Of note is that the sponsor's description of this study, as active comparison, is inconsistent with that set in the objective of the study, which specifies that each of the treatment group is to be compared with the inactive historical control and that the study was not designed to compare the two active treatments. Sample size calculation indicates, however, that comparison of each of the two active treatments against the historical control was intended, as will be discussed later.

The historical negative control group was prospectively defined to serve in place of a placebo or inactive control. This group included patients who were identified through a patients chart review conducted at the City of Hope national medical Center, Duart, CA. Patients were considered qualified for this historical group if they received the same emetogenic stimulus as the randomized patients in the trial. The use of a historical negative control group, rather than a placebo control group, was based on both ethical and logistical reasons; because TBI is a highly emetogenic as cisplatin.

The study population included male and female adult patients with malignancy, who were scheduled to undergo bone marrow transplantation and receive a total of 11 fractions of radiation from a 10 MeV linear accelerator for a total of 4 days (Days 0 to Day 3). Patients received three fractions of TBI for three days followed by two fractions of radiation on the fourth day at a dose of 120 cGy per fraction. The total dose of radiation to be given was 1320 cGy.

Patients were to be assessed for eligibility according to the inclusion and exclusion criteria, and their medical history would be recorded, which must include diagnosis of primary disease (malignant disease or aplastic anemia) and demographic information. An eligible patient would be admitted to the clinic or hospital and randomize to receive Kytril Tablets (2 mg once daily) or ondansetron tablets (8 mg three times daily) prior to each fraction of radiation during the 4-day study period. The sponsor indicated that, in order to maintain the double-blind through the study, patients were administered placebo tablets to match the other treatment group.

There are 3 amendments for the original protocol, approved 7/10/1996. These 3 amendments, dated 8/1/1996, 11/14/1996 and 10/17/1997 respectively, dealt with different aspects of the study. In particular the last amendment, according to the sponsor, was to revise the protocol synopsis section and study population to include new sample size and number of patients in the new historical negative control group.

III.B Efficacy Assessment:

Efficacy and Safety Parameters: The protocol defined the primary efficacy endpoint to be the proportion of patients with 0 emetic episodes (vomiting or retching) over the entire 4-day study period. In addition, the sponsor analyzed the proportion of patients who had complete emetic control (0 emetic episodes and no rescue medication over the 4-day study period). However, as the two endpoints are highly correlated, their efficacy assessment is expected to be similar. The sponsor indicated that nausea assessment were not included in the prospectively defined endpoints because it was presumed that reliable information concerning this symptoms would be unavailable for the historical control group.

The secondary efficacy endpoints consisted of: 1) number of emetic episodes on Day 0 (24 hours) and over the entire 4-day study period; 2) proportion of patients with no emetic episodes on Day 0 (24 hours); and 3) time to first emesis. In addition, the sponsor listed other efficacy variables which 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.

The sponsor definition of the patients population analyzed (ITT and per-protocol) and the safety assessment in this study are similar to those of Study # 259 and will not be repeated here.

III.C Statistical Analysis Plan:

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Sample Size Calculation: This, according to the sponsor, was based on the assumption that the expected no vomiting rate in patients given Kytril Tablets or ondansetron is at least 30% and 0% rate for the historical control. Under these assumptions, the fourth amendment of the protocol estimated that a sample size of 18 patients per active treatment group and 91 patients in the historical control group would be needed to provide 92% power to demonstrate a significant difference for each treatment group versus the historical control group, at the adjusted α level of 0.01. Whereas the above number of patients were used in the analyses, the sponsor's submission showed different number of patients in the original protocol and the other amendments. It is not clear from the submission how these various numbers of patients were calculated. We will revisit this issue in Section IV which lists the reviewer's comments.

Methods of Analysis: The protocol specified that the primary efficacy analysis to be comparison of the proportion of patients with 0 emetic episodes over the entire 4-day study period, for Kytril tablets and ondansetron tablets versus the historical control group. This was to be done by presenting proportion of patients with 0 event and 99% confidence intervals of the difference each treatment versus the historical control group.
The secondary efficacy endpoints were analyzed as follows: number of emetic episodes for Kytril versus the historical control group and ondansetron versus the historical control group were to be analyzed over the entire 4-day study period by presenting the 99% exact confidence interval of the differences. Also, the same approach was to be used for analyzing the proportion of patients with no emetic episodes over 24 hours and the number of emetic episodes over 24 hours.

In addition, point estimates of the median time to event were to be presented for each treatment group. Patients who do not experience the event were to be censored. 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 (i.e, time to first nausea or rescue medication).

Tests of the hypothesis concerning the efficacy of Kytril versus the historical control group was to be two-tailed at an $\alpha = 0.01$. The overall α level of 0.02 is adjusted since there are two comparisons of interest.

III.D Patient Disposition:

A total of 36 patients were screened, of whom 34 patients were randomized to study medication (18 on Kytril and 16 on ondansetron). One patient (# 448.006.0013) received ondansetron tablets but was excluded from the ITT population because no radiation was given. Consequently, 33 are included in the ITT analysis. A total of 21 of 34 patients in the randomized population were withdrawn prior to completing the 4-day study period (11 receiving Kytril tablets and 10 receiving ondansetron tablets). The primary reason for withdrawal was lack of efficacy or use of rescue medication (9 in each of the treatment group); 3 patients were withdrawn from the study due to deviation from protocol (2 Kytril, 1 ondansetron) including no compliance. Among these 3 patients one patient, # 448.006.0019 on Kytril treatment, also used rescue medication prior to withdrawing from the study. Thus, a total of 13 patients completed the study.

For the historical control group, 90 of the 262 patients identified from the Bone Marrow Transplant Registry were included in the historical control group. Of these 90 patients, 2 patients

received less than 11 fractions of radiation over the 4-day radiation regimen and were considered protocol violators because they did no receive the protocol specified amount of radiation. Thus 88 of the 90 patients in the historical control group were include in the protocol defined population.

III.E Efficacy Results

III.E.I Primary Efficacy Parameters:

Proportion of patients with No Emetic Episodes Over the Entire 4-Day Study Period:

Table 6 compares the proportion of patients with 0 emetic episodes over the entire 4-day study period with that of the historical control for the ITT population. Also, the table presents the results of a similar comparison for the proportion of patients with complete emetic episode. These comparison are based on constructing 99% exact confidence intervals for the differences in the response rates for each of Kytril Tables and ondansetron against the historical control. Also, the table shows the results of testing each of the active treatments versus the historical control, using 2-tailed test at $\alpha = 0.01$.

Table 6 (sponsor's table): Comparison of the proportion of patients with 0 emetic episodes and complete emetic control for the active treatments versus the historical control, ITT analysis

Primary Efficacy parameters	Kytril n/N (%)	Ondansetron n/N (%)	Historical Control (HC) n/N (%)	99% CI	
				Kytril vs HC	Ond. vs HC
0 Emetic Episode	6/18 (33.3)	4/15 (26.7)	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) *

* $p < 0.01$

Source: Sponsor's table in page 10, Vol. 26,

The results of Table 6 show that 33.3% for Kytril Tablets patients and 27.6% for ondansetron patients did not experience any emetic episodes during the 4-day study period compared to 0% for the historical control group. Also, it reports significant treatment differences favoring the active treatment against the historical control. Results for the complete emetic control (where no rescue medication was taken) are similar. However, it should be noted these rates are based on small number of patients, and thus their findings might not be very robust, as will discussed later.

III.E.II Secondary Efficacy Parameters:

Table 7 summarizes the sponsor's efficacy results for the number of emetic episodes during Day 0 and during the 4-day study period.

Table 7 (Sponsor's results): Number of Emetic Episodes During Day 0 and During the 4-Day Study Period

Period	Number of Episodes	Kytril n/N (%)	Ondansetron n/N (%)	Historical Control (HC) n/N (%)	99% CI	
					Kytril vs HC	Ond. vs HC
Day 0 (24 hrs)	0	11/18 (61.1)	7/15 (46.7)	6/90 (6.7)	(20.9, 84.7) *	(5.5, 78.0) *
	1-2	1/18 (5.6)	4/15 (26.7)	48/90 (53.3)		
	3-5	6/18 (33.3)	4/15 (26.7)	31/90 (34.4)		
	>5	0/18 (0.0)	0/15 (0.0)	5/90 (5.6)	(-17.7, 23.8)	(-17.8, 27.7)
over 4-Day Study Period	0	6/18 (33.3)	4/15 (26.7)	0/90 (0.0)	(6.4, 69.2) *	(0.9, 67.3) *
	1-2	4/18 (22.2)	3/15 (20.0)	10/90 (11.1)		
	3-5	8/18 (44.4)	5/15 (33.3	30/90 (33.3)		
	>5	0/18 (0.0)	3/15 (20.0)	50/90 (55.6)	(-71.4, -24.2)	(-63.1, 1.8)
Time to first Emesis (median time)		36 hrs	15.8 hrs			

Source: Source: Sponsor's table in page 10, Vol. 26

The results of Table 7 show that 61.1% of the patients who received Kytril Tablets had complete emetic control on Day 0 compared to 2.2% of the patients in the historical control group. A greater proportion of patients who received ondansetron tablets had complete emetic control on Day 0 compared to 46.7% in the historical control group. The observed treatment difference between the active agents and the historical control group is statistically significant.

IV. Reviewer's Comments and Analyses:

IV.A Comments and Analyses on Study# 259:

For this study we address the sample size calculations and present the results of survival analysis carried out on the time to first emesis and nausea.

IV.A.I Sample Size Determination:

As discussed in Section IV, the primary endpoint was the time to event (emesis) whereas the sample size was determined on the basis of event rate. The sponsor in their response, of May 19, 1999, to this reviewer's request indicated that an assumption was made that the times to the event are exponentially distributed. However, as clinicians are more inclined to provide predicted proportion of responders than to predict mean times to event, such inputs were used. Based on the inputs it was assumed that at the end of the 4 week study 40% patients in the treatment and that 60% of the patients on the placebo treatment would have experienced the event in question. Based on these assumptions, one can solve for the mean time to response for each of the treatment group. Then, these estimates can be used in sample size software or algorithms to calculate sample size.

By providing the underlying assumptions used for determining the sample size, the sponsor's response concerning the estimated number of patients enrolled in the trial seems reasonable.

IV.A.II Time to Event Survival Analysis:

The results of this reviewer's re-analysis for the time to first emesis episode for the ITT population confirmed the sponsor's results for the median time to response as given in Table 1. Figures 1.a and 1.b compare the time to the first emesis and nausea, respectively, for the Kytril and placebo treatment groups.

Figures 1.a and 1.b: Survival curves for the time to first emesis and time to first nausea for Kytril and placebo treatments, ITT analysis, Study # 259

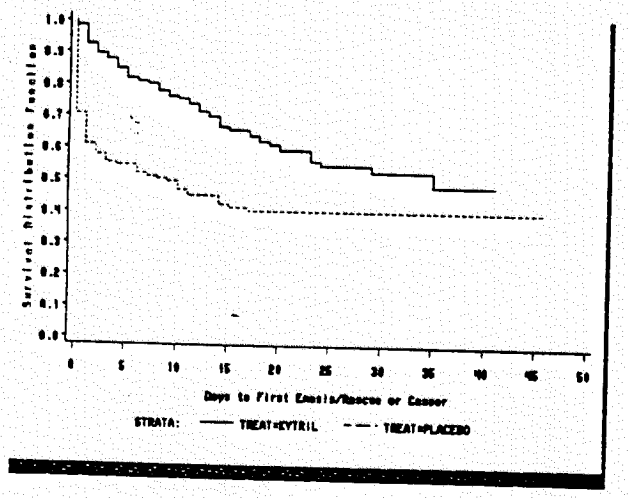

Figure 1.a: Survival curves for emesis

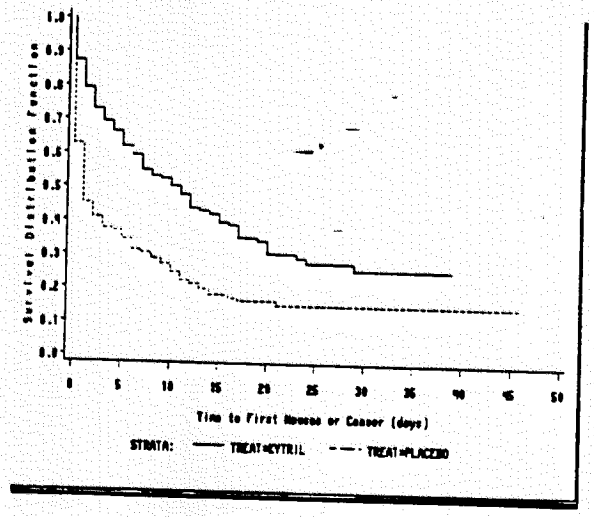

Figure 1.b: Survival curves for nausea

The results of three statistical comparisons of the survival curves are given in the following table, which show significant findings in favor of Kytril treatment.

Test of Equality Over Strata (Treatment)

Time to First Emesis				Time to First Nausea			
Test	$\chi 2$	DF	Pr > $\chi 2$	Test	$\chi 2$	DF	Pr > $\chi 2$
Log-Rank	14.1356	1	0.0002	Log-Rank	19.0541	1	0.0001
Wilcoxon	27.0998	1	0.0001	Wilcoxon	29.5825	1	0.0001
-2Log(LR)	21.0862	1	0.0001	-2Log(LR)	30.9464	1	0.0001

IV.B Comments and Analyses on Study # 448:

IV.B.I Sample Size Calculations:

The protocol and its various amendments referred to different sample sizes. The sponsor in their response of May 19, 1999 indicated that the sample size was calculated based on the expected no vomiting rate of at least 30% in patients given Kytril and ondansetron and 0% rate for the

historical control patients. Assuming that a sample size of 39 patients in the historical control group, it was estimated that a sample size of 42 patients per treatment group was needed for 90% power and adjusted α level of 0.01 (overall α of 0.02). Later, the sponsor noted that the previous historical control group was inadequate, and instead they used the Bone Marrow Transplant Registry to identify patients who received TBI regimen as in the trial. Consequently, in Amendment # 3 the active treatment groups were based on 105 historical control patients. Later, however, the sponsor indicated that due to the difficulty in identifying the above 105 patients, sample size was re-calculated in Amendment # 4, assuming that 91 patients in the historical control group. With these numbers of the historical control it was estimated that 18 patients per active treatment group were needed to show a difference between Kytril and historical control at α level of 0.01 and power of at least 92%. The sponsor noted that BASS software was used for determining the sample size.

IV.B.II Number of Patients with Efficacy Results:

The sponsor, in their submission of October 15, 1998, provided two data listing for Study 448. The first listing (Eff1_448), presented in Attachment I, show the emesis flag-censoring variable (Emiventf) and hours to first emesis/rescue or censor (Tfrstemi). Similar variables were given for the nausea event. The second listing (Eff2_448) gives emesis and nausea results for each day of the study for the active treatments (Kytril and ondansetron) and the historical control patients. Comparison of the two data listings and the sponsor's efficacy results show the following:

- The first data listing, as given in Attachment I, shows there are 5 patients who were emesis free during the study period, whereas the sponsor's results, as summarized in Table 6 of this review, refers to 6 Kytril treatment successes. It is not clear to this reviewer the source of the difference between the two numbers.

- The first data listing shows that the time to first emesis/rescue or censor (Tfrstemi) for patient # 448.001.0002 (Granisetron or Kytril) was 18.5 hours; with 'no emesis' reported in the 'emievent' column. The second data listing show that no emesis event occurred during Day 0, and overall the period. However, data for Day 1 through Day 3 were not reported. The sponsor indicated in their submission that this patient took radiation for 1 day only. It is questionable, in this reviewer's judgement, to treat this patient as emesis free for the entire study period when exposure and measurements are available for the first day of study.

- The second data listing shows that there are data for 34 patients out of total 90 historical control patients, who were emesis free for at least one day during the period considered. However, since efficacy assessment was based on the event of emesis free for the total period, for the active treatments and the historical control, this should not bias the efficacy results since the same rule was applied to the two populations. However, if the comparison was made on daily events, then the observed response for the historical control group patients might affect the efficacy results.

As the number of patients on the Kytril treatment is relatively small with only 6 'successes', according to the sponsor's results as summarized in Table 6, we investigate here the robustness of the efficacy results if we have 4, instead of 6, treatment successes. These 4 successes arise from the observed 5 successes in the sponsor's data and excluding the results for patient # 448.001.0002, for the reasons discussed above. The results of the statistical comparison between Kytril and the historical control group in this case is given in the following table.

Reviewer's Analysis: Comparison of the proportion of patients with 0 emetic episodes for Kytril and the historical control patients, ITT analysis, Study # 448

Treatment	Number and (%) success	Difference in Treatment Success (Kytril - Historical Control)				
		%	P-value		99% CI	
			Asymptotic	Exact	Asymptotic	Exact
Kytril	4/18 (22.2%)	22%	0.023	0.002	(-0.030, 0.475)	(-0.002, 0.591)
Historical Control	0/90 (0.0%)					

The results of the above table show that the 99% confidence interval of the difference between the Kytril response rate and that of the historical control includes zero. Thus, indicating no statistically significant difference between the two treatment groups. However, due to the small number of patients in the Kytril treatment group, with 4 successes only, the findings of this comparison are not robust, as can be seen from comparison of the conclusions based on the p-values and the confidence intervals. Also, the small sample size is the source of difference between the asymptotic and the exact p-values. As one can not attach much reliability on efficacy results based on small number of patients due to their large variations, one might conclude that the results of this trial are marginal from statistical perspective.

V. Overall Summary:

To support their claim for efficacy and safety of Kytril® Tablets, 2 mg once daily, for the prevention of nausea and vomiting associated with radiation, including total body irradiation (TBI) and fractionated abdomina, the sponsor presented the results of two pivotal studies conducted in the United States.

The first study (Protocol # 259) is a double blind, parallel group, placebo controlled, US multicenter study (48 investigators from 38 sites), comparing the safety and efficacy of Kytril Tablets with placebo in the prophylaxis of nausea and vomiting in patients receiving at least 10 (maximum 20) fractions of upper abdominal radiation for malignancy. A total of 264 patients were enrolled into the study and randomized to study drug (134 Kytril tablets and 130 placebo). The primary efficacy parameters were: a) the time to first emesis following the start of the first fraction of radiation (Time 0) and, b) the time to first nausea following the start of the first fraction of radiation.

The efficacy results of this study show statistically significant comparison in favor of Kytril. In particular, as shown in Table 1, the median time to first emesis in the ITT analysis was 35 days for Kytril treatment patients in comparison to 9 days for placebo treatment patients (p-value for relative risk of 0.001). The same differences were evident for males and females, although females tended to have a shorter time to emesis in both treatment groups than males. In addition, the results of Table 3, show of the median time to first nausea episode was 11 days for Kytril patients and 1 day for placebo patients. Similar results were observed in the protocol-defined analysis

The second study (Protocol # 448) was a double-blind, randomized, parallel group, US multicenter study (3 centers). The objective of the study was to compare the proportion of patients with no emetic episodes of each of two active treatments, Kytril Tablets 2 mg once daily and Ondansetron Tablets 8 mg three times daily, in patients receiving hyperfractionated Total Body Irradiation (TBI) to that of a historical control group. A total of 34 (18 received Kytril and 16 received ondansetron tablets) patients were enrolled in the study and their results was compared with those of 90 patients in the historical control group .

The results of this study shows that 33% (6/18) [22.2% (4/18) according to this reviewer's analysis] were emesis free during the 4-day study period. The 99% confidence interval of the difference between the Kytril and the historical control response rates includes the value zero

according to this reviewer's analysis, but not according to the sponsor's analysis. However, these confidence interval were wide due to the small number of patients of the Kytril treatment. Thus, due to the large variability in the efficacy results of this study, one might view these results to be marginal in favor of Kytril.

VI. Conclusion:

The results of Study # 259, for patients receiving upper abdominal radiation for malignancy, shows that the median time to first emesis following the start of the first fraction of radiation (Time 0) is significantly higher for patients receiving Kytril treatment compared to those on placebo treatment. The results for the pivotal study # 448 show that, for patients receiving total body radiation, the proportion of patients with 0 emetic episode is marginally in favor of Kytril, in comparison to those in the inactive historical control group. These marginal results can be attributed to the small number of patients enrolled in the active treatment arms of the trial. Thus, from statistical perspective, the sponsor's results from both studies may support the efficacy claim for Kytril.

/S/

Mohamed Al-Osh, Ph.D. 6/7/99
Mathematical Statistician

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Concur: /S/ 6/7/99
Michael Welch, Ph.D

cc:
Archival/ NDA 20,305/SE1-004
HFD-180/ Dr. Talarico/ Dr. Gallo-Torres/ Dr. Holzbach/ Ms. Johnson
HFD-180/File Copy
HFD-715/ Dr. Nevius/Dr. Welch /Dr. Al-Osh
HFD-715/File Copy

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This review contains 22 pages of text and one attachment.

Aloshm, nda180review (Kytril), 5/29/99

Attcahment I:

Sponsor's first data listing for Study# 448 (Eff1_448), October 18, 1998 submission

OBS	PID	RAD1DAY	TREAT	TFRSTEMI	EMIEVENT	TFRSTNAS	NASEVENT
1	448.001.0002	Yes	GRANISETRON	18.5000	No Emesis	18.5000	No Nausea
2	448.001.0003	No	GRANISETRON	90.0000	No Emesis	24.2500	Nausea
3	448.001.0006	No	GRANISETRON	75.8333	Emesis	75.5000	Nausea
4	448.001.0018	No	GRANISETRON	26.0000	Emesis	11.5000	Nausea
5	448.001.0019	No	GRANISETRON	37.5000	Emesis	37.5000	Nausea
6	448.001.0022	No	GRANISETRON	40.9167	Emesis	13.0000	Nausea
7	448.002.0033	No	GRANISETRON	36.0000	Emesis	36.0000	Nausea
8	448.002.0034	No	GRANISETRON	97.5000	No Emesis	49.5833	Nausea
9	448.002.0038	Yes	GRANISETRON	8.3667	Emesis	8.3667	Nausea
10	448.002.0039	Yes	GRANISETRON	7.6667	Emesis	7.6667	Nausea
11	448.002.0066	Yes	GRANISETRON	9.0833	Emesis	9.0833	Nausea
12	448.002.0067	Yes	GRANISETRON	12.0000	Emesis	12.0000	Nausea
13	448.002.0068	No	GRANISETRON	40.5000	Emesis	40.5000	Nausea
14	448.002.0069	Yes	GRANISETRON	11.0000	Emesis	11.0000	Nausea
15	448.006.0009	Yes	GRANISETRON	9.7500	Emesis	9.7500	Nausea
16	448.006.0012	No	GRANISETRON	97.5833	No Emesis	27.0000	Nausea
17	448.006.0014	Yes	GRANISETRON	5.1667	Emesis	8.8333	Nausea
18	448.006.0016	No	GRANISETRON	97.6500	No Emesis	25.6500	Nausea
19	448.001.0001	No	ONDANSETRON	30.8333	Emesis	30.1667	Nausea
20	448.001.0004	No	ONDANSETRON	15.7500	Emesis	52.0000	Nausea
21	448.001.0005	No	ONDANSETRON	90.3333	No Emesis	90.3333	No Nausea
22	448.001.0007	Yes	ONDANSETRON	14.9333	Emesis	14.9333	Nausea
23	448.001.0017	Yes	ONDANSETRON	7.2500	Emesis	7.2500	Nausea
24	448.001.0020	No	ONDANSETRON	98.2500	No Emesis	13.5000	Nausea
25	448.001.0021	No	ONDANSETRON	77.5000	Emesis	13.5000	Nausea
26	448.002.0035	No	ONDANSETRON	8.5000	Emesis	8.3333	Nausea
27	448.002.0036	No	ONDANSETRON	97.1667	No Emesis	97.1667	No Nausea
28	448.002.0037	Yes	ONDANSETRON	10.0000	Emesis	10.0000	Nausea
29	448.002.0040	No	ONDANSETRON	5.4333	Emesis	4.5500	Nausea
30	448.002.0065	No	ONDANSETRON	13.5833	Emesis	13.5833	Nausea
31	448.006.0010	No	ONDANSETRON	97.5000	No Emesis	6.5000	Nausea
32	448.006.0011	Yes	ONDANSETRON	10.5000	Emesis	10.5000	Nausea
33	448.006.0013	No	ONDANSETRON	.	No Emesis	.	No Nausea
34	448.006.0015	No	ONDANSETRON	36.5000	Emesis	3.1667	Nausea

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