day study	11		10			
Demographic Characteristics						
Male	12	66.7%	11	68.8%	57	63.3%
Female	6	33.3%	5	31.3%	33	36.7%
Mean Age (years) ± SD	38.8± 12.2		44.1 ±10.1		30.6 ± 8.1	

(Modification of sponsor's table in Vol. 8, p.9)(*Of the 36 patients screened, 34 were randomized to study medication. Of the 16 patients who received ondansetron, one patient is excluded from the ITT population because no radiation was given.)(**Two of these patients received less than 11 fractions of radiation over the 4-day regimen and were therefore considered protocol violators. Thus. 88 of the 90 patents in the historical control group were included in the protocol-defined population.)

The sponsor provides further information to supplement the data given in Table 19 as follows. A total of 33 randomized patients are included in the ITT population: All 18 patients (100%) who received granisetron tablets and 15 of 16 patients (93.8%) who received overencapsulated ondansetron tablets. One patient (448.006.0013), who received overencapsulated ondansetron tablets received study medication, but is excluded from the ITT population because no radiation was given.

Reviewer's comment: Again, as in study #259, we are dealing with a "modified" ITT population-see above review on this point

The sponsor indicates that ninety of the 262 patients identified from the Bone Marrow Transplant Registry were included in the historical control group.

As shown in Table 19, a total of 21 of 34 patients in the randomized population were withdrawn prior to completing the 4-day study period: 11 receiving granisetron tablets and 10 receiving overencapsulated ondansetron tablets. The primary reason for withdrawal was lack of efficacy (or use of rescue medication); this applied to nine patients receiving granisetron tablets and nine patients receiving overencapsulated ondansetron tablets. Three patients were withdrawn from the study due to deviation from protocol, including non-compliance; two of these patients were receiving granisetron tablets and one patient was receiving overencapsulated ondansetron tablets. One patient who received granisetron tablets (448.001.0019) withdrew from the study due to deviation from protocol, including non-compliance, but the patient also received rescue medication prior to withdrawing himself from the study.

b) **Clinical Response** (according to the sponsor)

In the IND protocol and in the present completed study, the powering calculations were intended to compare each active treatment group against the prospectively defined historical negative control group, but not to compare the efficacy of granisetron tablets with ondansetron tablets. It can therefore be surmised from the information in the protocol that the design objective in this study is superiority of both test drugs to historical controls. Table 20 provides an overall summary of the efficacy results.