CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-982
20-936/S-008

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

FEB 25 1999

NDA #	20-982
Applicant	SmithKline Beecham
Name of Drug	Paxil CR (paroxetine hydrochloride)
Indication	Panic Disorder with or without agoraphobia
Documents Reviewed	Volumes 1.001, 1.002, 1.041, 1.046, 1.049, 1.058, 1.065
Reviewer	Kallappa M. Koti (HFD-710)
Medical Officer	Dr. Greg Dubitsky

I. BACKGROUND AND INTRODUCTION

Panic Disorder is a significant public health issue worldwide. Its prevalence is estimated between 1.5 and 4.2%. It is estimated that up to 50% of patients with Panic Disorder also suffer from agoraphobia. Until the last several years, Panic Disorder has been treated primarily with benzodiazepines and tricyclic antidepressants etc. These medicines can produce a number of serious side effects. The need for effective and safe therapy for the treatment of Panic Disorder is paramount.

Paroxetine was first launched in the U.K. in 1991. It was approved for the treatment of depression in the U.S. in 1992, and more recently has been approved for the treatment of obsessive compulsive disorder and panic disorder. The immediate-release (IR) formulation of paroxetine has a favorable tolerability and overall safety profile. One of the most common side effects assocaited is that of nausea. It has been hypohesized that a reduction in the incidence of nausea could be achieved by controlling the rate and site of paroxetine absorption. A new formulation of paroxetine (paroxetine CR) was developed. Based upon the pharmacokinetic profile of paroxetine CR a decision was made to conduct Phase III studies with this formulation in panic disorder.

The Paroxetine Protocol 29060/494, 29060/495 & 29060/497 submitted by SmithKline Beecham is reviewed. The protocol deals with a multi-center, double-blind, placebo-controlled, flexible dosing identical trials. The term depression is defined as follows.
A major depressive episode implies a prominent and relatively persistent depressed mood or loss of interest or pleasure in usual activities, that usually interferes with daily functioning or causes clinically significant distress (nearly every day for at least 2 weeks); it should include at least 4 of the following symptoms: change in appetite or weight, change in sleep, psychomotor agitation or retardation, fatigue or loss of energy, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

II. THE PROTOCOL: OBJECTIVES AND DESIGN

Objectives

The primary objective of Study 494, 495 and Study 497, is to demonstrate the efficacy of the controlled release paroxetine in the treatment of panic disorder with or without agoraphobia among non-elderly people. The secondary objective of this study is to assess the safety of controlled release paroxetine in the treatment of panic disorder with or without agoraphobia among non-elderly people.

Study Design

Studies 494, 495 and 497 are identical trials. They are double-blinded, placebo-controlled, flexible dosing trials to evaluate the efficacy of controlled-release paroxetine.

The diagnosis of Panic Disorder is confirmed at Screening Visit. Patients with a minimal panic attack frequency were identified during a single-blind placebo run-in phase of two-weeks duration. Baseline is defined as Visit 3 that falls in week 3. At Baseline Visit patients were randomized in a balanced fashion to two treatments: flexible-doses of paroxetine controlled-release and placebo. The duration of the double-blind Treatment Phase is of 10 weeks. Post-Baseline Visits during the Treatment Phase are scheduled weekly at Week 1 through Week 6, then at Week 8 and Week 10. During the run-in phase, patients took one single-blind placebo capsule daily in the morning. During the double-blind Treatment Phase, the paroxetine CR daily dose level varied from 12.5 to 75 mg based upon the therapeutic response. During Week 1 and 2, dosing was fixed at levels 1 and 2 for all randomized patients, respectively, i.e., for paroxetine CR-treated patients, 12.5 mg per day during Week 1 and 25 mg per day during Week 2. Thereafter, increases in dosage increments of one dosage level (12.5 mg per day) were permitted if the patient's therapeutic response was deemed inadequate by the investigator. Dosage level increases were permitted no more frequently than every 7 days. One dosage level reduction, consequent to an adverse experience, was permitted after the Week 2 Visit. Patients requiring a dosage reduction prior to the Week 1 Visit were permitted to interrupt level 1 or level 2 dosing, respectively, for a maximum of two days.

Each visit during the Treatment Phase included the evaluations:
(i) Review and/or dispense panic inventory diary, (ii) Clinical Global Impressions, Global Improvement, (iii) Clinical Global Impressions, Severity of Illness, (iv) Hamilton anxiety total score (at Week 6 and Week 10 or early termination only), (v) MSPS fear and avoidance score (at Week 6 and Week 10 or early termination only) and (vi) adverse experience monitoring etc.

The Flow Chart of Patient Evaluations is in Table 1A. Table 1B provides the summary of patient populations.

Table 1A

Flow Chart of Patient Evaluation

	Screen Visit D -14	Run-in Visit D -7	Baseline Visit D 0	Week 1 2 3 4 5 6 8 10	Early Term	Taper-End Visit
Screen/Baseline Evaluations						
General Patient Information	X					
SCID-P	X					
Psychiatric and Medical history	X					
ECG Record	X	X				
Inclusion Criteria	X		X			
Patient Randomiz.			X			
Informed consent	X					
Effic. Evaluations						
Review/Disperse Panic Inv. Diary	X	X	X	X X X X X X X X	X	
CGI (GI. Impr.)				X X X X X X X X	X	
CGI (Severity Ill.)			X	X X X X X X X X	X	
HAM-A			X	X X	X	
MSPS			X	X X	X	
Safety Evaluations						
Vital Signs etc.	X	X	X	X X X X X X X X	X	X
Misc. Records						
Dispence Medicine	X		X	X X X X X X X X[e]	X[e]	
Study Medication Record/Compliance	X		X	X X X X X X X X	X	X
Study Term Rec.				X[f]	X[f]	X

e: If patient entered Taper Phase; f: If patient did not enter Taper Phase

Table 1B

Summary of Patient Population by Study

	Paroxetine CR		Placebo		Total	
	n	%	n	%	n	%
Study 494						
ITT Population	139	100.0	144	100.0	283	100.0
Completing study	103	74.1	109	75.7	212	74.9
Study 495						
ITT Population	158	100.0	163	100.0	321	100.0
Completing study	105	65.5	123	75.0	228	71.0
Study 497						
ITT Population	147	100.0	138	100.0	285	100.0
Completing study	103	70.1	96	69.6	199	69.8
All Studies Combined						
ITT Population	444	100.0	445	100.0	889	100.0
Completing study	311	70.0	328	73.7	639	71.9

III. EFFICACY ASSESSMENTS

During the run-in and Treatment Phases, patients logged in daily diaries the number of panic attacks they experienced per day, and categorized each attack as to number of panic symptoms and whether the attack was situational or unexpected. Patients also recorded the percent of a 24-hour day they worried about attacks or going into a situation that might have brought on an attack, but an attack did not occur (anticipatory anxiety). These daily diaries were summarized in the CRF at every clinical visit and were combined into two-week periods for efficacy assessment for Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6; diaries for two-week dosing intervals, Week 7 and 8 and Weeks 9 and 10, were also summarized.

At the termination of the trial or at the time of early withdrawal, patients entered a two-week Taper Phase during which the dosage was reduced to 25 mg/day.

Overall, demographic characteristics were similar between treatment groups within a study and between studies. They are shown in Table 2.

Table 2
Summary of Demographic Characteristic by Study
ITT Population

Characteristic	Study 494		Study 495		Study 497	
	Par CR N=139	Placebo N=144	Par CR N=158	Placebo N=163	Par CR N = 147	Placebo N=138
Age	Years		Years		Years	
Mean (SD)	38.1 (10.1)	37.0 (10.2)	36.5 (10.1)	36.6 (10.7)	38.2 (10.4)	40.1 (10.7)
Min., Max.	19, 63	20, 61	19, 62	19, 72	20, 65	19, 64
Gender	n %	n %	n %	n %	n %	n %
Female	81 58.3	80 55.6	105 66.5	103 63.5	96 65.3	68 49.3
Male	58 41.7	64 44.4	53 33.5	60 36.8	51 34.7	70 50.7
Race	n %	n %	n %	n %	n %	n %
White	117 84.2	135 93.7	146 92.4	146 89.6	117 79.6	108 78.3
Black	8 5.8	4 2.8	7 4.4	8 4.9	19 12.9	14 10.1
Oriental	0 0.0	2 1.4	1 0.6	1 0.6	0 0.0	0 0.0
Other	14 10.1	3 2.1	4 2.5	8 4.9	11 7.5	16 11.6

Principal Efficacy Variables

Studies 494, 495 and 497 are identical trials. The following is true for all the three studies.

1. The percentage of patients who achieved zero full panic attack per two weeks at study endpoint (protocol-defined primary efficacy parameter);
2. The median change from baseline in total number of full panic attacks per two weeks at study endpoint;
3. The median change from baseline in CGI Severity of Illness score at study endpoint.

Secondary Efficacy Variables

The sponsor has considered several secondary efficacy variables. The medical officer asked this reviewer to look at the following three secondary variables.

1. Anticipatory anxiety change from baseline at study endpoint.
2. The Marks-Sheehan Phobia Scale Total Fear Score.
3. Change in Marks-Sheehan Phobia Scale total avoidance score.

IV. EFFICACY DATA ANALYSIS

Threre were no interim analyses. Statistical conclusions concerning the efficacy of paroxetine CR are made using data from each patient's last post-baseline assessment carried forward (LOCF) to Week 10 (study endpoint) of the ITT population. For statistical analysis small centers are combined to form a new character variable CENTGP as shown in Table 2 below. **A significant treatment by center group interaction was observed in the analysis of change from baseline in HAM-A total score.** On further investigation, center group 005 and 033 had a larger treatment effect favoring paroxetine CR than any other center group. Removal of center 033 from the analysis resulted in loss of the significant treatment by center group interaction. This center was also involved in significant treatment by center group interactions involving key efficacy parameters in an identical paroxetine CR study in panic disorder (Study 495). The results from both studies 494 and 495, for efficacy parameters involved in these interactions, consistently favored paroxetine CR over placebo at this center. Because of the consistent nature of treatment by center group interactions involving center 033 in studies 494 and 495, all patients enrolled in this center in Study 494 were excluded from efficacy but not safety analysis.

Table 3a: **Study 494 Center Groups**

CENTGP	# of Patients
001/007/009/013/014/015/027/029	75
002/004/005/006/021/022/025/033	62
003/012/016/019/020/023/024/031	79
008/010/011/017/026/028/030/032	73
Total	289

Table 3b: **Study 495 Center Groups**

CENTGP	# of Patients
001/002/005/018/ 028	64
003/009/013/026	49
004/012/016/020	36
006/017/019/024	41
007/023/025/027	47
008/010/014/030	44
011/021/022/031	46
Total	327

Table 3c: **Study 497 Center Groups**

CENTGP	# of Patients
001/004/009	38
002/015	26
003/005	15
006/018	14
007/025	17
008/012	16
010/014/017/029	44
011/013	19
016/022/027/028	35
019/020/027/028	28
024/031	13
Total	265

Categorical efficacy variables (i.e., responders based on zero full panic attacks, CGI Global Improvement) will be analyzed using logistic regression, allowing for center effects. The effect of adding treatment by center interaction into the model will be discussed. The effects of the covariates, age and baseline panic disorder severity, will be evaluated; other suitable covariates may also be investigated in additional analyses.
Adequacy of the model fit will be explored by inspecting plots of the Pearson residuals and deviance residuals. For each treatment group there is an odds of a patient being classed as a responder. The results will be presented in terms of odds ratios (i.e., the odds of the response on paroxetine relative to the odds of response on placebo). 95% confidence intervals for around the odds ratios will be provided.

Provided the underlying assumptions are satisfied, continuous efficacy (e.g., change from baseline in total number of full panic attacks) will be analyzed by analysis of variance and allowing for center effects. The effect of adding treatment by center interaction into the analysis will be assessed. The effects of the covariates, age and baseline panic disorder severity, will be evaluated; other suitable covariates may also be investigated in additional analyses. Results will be presented as the point estimate and 95% confidence interval for the difference between paroxetine and the placebo group. The assumptions of normality and homogeneity of variance will be assessed by inspection of normal probability plots and residual plots. If these assumptions are not met, appropriate non-parametric methods will be used.

The sponsor's results of LOCF data sets of Study 494 are reproduced in Table 4, Table 5.

Table 4
Study 494
Response to Treatment – Principal Efficacy Parameters
Excluding Center 033
Intention-To-Treat Population, Week 10 LOCF

Table 4a: **Percentage of Patients Free of Full Panic Attacks**

Paroxetine CR			Placebo			Pairwise Comparisons[a]	
n	%	N	n	%	N	Odds Ratio 95% CI	p-value
84	68.9	122	65	50.4	129	2.21 (1.289, 3.789)	0.004

[a] Statistical analysis adjusted for center group and covariates.

Table 4b: **Median Change from Baseline in Total Number of Full Panic Attacks**

Paroxetine CR				Placebo				Pairwise Comparisons	
med.	min	max	N	med.	min	max	N	median diff (95% CI)	p-value
-4	[illegible]		122	-3	[illegible]		128	-1 (-2, 0)	0.08

Table 4c: **Distribution of CGI Severity of Illness Scores**

CGI Severity of Illness Score	Paroxetime CR			Placebo			Pairwise Comaprisons[a]	
	n	%	N	n	%	N	Median Difference (95% CI)	p-value
normal, not at all ill	31	23.5	132	18	13.0	138		
borderline ill	28	21.2	132	35	25.4	138		
mildly ill	37	28.0	132	29	21.0	138		
moderately ill	27	20.5	132	37	26.8	138		
markedly ill	6	4.5	132	17	12.3	138		
severely ill	3	2.3	132	2	1.4	138		
among the most extremely ill	0	0.0	132	0	0.0	138		
Total	132	100	132	138	100	138	0 (-1, 0.0)	0.032

[a] Statistical analysis based on change from baseline in CGI Severity of Illness scores.

Table 5
Study 494
Response to Treatment – Additional Efficacy Parameters
Excluding Center 033
Intention-To-Treat Population, Week 10 LOCF

Parameter	Paroxetine CR			Placebo			Pairwise Comparison	
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff.[a] (95% CI)**	**p-value**
HAM-A total score	-10.0	0.86	115	-8.0	0.81	124	-2.0 (-4.1, 0.0)	0.052
% of day with anticipatory anxiety	-12.9	1.93	122	-9.2	1.82	128	-3.7 (-8.2, 0.7)	0.10
MSPS total fear score	-20.2	2.35	114	-15.2	2.21	124	-5.0 (-10.5, 0.5)	0.078
MSPS total avoidance score	-6.6	0.86	114	-5.4	0.81	123	-1.3 (-3.3, 0.8)	0.23
Median Change from Baseline	**Median**	**Min., Max.**	**N**	**Median**	**Min., Max.**	**N**	**Median Diff. (95% CI)**	**p-value**
Number of unexpected full panic attacks/2 wk	-1		122	-1		128	0 (0, 1)	0.56
Number of situational full panic attacks/2 wk	-3		122	-2		129	-1 (-2, 0)	0.003
Number of all panic attacks/2 wk	-11		122	-8		128	-3 (-6, 0)	0.021
Percentage of Patients	**n**		**N**	**n**		**N**	**Odds Ratio (95% CI)**	**p-value**
% with 1 or 2 on CGI Global Improvement item	94		132	72		136	2.30 (1.36, 3.90)	0.002

The sponsor's results of LOCF data sets of Study 495 and Study 497 are reproduced in Table 6 and Table 7, respectively.

Table 6
Study 495
Response to Treatment at Study Endpoint
(Week 10 LOCF Datasheet, Excluding Center 5)
Intention-to-Treat Population

	Paroxetine CR			Placebo			Pairwise Comparison	
Percentage of Patients	**n**	**%**	**N**	**n**	**%**	**N**	**Odds Ratio[a] (95% CI)**	**p-value**
% patients with zero full panic attacks	70	56.9	123	70	51.5	136	1.38 (.83, 2.32)	0.217
% with 1 or 2 on CGI Global Improvement item	82	61.7	133	60	42.0	143	2.31 (1.41, 3.78)	<.001
CGI Severity of Illness Score	**n**	**%**	**N**	**n**	**%**	**N**	**Median Diff (95% CI)**	**p-value**
normal, not at all ill	18	13.1	137	17	11.6	147		
borderline ill	35	25.5	137	15	10.2	147		

mildy ill	43	31.4	137	37	25.2	147	
moderately ill	22	16.1	137	52	35.4	147	
markedly ill	11	8.0	137	21	14.3	147	
severely ill	7	5.1	137	5	3.4	147	
among the most extremely ill	1	0.7	137	0	0.0	147	
Total	137	100	137	147	100	147	0 (-1, 0.0) 0.004
Median Change from Baseline in Frequency/2 Weeks	**Median**	**Min, Max**	**N**	**Median**	**Min, Max**	**N**	**Median Diff (95% CI)** **p-value**
Full panic attacks	-5	-1 [illegible] 4	123	-3	[illegible]	136	-2 (-4, -1) <.001
Situational full panic attacks	-2	-1	123	-2		136	-1 (-2.0, 0) 0.02
Unexpected full panic attacks	-2	-[illegible]	123	-1		136	-1 (-2.0, 0) 0.01
All panic attacks	-11	-1 [illegible]	123	-6		136	-4 (-8, -1) <.001
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff [a] (95% CI)** **p-value**
HAM-A total score	-9.4	0.86	112	-6.6	0.78	129	-2.7 (-4.7, -.76) 0.007
% of day with anticipatory anxiety	-14.7	1.89	122	-8.5	1.72	136	-6.2 (-10.49, -1.88) 0.005
MSPS total fear score	-19.9	2.35	114	-12.2	2.16	128	-7.7 (-13, -2.3) 0.005
MSPS total avoidance score	-7.1	0.86	114	-4.0	0.79	128	-3.0 (-5.0, -1.1) 0.003

Principal efficacy parameters are presented in italics.

[a] Statistical analysis adjusted for center group, age, gender, and baseline panic disorder severity.

[b] Statistical analyses based on change from baseline in CGI Severity of Illness scores.

Table 7

Study 497

Response to Treatment at Study Endpoint

(Week 10 LOCF Dataset)

Intention-to-Treat Population

	Paroxetine CR			**Placebo**			**Pairwise Comparison**
Percentage of Patients	**n**	**%**	**N**	**n**	**%**	**N**	**Odds Ratio[a] (95% CI)** **p-value**
% patients with zero full panic attacks	82	62.1	132	73	56.2	130	1.53 (0.89, 2.62) 0.127
% with 1 or 2 on CGI Global Improvement item	84	59.2	142	63	46.3	136	2.17 (1.29, 3.67) <.004
CGI Severity of Illness Score	**n**	**%**	**N**	**n**	**%**	**N**	**Median Diff (95% CI)** **p-value**
normal, not at all ill	27	18.8	144	15	11.0	136	
borderline ill	34	23.6	144	31	22.8	136	
mildy ill	36	25.0	144	31	22.8	136	
moderately ill	36	25.0	144	36	26.5	136	
markedly ill	8	5.6	144	19	14.0	136	
severely ill	3	2.1	144	4	2.9	136	
among the most extremely ill	0	0.0	144	0	0.0	147	
Total	144	100	144	136	100	136	0 (-1, 0.0) 0.004

Median Change from Baseline in Frequency/2 Weeks	Median	Min, Max	N	Median	Min, Max	N	Median Diff (95% CI)	p-value
Full panic attacks	-4		132	-3		130	-1 (-2, 0)	0.239
Situational full panic attacks	-2		132	-2		130	-1 (-1, 0)	0.066
Unexpected full panic attacks	-1		132	-2		130	0 (-1, 1)	0.980
All panic attacks	-9.5		132	-6		130	-3 (-6, 0)	0.028
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff [a] (95% CI)**	**p-value**
HAM-A total score	-9.4	0.86	112	-6.6	0.78	129	-2.7 (-4.83, -.53)	0.015
% of day with anticipatory anxiety	-11.5	1.72	132	-8.5	1.62	130	-3.0 (-7.33, -1.27)	0.166
MSPS total fear score	-18.6	2.14	127	-11.0	1.98	125	-7.6 (-12.87, -2.36)	0.005
MSPS total avoidance score	-5.8	0.80	126	-3.2	0.74	125	-2.5 (-4.53, -0.57)	0.012

Principal efficacy parameters are presented in italics.

[a] Statistical analysis adjusted for center group, age, gender, and baseline panic disorder severity.

[b] Statistical analyses based on change from baseline in CGI Severity of Illness scores.

V. SPONSOR'S CONCLUSIONS

The percentage of patients free of full panic attacks is the protocol-defined primary efficacy parameter. The following table shows the effect of Paroxetine CR on the percentage of patients free of full attacks for the three studies (Vol. 1.002, p. 127).

Table 8

Percentage of Patients Free of Full Panic Attacks Per Two Weeks
Studies 494, 495 and 497
ITT Population

Two Week Period	Paroxetine CR n	%	N	Placebo n	%	N	Paroxetine CR vs. Placebo[a] Odds Ratio (95 % CI)	p-value
Study 494 (Excluding Center 033)								
Week 10 Observed Case	69	78.4	88	60	58.8	102	2.85 (1.44, 5.61)	0.003
Week 10 Endpoint	84	68.9	122	65	50.4	129	2.21 (1.29, 3.79)	0.004
Study 495 (Excluding Center 005)								
Week 10 Observed Case	57	71.3	80	55	56.1	98	2.40 (1.22, 4.72)	0.012
Week 10 Endpoint	70	56.9	123	70	51.5	136	1.38 (0.83, 2.32)	0.217
Study 497								
Week 10 Observed Case	66	69.5	95	63	65.6	96	1.43 (0.72, 2.86)	0.306
Week 10 Endpoint	82	62.1	132	73	56.2	130	1.53 (0.89, 2.62)	0.127

[a] Statistical analysis adjusted for center group, age group, gender, and severity of panic disorder at baseline.

In Study 494, treatment with paroxetine CR resulted in a greater percentage of patients at Week 10 Endpoint who were free of full panic attacks compared to placebo. For patients who completed the 10-week Treatment Phase in Study 495, the odds of responding to paroxetine CR increased to 2.8-fold that of placebo.
Study 495 and 497 did not demonstrate a statistically or clinically significant effect of paroxetine CR on the percentage of patients free of full panic attacks at Week 10 Endpoint (Vol. 1.002, p. 126).
The overall interpretation of the results of Study 494 demonstrate that, treatment with paroxetine CR results in a significant decrease in the frequency of panic attacks (Vol. 1.041, p.07).

The following table shows the effects of paroxetine CR on the median change from baseline in the number of full panic attacks at Week 10 Endpoint and for observed cases at Week 10.
In study 495, treatment with paroxetine CR resulted in a significantly greater reduction in panic attack frequency compared to placebo, with the median difference being 2 full panic attacks for all patients (i.e., at Week 10 Endpoint), and 3 full attacks for patients who completed the 10-week Treatment Phase. Study 494 and 497 did not demonstrate a statistically significant effect of paroxetine CR on the change in number of full panic attacks at Week 10 Endpoint or at Week 10 for observed cases, although paroxetine CR was numerically superior to placebo.

Table 9
Median Baseline and Reductions from Baseline in Number of Full Panic Attacks Per Two Weeks
ITT Population

Two Week Period	Paroxetine CR Median	Min, Max	N	Placebo Median	Min, Max	N	Paroxetine CR vs. Placebo Median Diff (95 % CI)	p-value
Study 494 (Excluding Center 033)								
Baseline	5		122	5		128		
WK 10 OC	-5		88	-3		102	-1, (-2, 0)	0.072
LOCF Endpoint	-4		122	-3		128	-1, (-2, 0)	0.08
Study 495 (Excluding Center 005)								
Baseline	7		123	5		136		
WK 10 OC	-6		80	-3		98	-3, (-5, -1)	<0.001
LOCF Endpoint	-5		123	-3		136	-2, (-4, -1)	<0.001
Study 497								
Baseline	5		122	5		128		
WK 10 OC	-4		95	-3		96	-1, (-2, 0)	0.088
LOCF Endpoint	-4		132	-3		130	-1, (-2, 0)	0.239

Study 494 demonstrated significant effects of paroxetine CR on the change in CGI Severity of Illness score at Week 10 Endpoint, with the reductions for paroxetine CR being statistically superior to placebo (median difference between treatment groups=0, 95% confidence interval –1 to 0, p-value=0.032. See Table 3c). Compared to all treated patients (i.e., at Week 10 Endpoint), statistically significant improvement relative to

placebo was also noted for paroxetine CR-treated patients who completed the 10-week Treatment Phase (median difference=0, 95% confidence interval –1 to 0, p-value=0.007). Study 495 also demonstrated statistically significant effects of paroxetine CR on the changes in CGI Severity of Illness score at Week 10 Endpoint (median difference=0, 95% confidence interval –1 to 0, p-value=0.004, Table 5) and at Week 10 for observed cases (median difference=-1, 95% confidence interval –1 to –1, p-value<0.001), with the reductions for paroxetine CR being statistically superior to placebo. Study 497 did not demonsrtate statistically significant effects of paroxetine CR on change in CGI Severity of Illness score at Week 10 Endpoint and at Week 10 for observed cases, although reductions in score with paroxetine CR tended to be numerically superior to placebo.

Secondary Variables

1. Change in Percentage of Day Engaged in Anticipatory Anxiety

The following table presents a summary of the Baseline and mean change from Baseline in the percentage of day spent with anticipatory anxiety at study endpoint for ITT popoulation by 2-week period and treatment group for Study 495.

Table 10

Baseline and Mean Change from Baseline in Percentage of Day with Anticipatory Anxiety Excluding Center 005

Study 495: ITT Population

Two Week Period	Paroxetine CR			Placebo			Pairwise Comparison Paxil CR vs. Placebo	
	Mean	SE	N	Mean	SE	N	Mean (95% CI)	p-value
Baseline	29.0	2.10	122	24.5	1.79	136		
Weeks 9 and 10	-17.3	2.10	80	-8.8	1.86	98	-8.6 (-13.36, -3.80)	<.001
70% Endpoint	-13.6	1.82	122	-8.0	1.65	136	-5.6 (-9.79, -1.49)	0.008
Week 10 Endpoint	-14.7	1.89	122	-8.5	1.72	136	-6.2 (-10.49, -1.88)	0.005

The sponsor observed that at Week 10 Endpoint the mean reduction in percentage of day engaged in anticipatory anxiety from baseline is 14.7% in the paroxetine CR treatment group versus 8.5% in the placebo treatment group. The mean difference in reduction in percentage of day engaged in anticipatory anxiety of –6.2% for paroxetine CR relative to placebo is statistically significant (p = 0.005). At 70% Endpoint and at Week 10 OC, statistically significant differences in the mean reduction in percentage of day with anticipatory anxiety for paroxetine CR versus placebo were also obtained.

2. Change in Marks-Sheehan Phobia Scale Total Fear Score

The following are obtained from the data for Study 495. At Week 10 Endpoint the mean reduction in MSPS total score (Maximum total score, 140) from Baseline was 19.9 in the paroxetine CR treatment group versus 12.2 in the placebo treatment group. The mean difference in MSPS total fear score of –7.7 for paroxetine CR relative to placebo was statistically significant at p=0.005 (95% confidence interval of –13.0 to –2.3). Results obtained for the Week 10 observed cases data set were very similar to results obtained for the Week 10 Endpoint.

3. Change in Marks-Sheehan Phobia Scale Total Avoidance Score

The following is observed for Study 495. At Week 10 Endpoint the mean reduction in MSPS total avoidance score (Maximum total score, 56) from Baseline was 7.1 in the paroxetine CR treatment group versus 4.0 in the placebo treatment group. The mean difference in MSPS total avoidance score of –3.0 for paroxetine CR relative to placebo is statistically significant at p=0.003 (95% confidence interval of –5.0 to –1.1). Results obtained for the Week 10 OC data set were similar to results obtained for the Week 10 Endpoint.

VI. REVIEWER'S DATA ANALYSES AND COMMENTS

Demographic characteristics, as seen in Table 2 on page 4, were similar between treatment groups within a study and between studies. Proportions of white subjects in Study 494, 495 and 497 are 0.94, 0.90 and 0.78, respectively. Descriptive statistics for the total baseline full panic attacks are presented in Table 11 below..

Table 11

Total Baseline Full Panic attacks

	Parexotine CR					Placebo				
	N	Mean	SD	Min.	Max.	N	Mean	SD	Min.	Max.
Study 494	122	9.918	24.06			129	11.07	18.52		
Study 495	139	11.52	14.91			151	8.9	10.36		
Study 497	132	8.96	11.41			130	8.65	12.11		

ANALYSIS OF PROTOCOL DEFINED PRIMARY EFFICACY VARIABLE.

1. Main Results

The percentage of patients who achieved zero full panic attack per two weeks at study endpoint is the protocol-defined primary efficacy variable. It is analyzed using logistic regression without any covariates. That is, the model considered is

$$\text{Logit}(p) = \alpha + \beta_1 TRT,$$

where p is the probability of zero full panic attacks and TRT =1 for paroxetine and TRT = 0 for placebo. The results are:

Table 12

Logistic Model Response = Treatment

	LOCF			OC		
	Odds Ratio	p-value *	c	Odds Ratio	p-value *	c
[a]Study 494	2.177	0.0031	0.596	2.542	0.0045	0.612
[b]Study 495	1.245	0.3806	0.527	1.938	0.0388	0.580
Study 497	1.281	0.3262	0.531	1.192	0.5702	0.522

TRT=Treatment. *$H_0 : \beta_1 = 0$. [a] Center 033 is excluded. [b] Center 005 is excluded.

The value of c, the predictive power of the model, is moderate in all six analyses. Each study contains observations that either are not well explained by the model or are extreme points in the design space or cause instability in the coefficient of treatment. The results of Study 494 may be interpreted as follows.

Study 494 LOCF Week 10 endpoint data indicate that the odds of responding to paroxetine CR increased to 2.2-fold that of placebo. The model based estimates of proportions of patients with no full panic attacks under placebo and paroxetine CR are 0.504 and 0.688, respectively. For patients who completed the 10-week treatment in Study 494, the odds of responding to paroxetine CR increased to 2.54-fold that of placebo. The model based estimates of proportions of zero full panic attacks under placebo and Paroxetine CR are 0.588 and 0.784, respectively. For patients who completed the 10-week treatment in Study 495, the odds of responding to paroxetine CR increased to 1.25-fold that of placebo. The model based estimates of proportions of zero full panic attacks under placebo and Paroxetine CR are 0.56 and 0.71, respectively.

The results of the logistic regression analysis that includes Centers 033 and 005 are:

Table 13

Logistic Model Response = Treatment (No Center Excluded)

	LOCF			OC		
	Odds Ratio	p-value *	c	Odds Ratio	p-value *	c
[a]**Study 494**	2.387	0.0008	0.607	2.882	0.0011	0.626
[b]**Study 495**	1.878	0.0084	0.578	3.347	0.0001	0.643

*$H_0 : \beta_1 = 0$.

Inclusion of Center 005 in Study 495 OC data makes TRT highly significant (p-value = .0001). For patients who completed the 10-week treatment in Study 495, the odds ratio of responding to paroxetine CR increased to 3.3-fold that of placebo. In the Study 495-LOCF case, TRT turns out to be significant. These contradict the earlier results of the analysis without Center 005.

2. Subgroups, Interaction and Covariates

Since more than 90% of the patient populations in Study 494 and 495 are white, RACE is not considered as a factor in this study.

Sex

Table 14a and Table 14b contain sex-wise observed percentages of zero full panic attacks under the two treatment groups for Study 494 and Study 495, respectively. The difference between the percentages is also included.

Table 14a
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR - Placebo

Sex	Paroxetine CR	Placebo	Difference
Male	66.07 (n = 56)	53.45 (n = 58)	12.62 (n = 114)
Female	72.86 (n = 70)	45.95 (n = 74)	26.91 (n = 144)
Total	(n = 126)	(n = 132)	(n = 258)

Table 14b
Study 495
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR - Placebo

Sex	Paroxetine CR	Placebo	Difference
Male	61.22 (n = 49)	42.11 (n = 57)	19.11 (n = 106)
Female	62.22 (n = 90)	48.94 (n = 94)	13.28 (n = 184)
Total	(n = 139)	(n = 151)	(n = 290)

There seems to be no difference in treatment effects between males and females.

Age-group
Age-group wise observed percentage of zero full panic attacks for Study 494 and Study 495 are shown in Table 15a and Table 15b, respectively. The difference = paroxetine-placebo of percentage is also shown.

Table 15a
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR – Placebo

Age-group	Paroxetine	Placebo	Difference
18-24	60.00 (n = 5)	30.77 (n = 13)	29.23 (n = 18)
25-34	67.39 (n = 46)	52.38 (n = 42)	15.01 (n = 88)
35-44	66.67 (n = 36)	47.83 (n = 46)	18.84 (n = 82)
45-54	76.67 (n = 30)	60.87 (n = 23)	15.80 (n = 53)
> 54	77.78 (n = 9)	37.50 (n = 8)	40.28 (n = 17)
Total	(n = 126)	(n = 132)	(n = 258)

Table 15b
Study 495
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR – Placebo

Age-group	Paroxetine	Placebo	Difference
18-24	63.16 (n = 19)	40.91 (n = 22)	22.25 (n = 41)
25-34	65.85 (n = 41)	51.92 (n = 52)	13.93 (n = 93)
35-44	55.56 (n = 45)	47.37 (n = 38)	8.19 (n = 83)
45-54	66.67 (n = 27)	44.44 (n = 27)	22.23 (n = 54)
> 54	57.14 (n = 7)	33.33 (n = 12)	23.81 (n = 19)
Total	(n = 139)	(n = 151)	(n = 290)

It appears that paroxetine CR is effective in patients of all age-groups.

Center Effects

Center-wise observed percentages of zero full panic attacks for both treatment groups for study 494 are presented in Table 16 below. The difference between the percentages of treatment groups is also included. It may be noted that the significance of the effect of paroxetine CR is not attributed to any one or to a fewer number of centers.

Table 16
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR- Placebo

Center	Paroxetine % (n)	Placebo % (n)	Difference %
029	50.0 (2)	100.0 (1)	-50.00
012	66.67 (3)	100.0 (3)	-33.33
025	66.67 (3)	33.33 (3)	-33.33
024	60.0 (5)	75.0 (4)	-15.0
0.31	50.0 (2)	66.67 (3)	-16.67
005	66.68 (3)	66.67 (3)	00.00
009	100.0 (1)	100.0 (1)	00.00
013	50.0 (6)	50.0 (8)	00.00
028	75.0 (4)	75.0 (4)	00.00
030	100.0 (1)	100.0 (1)	00.00
010	00.0 (1)	- (0)	- --
016	66.67 (6)	57.14 (7)	09.53
026	50.0 (8)	40.0 (5)	10.0
001	85.71 (7)	71.43 (7)	14.28
004	75.0 (4)	59.0 (5)	15.0

007	75.0 (4)	60.0 (5)	15.0
017	40.0 (5)	25.0 (4)	15.0
023	50.0 (2)	33.33 (3)	16.67
027	50.0 (6)	33.33 (6)	16.67
020	100.0 (5)	80.0 (5)	20.0
008	77.78 (9)	54.55 (11)	23.23
032	75.0 (4)	50.0 (2)	25.0
011	100.0 (2)	66.67 (3)	33.33
002	100.0 (3)	60.0 (5)	40.00
019	66.67 (9)	22.22 (9)	44.45
003	50.0 (2)	0.0 (2)	50.00
015	100.0 (2)	33.33 (3)	66.67
006	75.0 (4)	0.0 (4)	75.00
021	75.0 (4)	0.0 (5)	75.00
022	100.0 (3)	25.0 (4)	75.0

ANALYSIS OF PROTOCOL DEFINED SECONDARY EFFICACY VARIABLES

This reviewer was requested by the medical officer to study the variables- (i) change in percentage of day engaged in anticipatory anxiety, (ii) change in MSPS total fear score, and (iii) change in MSPS total avoidance score. The treatment groups were compared using one-way analysis of variance. The results for Study 494 are summarized in the following table.

Table 17
p-values for ANOVA model y = TRT
Study 494

Response Variable y	**WK 10 LOCF**	**WK 10 OC**
Change in percentage of day engaged in anticipatory anxiety	0.0829	0.1936
Change in Marks-Sheehan Phobia Scale total fear score	0.1029	0.3702
Change in Marks-Sheehan Phobia Scale total avoidance score	0.3236	0.7363

Study 494 did not demonstrate a significant difference between paroxetine CR and placebo with respect to these three secondary efficacy variables. However, Study 495 showed that, for each one of the secondary efficacy variables, the mean difference (Paxil CR-Placebo) to be statistically significant. The 95% confidence intervals for the mean difference (Paxil CR-Placebo) and p-values of the one-way ANOVA model for Study 495 are as follows.

Table 18
95% Confidence Interval and p-values for ANOVA model y = TRT
Study 495

Response Variable y	**WK 10 LOCF**	**WK 10 OC**

Response Variable y	WK 10 LOCF	WK 10 OC
Change in percentage of day engaged in anticipatory anxiety	(-10.32, -7.796) 0.0052	(-13.86, -4.45) 0.0002
Change in Marks-Sheehan Phobia Scale total fear score	(-12.55, -2.04) 0.0067	(-16.28, -10.07) 0.0016
Change in Marks-Sheehan Phobia Scale total avoidance score	(-4.74, -2.82) 0.0043	(-6.1, -3.81) 0.0013

VII. OVERALL CONCLUSIONS

- In Study 494, treatment with paroxetine CR resulted in a significantly greater percentage of patients at Week 10 Endpoint who were free of full panic attacks compared to placebo.
- The results of Study 495 are supportive: The Study 495 OC data demonstrated a statistically significant effect of paroxetine CR on the percentage of patients free of full panic attacks. In addition, The results of Study 495 showed that paroxetine CR to be statistically significantly superior to placebo with respect to (i) change in percentage of day engaged in anticipatory anxiety, (ii) change in MSPS total fear score, and (iii) change in MSPS total avoidance score.
- Study 497 did not demonstrate a statistically significant effect of paroxetine CR on the percentage of patients free of full panic attacks at Week 10 Endpoint.

/S/

Kallappa M. Koti
Mathematical Statistician

Concur:
Dr. Kun Jin /S/

Dr. George Chi /S/

CC:
Arch. NDA 20-982
HFD 120
HFD-120 / Dr. Katz
HFD-120 / Ms. Homonnay
HFD-120 / Dr. Laughren
HFD-120 / Dr. Dubitsky
HFD-710 / Dr. Chi
HFD-710 / Dr. Jin
HFD-710 / Dr. Koti
HFD-710 / Chron