Table 20

Summary of Efficacy Results for Primary and Secondary Endpoints-ITT Population

	Granisetron		Ondansetron		Historical Control (HC)		99% CI	
Primary Efficacy endpoint							Granisetron vs HC	Ondansetron vs HC
Proportion of patients with 0 Emetic Episodes Over the Entire 4-day Study Period	6/18	33.3%	4/15	26.9%	0/90	0%	(6.4, 69.2)*	(0.9, 67.3)*
Complete Emetic Control	5/18	27.8%	4/15	26.7%	0/90	0%	(2.9, 64.3)*	(0.9, 67.3)*
Secondary Efficacy Endpoints								
No. Emetic Episodes on Day 0 (24 hrs)								
0 episodes	11/18	61.1%	7/15	46.7%	6/90	6.7%	(20.9, 84.7)*	(5.5, 78.0)*
1-2 episodes	1/18	5.6%	4/15	26.7%	48/90	53.3%		
3-5 episodes	6/18	33.3%	4/15	26.7%	31/90	34.4%		
> 5 episodes	0/18	0%	0/15	0%	5/90	5.6%	(-71.4, -23.8)	(-17.8, 27.7)*
No. Emetic Episodes Over 4-day Study period								
0 episodes	6/18	33.3%	4/15	26.9%	0/90	0%	(6.4, 69.2)*	(0.9, 67.3)*
1-2 episodes	4/18	22.2%	3/15	20%	10/90	11.1%		
3-5 episodes	8/18	44.4%	5/15	33.3%	30/90	33.3%		
> 5 episodes	0/18	0%	3/15	20%	50/90	55.6%	(-71.4, 24.2)*	(-63.1, 1.8)
Time to First Emesis (median time in hrs)	36 hrs		15.8 hrs					

*p<0.01 (table represents a modification of sponsor's table in Vol. 8, p.10)
(Reviewer's comment: more than half of the enrolled patients were withdrawn before completing four days)

Primary Efficacy Endpoint

Proportion of Patients with no Emetic Episodes over the Entire 4 Day Study Period-ITT Analysis. (sponsor's assessment)

The proportion of patients who were free of any emetic episodes over the entire 4-day study period, irrespective of the use of rescue antiemetics, was defined as the primary efficacy endpoint. Patients in the historical negative control group reported a 0% no emesis rate over the 4-day study period. When comparing this rate to the percentage of patients who did not experience any emetic episodes in the two active treatment groups, a difference of approximately 30% was observed; (33.3%, 6/18 patients) in patients receiving granisetron tablets and (26.7%, 4/15 patients) in patients receiving ondansetron tablets. A comparative analysis demonstrated a statistical difference between patients receiving granisetron tablets and the historical control group (99%CI: 6.4, 69.2)(p=0.01). A significant treatment difference

favoring ondansetron over the historical control was also observed (99%% CI: 0.9, 67.3)(p=0.01).

Complete Emetic Control-ITT Population (sponsor's assessment)

The sponsor indicates in Table 20 that complete emetic control was defined as no emesis and no use of rescue antiemetic agents during the 4-day study period. One patient treated with granisetron tablets (448.001.0019) had no emetic episodes but received rescue medication. Overall 27.8% (5/8 patients) of patients treated with granisetron tablets experienced complete emetic control over the 4-day study period compared to the historical control (0%, 0/90 patients). This difference was statistically significant (99% CI: 2.9, 64.3). A significant treatment difference favoring ondansetron (26.7%) over the historical control was also observed (99% CI: 0.9, 67.3).

Sixty-one percent (61.1%, 11/18 patients) of patients who received granisetron tablets had complete emetic control on Day 0 compared to 6.7% (6/90 patients) of patients in the historical control group. A greater proportion of patients who received overencapsulated ondansetron tablets had complete emetic control on Day 0 (46.7%, 7/15 patients) compared to the historical control group. The observed treatment difference between the active agents and the historical control group was also statistically significant.

Protocol-Defined Analysis

The sponsor indicates that due to the large number of patients who were identified as protocol violators, a protocol-defined analysis of the primary endpoint was not performed. The majority of patients identified as protocol violators were rescued with an antiemetic agent and withdrawn from the study prior to receiving 11 fractions of radiation (1320 cGy). Table 21 provides a listing of the number and types of protocol violations.

Table 21

Number and Percent of Patients Excluded from the Protocol-Defined Analysis

Protocol Violation	Granisetron (n=18)		Ondansetron (n=16)	
	n	%	n	%
Nausea within 1 hr and/or emesis within 24 hrs before study medication	1	5.6	1	6.3
Missing nausea and/of emesis assessments	3	16.7	1	6.3
Treatment with agent having significant antiemetic effect within 24 hrs of Day 0	1	5.6	1	6.3
Received less than 11 fractions of TBI	10	55.6	10	62.5
Total Patients	12	66.7	11	68.8

(Note: a given patient may have been excluded for more than one reason.) (modified from Table 3 of sponsor's submission- Vol. 9, p.7)

Secondary Efficacy Endpoints

Number of Emetic Episodes over 4-Day Study period

The sponsor notes that there were no patients treated with granisetron tablets who experienced more than five emetic episodes during the entire 4-day study period. A total of 50 of 90 (55.6%) patients in the historical control group experienced more than 5 emetic episodes, while 3 of 15 (20%) patients who received overencapsulated ondansetron tablets experienced more than 5 emetic episodes. When a comparative analysis of the proportion of patients who had greater than 5 emetic episodes was performed between patients who received granisetron tablets and the historical negative group, a statistically significant difference was observed (99% CI: -71.4, -24.2). There was no significant treatment difference between the overencapsulated ondansetron tablet group and the historical control group (99% CI: -63.1, 1.8), as the interval includes zero (Table 20).

Proportion of Patients with no Emetic Episodes on Day 0 (24 hours)

As observed by the sponsor a total of 11 of 18 patients (61.1%) treated with granisetron tablets did not experience any emetic episodes on Day 0 compared to only 6 of 90 (6.7%) in the historical control group. This treatment difference was statistically significant (99% CI: 20.9, 84.7). A significantly greater percentage of patients (46.7%, 7/15 patients) who received overencapsulated ondansetron tablets had no emetic episodes on Day 0 when compared to the historical control group (99% CI: 5.5, 78.0). A total of 4 of the 6 patients in the historical control group who had no emetic episodes on Day 0 were administered rescue medication.

Time to First Emesis-ITT Population

The median time (hours) to first emesis in patients (n=18) treated with granisetron tablets was 36 hours. Patients (n=15) treated with overencapsulated ondansetron tablets experienced a median time of 15.8 hours. Due to the difficulty in identifying the time to first emesis for patients in the historical control group, no comparative analysis of the time to first event was performed.

(c) Results of Safety Evaluations (provided by the sponsor)

Most Frequently Reported Adverse Experiences

A summary of the most frequently reported adverse experiences is given below in Table 22. According to the sponsor, a total of 24 of 34 randomized patients (70.6%) reported one or more adverse experience during the 4-day study period: 13 of 18 patients (72.2%) who received granisetron tablets and 11 of 18 patients (68.8%) who received overencapsulated ondansetron tablets. The most frequent adverse experience in both treatment groups was headache. Diarrhea and asthenia were other frequently reported adverse experiences in patients who received granisetron tablets. Insomnia, peripheral edema, back pain, and rash were other

frequently reported adverse experiences in patients who received overencapsulated ondansetron tablets.

Table 22

Most Frequently Reported Adverse Experiences

	Granisetron (N=18)		Ondansetron (N=16)	
	n	%	n	%
Headache*	5	27.8%	3	18.8 %
Diarrhea*	4	22.2 %	1	6.3%
Asthenia	2	11.1%	0	0%
Insomnia	1	5.6 %	2	12.5 %
Peripheral Edema	1	5.6%	2	12.5%
Back Pain	0	0%	2	12.5%
Rash	0	0%	2	12.5%

(From sponsors table 18 in Vol 8, p 75)(* The difference between the two treatment groups for the incidence of both headache and diarrhea 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 finding of no significant difference for either comparison. Small sample size was probably responsible for this failure to find significant differences.)

Serious Adverse Experiences

Serious adverse experiences were defined by the sponsor as any event that was fatal, life threatening, disabling or incapacitating or resulted in hospitalization, prolonged a hospital stay or was associated with congenital abnormality, cancer or overdose (either accidental or intentional). For this study, adverse experiences that were expected to occur as a result of hyperfractionated total body irradiation, conditioning chemotherapy, or bone marrow transplantation and were not unusual in any way were not recorded as a serious adverse experience. These expected events were recorded on the Adverse Experience page in the case report form only. However, events that were **uncharacteristically different,** or **unusual** in regard to frequency, severity, or duration and were considered to be due to total body irradiation, conditioning chemotherapy, or bone marrow transplantation, *were* recorded as serious adverse experiences.

In the sponsor's opinion, no patient who received granisetron tablets experienced a serious adverse experience. One patient who received overencapsulated ondansetron tablets experienced a non-fatal serious adverse experience during the study period. The patient developed an irregular pulse shortly after receiving the overencapsulated ondansetron tablets on Day 0. The investigator felt that the arrhythmia was secondary to the patient's underlying heart disease and superimposed anxiety. The event was considered life threatening, moderate in nature and probably unrelated to the study medication.

Deaths

One patient, who successfully completed the 4-day study, died 7 days after receiving her last dose of overencapsulated ondansetron tablets. The cause of death was disseminated aspergillus infection and the investigator judged the event unrelated to study medication.

Withdrawals

The one patient (448.006.00013) who reported a serious adverse experience (arrhythmia) withdrew from the study prior to receiving total body irradiation.

Sponsor's Conclusion(s) (Study 448) (Vol 8, p 15-16)

In the sponsor's opinion, results from this study strongly indicate that the administration of granisetron tablets as a single 2 mg dose prior to patients receiving the first daily fraction of total body irradiation is effective in preventing nausea and vomiting attributed to total body irradiation. A significant difference favoring granisetron over the historical control group was observed in the proportion of patients who had no emetic episodes on Day 0 (61.1% vs 6.7%, $p<0.01$) and during the entire 4 day study period (33.3% vs 0%, $p<0.01$). A significantly greater percentage of patients (27.8%) who received granisetron tablets had complete emetic control (no emesis and no rescue medication) over the entire 4-day study period compared to 0% in the historical negative control group. No patients who received granisetron tablets experienced more than 5 emetic episodes during the entire 4-day study period compared to 55.6% of patients in the historical negative control group ($p<0.01$).

A similar efficacy profile was observed in patients who received ondansetron, further validating the design of this study. A significantly greater percentage of patients who received ondansetron had no emetic episodes on Day 0 (46.7% vs 6.7%, $p<0.01$) and over the entire 4-day period (26.7% vs 0%, $p< 0.01$) compared to the historical control group. A significant treatment difference favoring ondansetron over the historical control group was also observed in the proportion of patients who had complete emetic control over the entire 4-day period (26.7% vs 0%, $p<0.01$).

Nausea was also assessed in Study 448. According to the sponsor, a significantly greater proportion of patients who received granisetron had complete nausea control (no nausea and no rescue medication) on Day 0 compared to the historical negative group (44.4% vs 2.2%, $p<0.01$). However, this difference was not maintained over the 4 days of TBI administration, nor was it observed in patients with ondansetron.

The sponsor believes that granisetron was well tolerated. The most frequent adverse experience in both treatment groups was headache. Diarrhea and asthenia were other frequently reported adverse experiences in patients who received granisetron. Insomnia, peripheral edema, back pain, and rash were other frequently reported adverse experiences in patients who received ondansetron. The majority of the reported adverse experiences was of mild or moderate intensity and considered unrelated or probably unrelated to study medication.

Only one patient reported a serious adverse experience (considered life threatening) and was withdrawn from the trial prior to receiving the first fraction of radiation. One patient, who received ondansetron, died 7 days after receiving the last dose of study medication. The death was not considered related to study medication.

The sponsor concludes that the study establishes that granisetron tablets (2 mg once daily) are safe and effective in the prevention of nausea and vomiting induced by hyperfractionated total body irradiation prior to bone marrow transplantation. Reviewer's note: Support for this finding with granisetron and ondansetron is available in the published literature (3-5).

Reviewer's Comment: The sponsor puts forward a justification for their use of an historical negative control group, which represents a longstanding and conventional cause for concern. It should usually only be considered as a second alternative in the absence of an active control since the placebo comparison approach is currently widely considered no longer ethical (6). Citing several problems with this approach previously outlined in published form by Pocock (7), they provide responses to a number of these critical points. This is presented in Vol 8, pp 33-35 in the form of point and counterpoint (responses). Among the seven points taken from Pocock (7), the first two identified concerns are those least effectively addressed. Both involve some aspect of potential demographic difference between the historical controls and present active study participants. The points raised are the following: #1-A historical control group is less likely to have clearly defined criteria for patient inclusion; and #2-Since historical controls were recruited earlier and possibly from a different source, there could be a difference in the type of patient available for selection.

The responses given deal in part with these issues. An examination of certain demographic information (provided in the sponsor's submission) suggests the possibility that there may be potentially serious differences between the historical control group and the active participants in the current studies that could affect a comparison. The demographic information given previously in Table 19 comparing the three treatment groups does not include certain details about the historical control group in comparison to the active treatment groups. The following tabulated information (Table 23) indicates a lack of comparability between the active study groups and the historical negative control group. Among the more obvious differences are that the historical control group is almost by half comprised of demographic groups that are distinct from"White" (caucasian). Of the different components in this mixed component half are a large majority of "others", together with an almost 10% component of "Orientals". Of the 84 patients in this group on whom PIDs could be found, the racial distribution was 54% White, 10% Oriental, and 37% Hispanic. It is thus clear that the "Other"category shown in Table 23 consisted entirely of Hispanics. Both Hispanics in the Southwestern USA and Oriental racial groups are known to differ from mostly European-derived "Whites" regarding both metabolism of drugs and certain disease susceptibilities, e.g., gallstone prevalence (8). The population for the historical controls was entirely from one geographic locus, i.e., Southern California.

Table 23

Descriptive Statistics of Demographic Characteristics
All patients in Protocol-Defined Analysis

	Granisetron		Ondansetron		Historical Controls	
	N	%	N	%	N	%
Race						
White	6	100	5	100	46	52.3
Oriental	0	0	0	0	7	8.0
Black	0	0	0	0	2	2.3
Other	0	0	0	0	31	35.2
Missing	0	0	0	0	2	2.3
Total	6	100	5	100	88	100
Age-Mean	45.9		49.0		30.5	
± SD	12.3		10.1		8.1	
Weight-Mean	162.4		199.9		150.1	
± SD	38.6		46.4		31.2	

(devised by the reviewer from sponsors data found in Table 4 (b) in Vol 9, pp 14-16)

As a practical test of whether this potential source of concern matters, PIDs for the population indicated above in Table 19 were examined. Possible differences in outcome among these untreated patients during the 4-day course of fractionated irradiation were sought.

The findings confirmed results previously outlined in Table 20, indicating that untreated patients in all historical negative control subgroups, regardless of racial-genetic or gender differences fared equally poorly. Complete emesis-control over the entire 4-day study period never occurred, for example, compared with a prevalence of about 30% in the two actively treated groups. Absence of emetic episodes within the first 24 hours (Day 0) after beginning irradiation was only 6.7% in the overall historical negative controls versus 61.1% for granisetron and 46.7% for ondansetron in these much smaller treated groups. Thus, the issue of non-comparability between the untreated historical control group and the present actively treated groups was nullified by this overwhelmingly poor outcome in untreated patients.

One other comment is worthy of note. In the Statistical Methodology section, the sponsor indicates that according to pre-study assumptions and calculations, at least 18 patients should have been included in each of the two active arms of the study. In fact, as shown in Table 19, in the granisetron-treated group only 7 out of 18 patients that had been randomized actually completed the study. Similarly, in the ondansetron-treated group, only 6 out of 16 patients that had been randomized completed the study. This represents an extremely high and unexplained dropout rate.

Reviewer's Comment: Despite this unexplained and phenomenally high dropout rate, the data support the idea that both granisetron and ondansetron are superior to placebo (historical controls). Although the sponsor did not intend explicitly to demonstrate the comparability of these two treatments against placebo, it still would perhaps have been possible to obtain useful information on this point if the dropout rate had not been so excessive.

IV. Study #108 (October 1992-February 1994)

"A single blind study to compare the efficacy and safety of oral granisetron (1mg BID) with a standard anti-emetic treatment in the prophlaxis and control of emesis in patients undergoing fractionated chemotherapy and total body irradiation prior to bone marrow transplantation"

1. **Objective(s)** (as listed from the sponsor)

The primary objective was to compare the efficacy and safety of oral granisetron (1 mg BID) with a standard anti-emetic combination: chlorpromazine or dixyrazine plus metochlopramide, in the prophylaxis and control of vomiting induced by Total Body Irradiation (TBI), given in **one fraction** prior to Bone Marrow Transplantation.

A secondary objective was to compare the efficacy and safety of oral granisetron with a standard anti-emetic combination in the prophylaxis and control of vomiting induced by fractionated conditioning chemotherapy.

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

This was a randomized, single blind (to the patient), parallel group multicenter (4 in France, 1 in Sweden) entirely European study, comparing granisetron tablets with chlorpromazine (or dixyrazide) plus metoclopramide. Patients due to receive a bone marrow tranplantation were to be screened for inclusion into this study within 7 days of starting up to 8 days of conditioning chemotherapy. This was to be followed by total body irradiation (TBI) given in total doses of 10 Gy over a period of about 4-10 hours with dosage rates ranging between 2.3 and 13.4 cGy/min (sponsor's Appendix 5.2.1b, Vol 11, pp 14-16). Patients satisfying the Inclusion criteria were to be randomly assigned to receive either granisetron or the comparator antiemetic on two different occasions. The first was one hour before conditioning chemotherapy and the second was one hour before starting TBI. Patients who experienced any vomiting or worse than mild nausea during conditioning chemotherapy or during TBI were allowed rescue therapy. Patients were to be withdrawn from the study at any time if nausea and/of vomiting remained uncontrolled.

Nausea and vomiting as well as adverse events were assessed throughout the period of study and including the 7 days after the day of TBI. All patients received a final follow-up assessment 7 days after the day of TBI. Blood samples were taken on the day of screening as well as both 24 hours and 7 days after TBI. An outline schematic summary (flow chart) of study procedures with time-line is given in Figure 1 (provided by sponsor-Vol 10, p 200).

3. **Study Population** (from the sponsor)

The criteria for inclusion were typical for this type of study.

Table 24

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Hospitalized patients of both genders above the legal age of consent; • Patients having a hematologic malignancy who were due to receive fractionated chemotherapy and a single dose TBI of at least 8 Gy given within a 12 hour period prior to bone marrow transplantation; • Having a WHO Classification of Performance Status of ≤ 2; • Patients and/or guardian were to have given written or verbal witnessed informed consent, according to local regulatory requirements; • Patients who had not received any antiemetic medication during the 24 hours before the start of TBI; • Patients who had not experienced uncontrolled nausea and/or vomiting following rescue therapy during the 12 hour period prior to TBI.	• Patients due to receive TBI given over more than a 12 hour period; • Patients with chronic nausea and/or vomiting; • Patients with significant liver dysfunction-defined as a liver function test > 4X the upper limit of normal, unless a non-hepatic cause was demonstrated; • Patients with congestive heart failure defined by the NYHA classification grade III or IV; • Patients taking drugs during the study in doses likely to produce amnesia during the study period; • Patients who were due to receive any other investigaional new drug during the antiemetic period of this study; • Patients scheduled to take corticosteroids within 48 hours of the start of TBI; • Patients who had a partial or generalized seizure during the past year; • Patients with a symptomatic primary or secondary brain tumor; • Patients who were unwilling or unable to comply with protocol.

(Table devised by Reviewer from sponsor's information)

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

- Patients were twice randomly assigned at a ratio of 1:1 to receive either granisetron or the comparator combination of antiemetic medications at the time of initial conditioning chemotherapy and the subsequent TBI therapy. At this time both groups were then re-randomized on the same basis (**see Figure 1, top, page after next**). For the granisetron group, patients were to begin therapy one hour before the start of conditioning chemotherapy and to continue to take one capsule every 12 hours on all days of conditioning chemotherapy and on any intervening days until the day of TBI. On the day of TBI, patients re-randomized to receive granisetron were to take one (1 mg) capsule before the start of TBI and another capsule 12 hours later.

- For the comparator group, in accordance with the above succesive randomization or re-randomization pattern, patients were to be given either chlorpromazine or dixyrazine in combination with metoclopramide before either conditioning chemotherapy or TBI. Patients began therapy one hour before the start of conditioning chemotherapy.

Chlorpromazine was to be given intravenously at an initial dose of 25 mg followed by 25-50 mg every 4-6 hours (up to 200mg /24 hours), or dixyrazine, given together with metoclopromamide (100 mg tid) both given intravenously. Chlorpromazine or dixyrazine and metoclopramide were given on all days of conditioning chemotherapy and intervening rest days (until the day of TBI) and the dose could be adjusted as considered apppropriate by the investigator. On the day of TBI, patients re-randomized to receive the comparator combination began antiemetic therapy one hour before the start of TBI with treatment being continued for up to 24 hours.

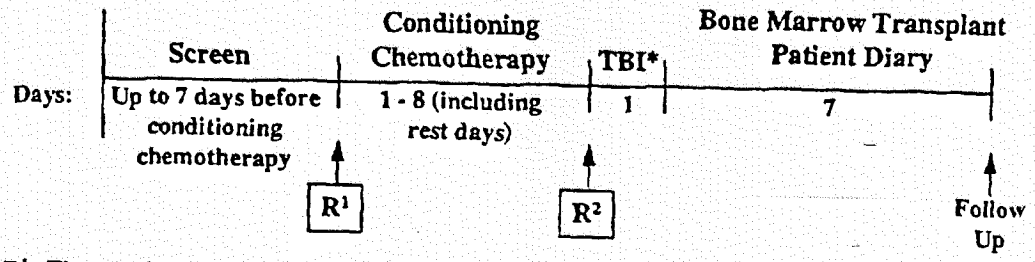
- Rescue Medication

a) Granisetron-If satisfactory control of nausea and/or vomiting was not obtained with oral granisetron, intravenous (IV) granisetron was to be used as rescue therapy but the patient was also to continue with oral granisetron therapy. Up to two 3-mg doses of IV granisetron could be administered within each 24-hour study period provided that no two doses were administered within 10 minutes of each other. If nausea and vomiting remained uncontrolled with rescue granisetron or antiemetics other than granisetron were given, the patient was to be withdrawn from the study. If patients received IV granisetron within the 12 hours before the start of TBI, the patient was to be withdrawn from the study.

b) Comparator- If satisfactory control of nausea and vomiting was not obtained with the original comparator group treatment program (see above), then other antiemetics were to be given at the discretion of the investigator.
Steroids or IV granisetron were not to be given as rescue therapy during the 48 and 24-hour periods, respectively, prior to the start of TBI. If nausea and vomiting remained uncontrolled following rescue therapy or if rescue therapy was given during the 24-hour period before starting TBI, the patient was to be withdrawn from the study.

c) Concomitant Therapy- All concomitant medication taken during the study was recorded. Patients receiving granisetron were not allowed to receive other antiemetics during that particular treatment period. Similarly, patients receiving the comparator antiemetic combination were not allowed to receive steroids or IV granisetron as rescue antiemetic therapy during conditioning chemotherapy throughout the 48 and 24 hour periods respectively, prior to the start of TBI. Steroids were allowed as rescue antiemetic therapy during TBI. Drugs acting on the central nervous system which were likely to affect symptom recall were proscribed, except for high dose Tranxene which was allowed to patients undergoing TBI provided that the same dose was administered (where possible) in each treatment arm.

Figure 1
Study Flow Chart



R¹ **First randomisation** - to anti-emetic treatment which was started before and continued during conditioning chemotherapy

R² **Second randomisation** - to anti-emetic treatment which was started one hour before TBI for patients who had not received any anti-emetic during the 24 hours before TBI was started and who were without vomiting or nausea during this 24 hour period

* Time 0 = Start of Total Body Irradiation (TBI)

TBI in one fraction (≤ 8Gy) over several hours

(figure 1 is from sponsor's submission-Vol 10, p 200)

- **Efficacy Endpoints**: Primary and Secondary Efficacy Parameters varied minimally between the two main phases (e.g.,TBI and conditioning chemotherapy) of the total treatment period:

  A. Total Body Irradiation-the patient's assessment of nausea and vomiting was recorded every 6 hours up to and including 24 hours after the start of TBI.

  Primary Efficacy Endpoints (principal clinical endpoint as amended) was the percentage of patients free from emesis in the first 24 hours following the start of TBI. This also included the Time of First Breakthrough of any nausea and vomiting and the Time to use of Antiemetic Medication after the Start of Irradiation.

  The **Secondary Efficacy Endpoint** was the Time to Use of Rescue Medication. An additional Efficicacy Variable was the Investigator's recorded global assessment of antiemetic treatment throughout the day of TBI. Recording was also available based on the patients logged diary card noting nausea and vomiting occurring during the 6 day period after TBI. These original protocol-based endpoints were eventually dropped because study circumstances with small patient numbers made them ineffective.

B. Conditioning Chemotherapy-patient recording of events was as described above for TBI. Efficacy Parameters were parallel to those for TBI.

Primary Efficacy Endpoints included the time to first nausea and vomiting and time to use of any rescue antiemetic medication.

Secondary Efficacy Endpoints was based on the Investigator's global assessment of the antiemetic treatment over the conditioning chemotherapy period.

5. **Statistical Methodology** (sponsor's description)

- The original and amended protocol was based on the assumption that there would be a comparator response rate of 40%. From this assumption, it was calculated that a total of 112 evaluable patients (56 per each treatment group) was sufficient to detect a difference of 30% between the treatment groups at the 5% significance level and with a 90% power.

- It was planned that all patients receiving at least one dose of randomized treatment and for whom at least one post-treatment assessment was available would be regarded as valid for the evaluation of efficacy and clinical tolerability. There were to be two Intention-To-Treat (ITT) Populations for analysis, namely, the TBI population, which was of primary interest and all patients in the conditioning chemotherapy period. An important change in clinical management occurred while the study was in progress, however. This consisted of giving TBI as a **fractionated** regimen, rather than as a **single dose**. This led to a drastic underrecruitment and a consequent insufficient number of patients available for analysis when the study was stopped. For this reason, the planned final formal statistical analysis was not possible.

6. **Results** (sponsor's description)

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

- Five Principal Investigators at five centers in Europe (4 in France, 1 in Sweden) conducted this study. These include:

Drs C Cordonnier and Henri Mondor, Hematologie, Hopital Creteil, France - Center = 2

Dr Gorin, Hematologie/Greffe De Moelle, Hopital St Antoine, Paris, France - Center = 4

Dr V Leblond, Hemato Pitie, Hopital Salpetriere, Paris, France - Center # 5

Dr E Gluckman, Hematologie/Greffe De Moelle, Hopital St. Louis, Paris, France – Center # 6
Dr O Ringden, Inst F Klinisk Immunogie, Huddinge Hospital, S-14186, Huddinge, Sweden Center # 3

Table 25

Patient Recruitment by Country and Center

Country	Center Number	Patient Population			
		Conditioning Chemotherapy		TBI	
		Granisetron (n=21)	Comparator Combination (n=18)	Granisetron (n=16)	Comparator Combination (n=14)
France	2	4	5	4	2
	4	3	2	2	2
	5	3	1	1	2
	6	2	3	2	2
Sweden	3	9	7	7	6

(derived from sponsor's table 6 in Vol 10, p. 46)

(b) Comparability of Groups/ Patient Demography

Thirty-nine patients from 5 centers in two countries (Table 25) were selected for inclusion into the study of whom, 21 of 39 (53.9%) and 18 of 39 (46.1%) were treated with oral granisetron or the comparator combination of oral chlorpromazine or dixyrazine plus metoclopramide, respectively, during conditioning chemotherapy. There were 30 patients from 5 countries available for re-randomization prior to TBI, which was the main focus of the study. On the day of TBI, 16 of 30 (53.3%) were re-randomized to treatment with oral granisetron, 8 of 30 (26.7%) to chlorpromazine plus metoclopramide, and 6 of 30 (20%) to dixyrazine plus metoclopramide, respectively. Figure 2 (**see page after next**) presents a flowchart accounting for the patients treated and also those withdrawn from the conditioning chemotherapy and TBI phases of the study.

The principal demographic parameters for patients receiving conditioning chemotherapy and TBI (by treatment group) are outlined in Table 26.

Table 26

Demographic Data on Patients Entering the Conditioning Chemotherapy and TBI Phases of the Study

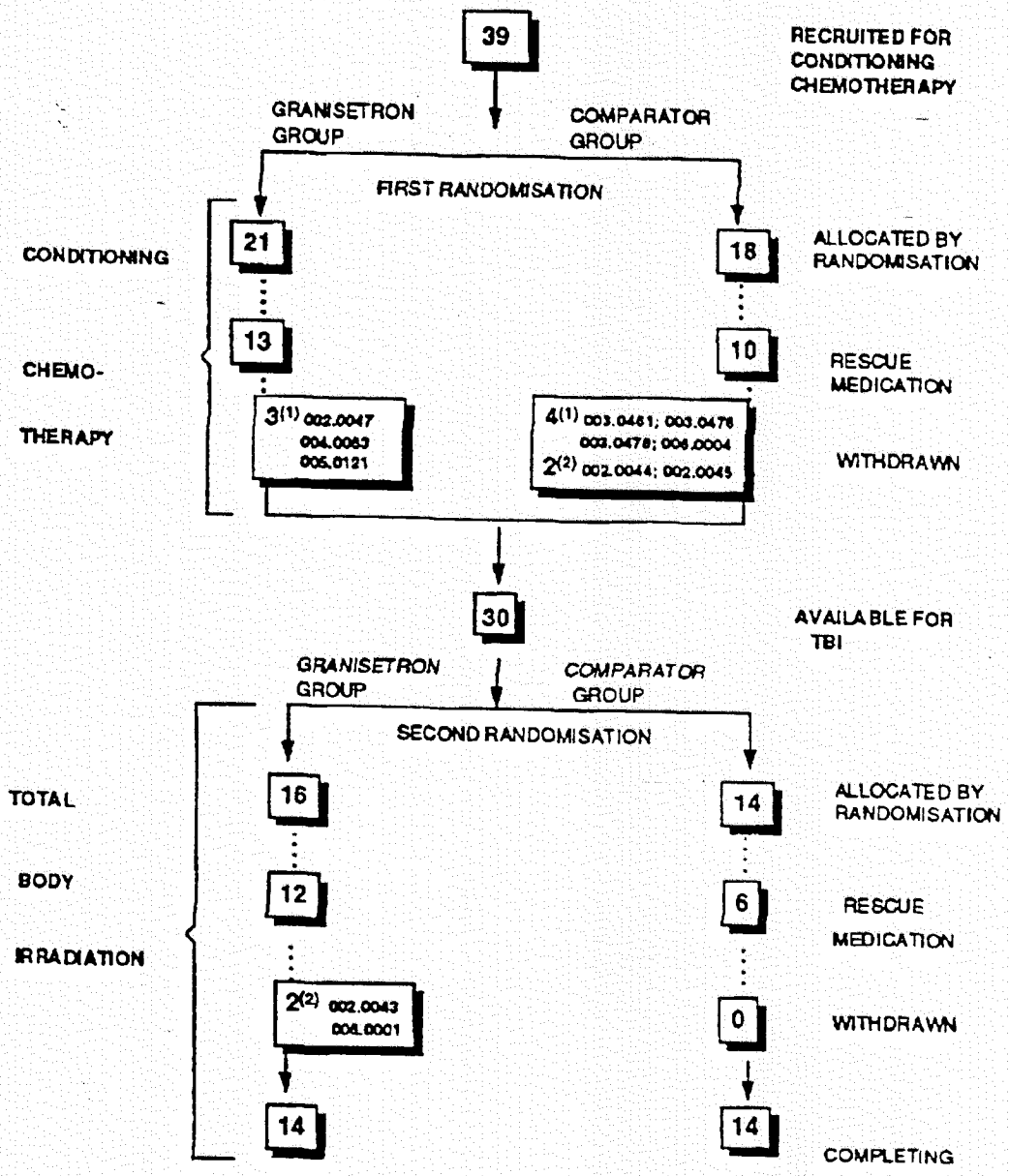
Variable	Conditioning Chemotherapy (n=39)		Total Body Irradiation (n= 30)	
	Granisetron (n=21)	Comparator Combination (n=18)	Granisetron (n=16)	Comparator Combination (n=14)
Males (n)(%)	15 (71.4)	10 (55.6)	10 (62.5)	8 (57.1)
Females (n)(%)	6 (28.6)	8 (44.4)	6 (37.5)	6 (42.9)
Age (mean+range)(yr)	38.4(22-55)	38.9(17-58)	39.0 (22-58)	38.9 (26-52)
Mean hgt (cm)	174	168.4	171.8	169.7
Mean wgt (Kg)	70.6	72.6	73.3	67.6

(modified from sponsors table 5 in Vol 10, p 45)

From this table it can be seen that the treatment groups for both the conditioning chemotherapy and TBI phases were well matched for demographic characteristics at baseline.

Data irregularities included the following: Of the 39 patients recruited for conditioning chemotherapy, only 30 patients received study medication during the TBI phase. Of the 9 patients who did not receive treatment according to protocol during the TBI phase, two patients received TBI and three patients received Bone Marrow Transplantation. Among missing data were the following: no height data on one patient; one patient was age =17 (below age of consent) at screening and therefore incorrectly entered into the study; for one patient who was included in the ITT population, the start time of TBI was missing.

FIGURE 2
SUMMARY OF PATIENT DISPOSITION IN DIFFERENT PHASES OF STUDY



Key to reasons for withdrawal:-

(1) = Lack of anti-emetic efficacy (2) = Significant adverse experience

(figure 2 is taken from sponsor's submission-Vol 10, p 201)

(c) Clinical Response (sponsor's description)

- **Primary efficacy Endpoint-No Emesis over 24 hour**

During Total Body Irradation

Since the primary interest is a comparison of granisetron against standard antiemetic combination during the TBI phase of the study, the results obtained during the TBI phase of the study are always presented before those obtained during conditioning chemotherapy. Moreover, although nausea was being recorded on the CRFs, following introduction of the Fifth and last amendment, it became no longer a relevant primary or secondary efficacy assessment. Accordingly, results on nausea will not be summarized or discussed under Efficacy.

By 24 hours, the proportion of emesis-free patients in the granisetron group (5/14=31.3%) and the comparator combination group (4/14=28.6%) were similar.

During Conditioning Chemotherapy

Over the entire conditioning chemotherapy period, only 5 of 21 (23.8%) and 2 of 18 (11.1 %) of patients in the granisetron group and comparator antiemetic combination groups, respectively, were emesis-free. During any one day of conditioning chemotherapy most patients in the granisetron and comparator antiemetic groups, respectively, had no emesis. Overall, there were no obvious differences between treatment groups, in part at least because the small size of the various groups being compared did not allow any intergroup distinctions to be drawn.

The same problem pattern of small sample sizes as specified in section #5 above, regarding statistical methodology, prevailed regardless of endpoint under consideration, e.g., Complete Response. Regardless of efficacy endpoint being applied, the sample sizes were too small to obtain a reasonable idea of whether intergroup differences in outcome might or might not be present. For example, clinician's global assessments were attempted on a qualitative basis to discern potential differences in treatment outcomes between groups. These too failed for the same reasons given above.

(d) Results of Safety Evaluations (sponsor's description)

Most Frequently Reported Adverse Experiences

According to the sponsor, during the TBI phase of the study, 11 of 16 (68.8%) and 12 of 14 (85.7%) of patients in the granisetron and the comparator combination groups, respectively, reported at least one adverse event. Events occurring in at least 10% of patients during TBI are shown in Table 27 below in descending order of frequency.