CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

Johnson

STATISTICAL REVIEW AND EVALUATION

Date: JUN 7 1999

NDA: 20-305/SE1-004
Drug Class: Class 3S
Drug name: KYTRIL® (Granisetron Hydrochloride), 1 mg Tablets
Applicant: SmithKline Beecham Pharaceuticals
Indication: Prevention of nausea and vomiting associated with total body irradiation or fractionated abdominal radiation
Documents Reviewed: Volumes #: 1 and #'s: 21-35, dated July 27, 1998, one volume dated October 15, 1998, one volume dated October 22, 1998 and one volume dated May 19, 1999.
Medical Officer: Thomas Holzbach, M.D., HFD-180
Statistical Reviewer: Mohamed Al-Osh, Ph.D., HFD-715

The issues in this review have been discussed with the Medical Reviewer, Dr. Holzbach, and the Medical Team Leader, Dr. Gallo-Torres.

Key Words and Phrases: Radiation-induced nausea and vomiting, survival analysis, historical control.

I. Introduction/ Background

Kytril® (Granisetron Hydrochloride), is a selective and potent $5HT_3$ antagonist. Both Kytril® Injection and Kytril® Tablets are approved for the prevention of chemotherapy induced nausea and vomiting (CINV). The sponsor indicated that in an animal model a dose-response relationship for prevention of radiation-induced nausea and vomiting (RINV) closely resembles that for CINV. Furthermore, they noted that the efficacy of Kytril Injection in preventing RINV has been demonstrated in a number of small studies. In this submission the sponsor is requesting approval of Kytril Tablets, 2 mg once daily, for the prevention of nausea and vomiting associated with radiation, including total body irradiation (TBI) and fractionated abdominal radiation.

To support their claim for efficacy and safety of Kytril® the sponsor submitted the results of two pivotal studies conducted in the United States. Based on the established efficacy and safety of the 2 mg daily dose of Kytril® Tablets in preventing CINV and the similarities of the underlying mechanisms of RINV and CINV; the same dose was chosen for the two RINV studies. The first study (Protocol # 259) was conducted in patients receiving fractionated upper abdominal radiotherapy for malignancy; and the second study (Protocol # 448) was conducted in patients

receiving Hyperfractionated Total Body Irradiation. The sponsor indicated that these two methods of radiation administration (fractionated upper abdominal radiotherapy and TBI) were chosen because of their frequent use in managing patients with malignant diseases

The sponsor also made a reference to a supportive study (# 108). Study # 108 was single-blind, randomized, parallel group comparing granisetron capsules 1mg bid vs metoclopramide + chlorpromazine or dixyrazine, for the prevention of RINV in TBI. The study enrolled 30 patients in 5 European centers (4 in France and 1 in Sweden) over the period October 1992 to February 1994, for treatment duration of about one week. This review is not going to address this study further, as it used a different radiotherapy and antiemetic medication regimen.

As the two pivotal studies differs in their designs and efficacy assessment, this review summarizes the main features and findings of each study separately. Section II discusses the design of Study # 259 along with its efficacy results. Section 3 discusses Study # 448 design and findings. Reviewers comments and re-analysis are given in Section IV. Section V presents an overall summary and conclusion.

II. Study # 259:

Sub-Section II.A describes the main features of the study design. Efficacy and safety parameters and the statistical methods used for the analysis are given in subsection II.B and II.C respectively. Patients disposition, efficacy and safety results are presented in subsection II.D - II.F respectively.

II.A Study Design:

This was a randomized, double blind, parallel group, placebo controlled, US multicenter study (48 investigators from 38 sites), comparing the safety and efficacy of Kytril Tablets 2 mg once daily with placebo in the prophylaxis of nausea and vomiting in patients receiving at least 10 (maximum 20) fractions of upper abdominal radiation for malignancy. The study was conducted over the period of 18 June 1996 to 4 November 1997. The treatment duration was the period of time required to receive about 20 (at least 10 and no more than 30) fractions of radiation, which was for about 4 weeks. It can be seen that the maximum number of fractions specified in the treatment duration exceeds that specified in the efficacy assessment.
The study population consisted of male or female patients, at least 18 years of age, who were diagnosed with cancer and scheduled to receive between 10 and 30 fractions of radiation.

Radiation were to be directed at the midplane of the treated volume, to fields encompassing the upper border of T11 through the lower border of L3, with a field size at least 100 cm^2. The acceptable dose of radiation dose was at least 180 cGy per fraction up to 300 cGy per fraction, with a total weekly dose of at least 900 cGy. Patients with seminoma were permitted to receive less than the 180 cGy/fraction and therefore, less than the total dose of at least 900 cGy per week.

Patients must not have received radiation within 24 hours before Day 0, the first day of radiotherapy, nor any emetogenic chemotherapy within 72 hours of administration of study medication or during the period of study. Patients scheduled to receive wedge-field radiation were excluded. Patients were excluded also if they received chronic or concurrent treatment with agents known to have significant effect on emesis, and/or if they had nausea within one hour and/or emesis within 24 hours before dosing with study medication.

Patients were screened within one week of the scheduled day of abdominal radiation. On the first day of radiation, eligible patients were randomized to receive either Kytril Tablets 2 mg (two 1 mg tablets) or two placebo tablets that were to be taken prophylactically each day for the duration of their participation in the study (the time required to receive 20 fractions of radiotherapy). Patients returned for a follow-up evaluation within 9 days of the last dose of study medication.

The study protocol, approved on 3/12/1996, was amended three times, with first two amendments, dated 4/22/1996 and 4/30/96 respectively, were initiated before the enrollment of the first patient into the study. These amendments, according to the sponsor, were to update the method of monitoring radiation therapy and to allow the entry of patients with seminoma. The third amendment, dated 7/29/1997, was to exclude patients who were scheduled to receive wedge field radiation to the spine or prophylactic radiotherapy to the central nervous system. The sponsor indicated that this amendment was made because such therapies are not emetogenic and, therefore, not suitable for this study.

II.B Efficacy Assessments:

Efficacy and Safety Parameters: 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 protocol indicated that, if the comparisons were significant, additional comparisons were to be made at 24 hours, after 10 fractions and after 20 fractions of radiotherapy.

The secondary efficacy parameters were: a) the proportion of emesis-free days, b) the number of emetic episodes, c) the proportion of nausea-free days, and d) the proportion of 'None'/ 'Mild' nausea grade days.

Safety parameters: The sponsor indicated that Adverse Experience (AEs) were elicited by the investigator asking the patients non-leading questions about adverse experiences and their severity.

Population analyzed: The primary analyses were to be based on the intent-to-treat (ITT) population. The ITT population was defined as all patients who were randomized and received at least one dose of study medication, had at least one fraction of radiation, and had a record of at least one post-dose efficacy assessment. In addition, efficacy evaluable (protocol-defined) population, was defined to exclude patients with significant protocol violations. Protocol defined analysis was performed only on the primary efficacy endpoints: the time to first emesis and the time to first nausea during the period of time required to receive up to 20 radiotherapy fractions.

II.C. Statistical Analysis Plan:

Target Sample Size: The trial was sized to detect a 20% difference in response rates between the treatment groups, assuming that 40% of the patients in the Kytril treated group experience an event (nausea or emesis). However, this response rate was not the primary endpoint. This reviewer will address this point in his comments in Section IV. The protocol estimated that 300 patients were required in order to obtain 260 evaluable patients (130 per group). This sample size would provide 90% power to detect a difference of 20% in response between regimens with alpha level of 0.05. The time to emetic events was assumed to be exponentially distributed. Patients were assigned by order of entry into the study and were allocated with equal probability to one of the treatment groups.

Methods of Analysis: The primary efficacy comparisons of Kytril tablets versus placebo (the time [days] to first emesis and the time [days] to first nausea) were to be performed using Cox Proportional Hazard (PH) model. If rescue antiemetic was taken in the absence of emesis or nausea, time to rescue was considered equivalent to the time of first emesis or nausea. The protocol specified that the Wilcoxon rank sum test stratified by center would be used for analyzing the following secondary efficacy variables: the proportion of emesis-free days, the proportion of nausea-free days, and the proportion of 'None'/ 'Mild' nausea grade days. In addition, the Cochran-Mantel-Haenszel test was to be used for comparing the proportion of:

(i) emesis-free days, (ii) nausea-free days, and (iii) 'None'/ 'Mild' nausea grade days on at least 80% of days on the study, in the two treatment groups.

The Wilcoxon rank sum test were to be used also for analyzing the number of emesis episodes, after adjusting for length of anti-emetic treatment and for center. Adjustment for length of antiemetic treatment was to be done by dividing the number of emetic episodes by the duration of treatment (number of days).

II.D Patient Disposition:

A total of 297 patients screened for entry, of these 264 patients were enrolled into the study and randomized to study drug (134 Kytril tablets and 130 placebo). Four patients were randomized to placebo but were not included in the ITT population. The sponsor indicated that two patients received no study medication or radiation and had no efficacy assessment recorded, one patient received one day of radiation and withdrew for lack of efficacy, and one patient had no efficacy assessment recorded (failed emetic and nausea control and took rescue medication). Thus, the ITT analysis comprised a total of 260 patients. A total of 78 patients (38 [28.4%] in the Kytril group and 40 [30.8%] in the placebo group) had protocol violation. Consequently, 186 patients (96 Kytril, and 90 placebo) were included in the protocol defined analysis.

Withdrawal: A patient was considered to have completed the study if he/she received at least 80% of the prescribed doses of study medication over the course of the 2 to 4-week study and returned for the follow up visit. A total of 121 (48 [35.8%] Kytril, and 73 [56.2%] placebo) patients withdrew before study end. The sponsor's classification of the reasons of study withdrawal shows that the majority of the patients (86 patients: 30 Kytril and 56 on placebo) withdrew due to lack of efficacy and /or use antiemetic rescue medication.

Demographic and Baseline Characteristics: The sponsor's comparison of the demographic characteristics of the randomized patients shows that the treatment groups were comparable with respect to gender, age, race, body wight, height and average weekly use of alcohol.

Approximately 65% of the patients in each treatment group were male, 78% of the patients were Caucasian. The mean age of patients enrolled in the study was 55 years.

The sponsor's classification of all randomized patients by the primary disease site, prior and concomitant medication and types of agents used show that there were no important differences

were observed between the two treatment groups with respects to these baseline characteristics.

II.E Efficacy Results:

Subsection II.E.I presents the efficacy results for the primary endpoints. Results for the secondary endpoints and safety results are presented in subsection II.E.II and II.E.III respectively.

II.E.I Primary Efficacy variables:

II.E.I.a Time to First Episode of Emesis:

Table 1 presents the sponsor's results for comparing the time interval (in days) between the start of the first fraction of radiation (Time 0) and the first occurrence of emesis for the ITT population. As indicated in Subsection II.C, when antiemetic rescue medication was taken in the absence of emesis, the time rescue was considered to be equivalent to the time of first emesis.

Table 1 (Sponsor's Results): Comparison of the Time to First Emesis Episode for Kytril and Placebo Treatment, ITT and Protocol-Defined Analyses Classified by Gender, Study# 259

Population /Gender	Median Time (Days)		Risk Ratio	p-value for Relative Risk	95% CI for Risk ratio Kytril vs placebo
	Kytril (N)	Placebo (N)			
ITT	35.0 (134)	9.0 (126)	1.89	<0.001	1.33, 2.67
Males	>28 [1] (87)	14.0 (82)			
Females	35.0 (47)	2.5 (44)			
Protocol-defined Pop.	>28 [1] (96)	6.0 (90)	2.07	0.001	1.35, 3.17
Males	>28 [1] (61)	9.0 (58)			
Females	23.0 (35)	4.0 (32)			

[1] unable to compare median time to event as too few patients had emesis

Source: Combined from the sponsor's Table 17a, 17b, 18a and 18b, pp.67-70, volume 23.

The results of Table 1 show that 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. In addition, placebo group patients had a significantly higher risk of emesis (1.89, with 95% CI: 1.33, 2.67) than patients who received Kytril. 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.

The results for the protocol-defined analysis are similar.

The sponsor presented the Kaplan-Meier curves for time to first episode emesis. However, instead of attaching the sponsor's plot we will present in the Section IV more detailed results of the survival analysis for the time to first emesis.

II.E.I.b Complete Emetic Control:

Since survival analysis for time to first emesis demonstrated a significant difference between patients who received Kytril and placebo treatments, the sponsor compared the treatment groups with respect to occurrence of complete emetic control at 24 hours, 10 fractions and 20 fractions. The results of this comparison are given in Table 2.

Table 2 (Sponsor's Results): Comparison of the Proportion of Patients with No Emesis at 24 hours, 10 and 20 Fractions of Radiation, for Kytril and Placebo Treatments, ITT analysis, Study 259

Time	Kytril		Placebo		p-value
	n/N	%	n/N	%	
24 Hours	124/134	92.5	78/126	61.9	< 0.0001
10 Fractions	89/104	85.6	51/74	68.9	0.0012
20 Fractions Total	40/52	76.9	23/36	63.9	0.0636
Overall	77/134	57.5	53/126	42.1	0.0047

Source: Sponsor's Table 15, Vol 22, page 65

The results of Table 2 show statistically significant differences between treatment groups, favoring Kytril, in the proportion of patients who were emesis free at 24 hours ($p \leq 0.0001$) and after 10 fractions ($p= 0.0012$). The treatment groups differed less as more fractions of radiation were received. The sponsor indicated that this is likely due the fact that more patients in the placebo group withdrew early in the study, primarily for lack of efficacy, thereby resulting in a smaller treatment difference. For the overall endpoint analysis 57.5% of patients who received Kytril Tablets and 42.1% of placebo-treated patients were emesis free. This difference was statistically significant, with p-value of 0.0047.

II.E.I.c Time to First Episode of Nausea:

Table 3 shows the sponsor's efficacy results for comparing the time to first episode of nausea for the ITT and protocol defined population.

Table 3 (Sponsor's Results): Comparison of the Time to First Episode of Nausea for Kytril and Placebo Treatment, ITT Population, Study 259

Population /Gender	Median Time (Days)		Risk Ratio	p-value for Relative Risk	95% CI for Risk ratio Kytril vs placebo
	Kytril (N)	Placebo (N)			
ITT Males Females	11.0 (134) 1.0 (87) 11.0 (47)	1.0 (126) 1.0 (82) 0.5 (44)	1.78	<0.001	1.34, 2.36
Protocol-defined Pop. Males Females	12. 0 (96) 14.0 (61) 11.0 (35)	1.0 (90) 1.0 (58) 0.5 (32)	1.99	<0.001	1.41, 2.80

Source : Table 16, Vol 22, p. 66

The results of the ITT analysis in Table 3 show that the median time to first nausea episode was 11 days for Kytril patients and 1 day for placebo patients. The risk ratio at this endpoint was 1.78 (with 95% CI: 1.34, 2.36; $p \leq 0.001$). That is, placebo group patients had a higher risk of nausea than patients who received Kytril. Similar results were observed in the protocol-defined analysis

The sponsor presented the Kaplan-Meier curves for time to first episode of nausea. However, instead of attaching the sponsor's plot, we will present in Section IV more detailed results of the survival analysis for the time to first nausea.

II.E.I.d Complete Nausea Control:

Table 4 summarizes the sponsor's results for comparing the proportion of patients with no nausea at 24 hours, 10 and 20 fractions of radiations, between the two treatment groups.

Table 4 (Sponsor's Results): Comparison of the Proportion of Patients with No Nausea at 24 hours, 10 Fractions and 20 Fractions of Radiation, for Kytril and Placebo Treatments, ITT analysis, Study # 259,

Time	Kytril		Placebo		p-value
	n/N	%	n/N	%	
24 Hours	106/134	79.1	57/126	45.2	< 0.0001
10 Fractions	55/104	52.9	24/74	32.4	0.0064
20 Fractions Total	18/52	34.6	11/36	30.6	0.5202
Overall	41/134	30.6	21/126	16.7	0.0042

Source: Sponsor's Table 18, Vol. 22, p. 69

The results of Table 4, are similar to those of Table 2, that is the proportion of patients with no nausea at 24 hours, 10 Fractions are significantly higher in the Kytril treatment group in comparison to the placebo group. However, the difference becomes not statistically significant for 20 fractions of therapy, probably due to patients withdrawal from the study. In the overall endpoint analysis the last observation from every patient prior to his or her withdrawal from the study was used. The results of this analysis are significantly (p=0.0042) in favor of Kytril.

II.E.II Secondary Efficacy Variables:

II.E.II.a Proportion of Emesis Free days

Table 5 shows the sponsor' s results for comparing each of the emesis-free days and nausea-free days between the two treatment groups:

The results of Table 5 show that there were higher proportions of Kytril patients (66.4%) than placebo patients (48.4%) who were emesis-free on all days of the study. Similarly, there were higher proportions of Kytril patients (31.3%) than placebo patients (16.7%) who were nausea-free on all days of the study. Comparison of the proportion of emesis-free, nausea free and 'none'/ 'mild' nausea grade days, adjusting for center, were performed, statistically significant differences, favoring Kytril, were observed ($p \leq 0.001$, $p \leq 0.001$, and $p = 0.001$) respectively.

Table 5 : Proportion of Emesis-Free and Nausea-Free days, ITT analysis, Study 259

Proportion of Emesis (Nausea) free days	Proportion of Emesis free days				Proportion of Nausea free days			
	Kytril (n=134)		Placebo (126)		Kytril (n=134)		Placebo (126)	
	n/N	%	n/N	%	n/N	%	n/N	%
0.0 - < 0.2	2/134	1.5	123/126	18.3	11/134	8.2	31/126	24.6
0.2 - < 0.4	0/134	0	4/126	3.2	8/134	6.0	10/126	7.9
0.4 - < 0.6	3/134	2.2	9/126	7.1	11/134	8.2		10.3
0.6 - < 0.8	6/134	4.5		4.8	17/134	12.7	13/126	12.7
0.8 - < 1.0	34/134	25.4	6/126	18.3	45/134	33.6	16/126	27.8
1.0	89/134	66.4	23/126	48.4	42/134	31.3		16.7
			61/126				35/126	
							21/126	

Source : Tables 19 and Table 20 ;Vol 22, pp. 69- 70

II.E.II.b Number of Emetic Episodes:

The sponsor's results for comparing the number of emetic episodes at 24 hours, after 10 fractions and after 20 fractions of radiotherapy for the two treatment groups, ITT population, show that Kytril treatment patients in general have smaller number of emetic episodes than those of placebo patients. The difference between the two treatment groups is the highest for the 24 hours period and decreases as the number of fractions of radiotherapy increase.

Subset analysis: In addition to the efficacy analysis by gender, the sponsor reported efficacy results for patients with < 10 fractions of radiotherapy. The results of the analysis in this population were similar to those observed in the ITT and Protocol-defined populations.

II.E.III Safety Results:

The sponsor's safety results show that 200 of the 264 randomized patients (75.8%) reported adverse experiences. Of these 110 patients were on Kytril treatment and 90 were on placebo treatment. Statistical comparison of the percentage of patients with adverse experiences in Kytril patients (82.1%) with that of placebo patients (69.2%) shows significant difference between the two treatment groups (p=0.015).

The sponsor's safety results show that the most commonly reported adverse experiences among patients who received Kytril were diarrhea (27.6%) asthenia (25.4%) and constipation (19.4%). The most commonly reported adverse experiences among placebo patients were diarrhea (33.8%) asthenia (19.2%) and headache (11.5%). Twenty (20) patients in each treatment group (14.9% Kytril, 15.4% placebo) reported sever adverse experience.

A total of 33 patients (15 Kytril and 18 placebo) reported serious adverse experiences. The sponsor attributed all serious event, except for 3 patients (2 Kytril and 1 placebo), to be unrelated to treatment medication. A total of 11 deaths (4 in the Kytril and 7 in placebo) occurred within 30 days of the last dose of study medication. Also, 4 additional deaths (2 in each arms) occurred more than 30 days after the last dose of study medication. According to the sponsor, all these deaths were considered to be unrelated to treatment medication.

III. Study 448:

Sub-Section III.A describes the main features of the study design. Efficacy and safety parameters are defined in subsection III.B and the statistical analysis methods are given in and III.C. Finally, subsection II.D- II.F present, respectively, the patients disposition, efficacy and safety results.

III.A Study Design:

This was a double-blind, randomized, historical-controlled, parallel group, US multicenter study (3 centers), comparing the safety and efficacy of Kytril Tablets 2 mg once daily and Ondansetron Tablets 8 mg three times daily in patients receiving hyperfractionated Total Body Irradiation (TBI) prior to bone marrow transplantation. The study was conducted over the period of 18 November 1996 to 4 November 1997.

The objective of the study was to compare the response rate, proportion of patients with no emetic episodes, of each of the two treatment groups with the documented response rate of a historical negative (inactive) control group. The protocol indicated that the study was not designed to demonstrate comparable efficacy of the two antiemetic treatment groups. The sponsor indicated that the purpose of the ondansetron control group in the study was to provide a means of establishing the context of the efficacy observed in the granisetron treatment group.