CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW

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Statistical Review and Evaluation

NDA #:	20031/S-026
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paxil Tablets
Indication:	Generalized Anxiety Disorder
Date received:	4-28-2000
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1. INTRODUCTION

Generalized Anxiety Disorder (GAD) has been recognized as a distinct Axis I anxiety disorder since its introduction in the third edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association in 1980. GAD is characterized by excessive anxiety and worry, occurring in more days than not for at least six months, about a number of events or activities such as school or work performance. Epidemiology studies have shown that the lifetime prevalence of DSM-defined GAD is 5.1% in the U.S. and between 1.9 and 5.4% in various regions of Europe. GAD primarily affects females, and exhibits a high degree of chronically.

Effective pharmacological treatment for GAD has been demonstrated in controlled clinical trials with benzodiazepines, buspirone, and venlafaxine, but the clinical utility of these agents has been limited. Interest has therefore developed to explore the potential utility of other pharmacotherapies to treat GAD, specifically the selective serotonin uptake inhibitors. Paroxetine (Paxil®) is a selective serotonin reuptake inhibitor approved for the treatment of depression, Panic Disorder, Obsessive Compulsive Disorder (OCD) and Social Anxiety Disorder. This submission deals with the the sponsor's completed clinical program that is supposed to demonstrate that paroxetine is safe and effective in the treatment of Generalized Anxiety Disorder.

2. DESIGN AND EFFICACY

The use of paroxetine in the treatment of GAD is supported by the findings from three randomized, parallel-group, double-blind, placebo-controlled multi-center studies, identified as Studies 637, 641 and 642. These three trials included an 8-week treatment phase, and were initiated in the autumn of 1998; all were completed in 1999. In addition, there is an ongoing study assessing relapse in GAD patients. This study, identified as protocol 646, is being conducted in Europe.

2.1 Methodology

Each of the three completed studies 637, 641 and 642 were multi-center, randomized, double-blind, placebo controlled parallel group studies of outpatients with a predominant psychiatric diagnosis of Generalized Anxiety Disorder.

At entry all patients were given a physical examination to include a medical history, clinical laboratory assessments and an ECG. Each patient's psychiatric status and history was evaluated in a formal interview that included the completion the Mini International Neuropsychiatric Interview (MINI). Eligible patients underwent a one-week, single blind, run-in phase to further evaluate their suitability for study, and to identify placebo responders. Following the run-in phase, patients who continued to meet the inclusion and exclusion criteria were randomized to receive paroxetine or placebo. Individuals diagnosed with comorbid Axis I disorders and those with significant depressive symptomatology were denied entry. However, patients with comorbid Dysthymia were permitted to enter the trials as long as it was not the predominant diagnosis.

In study 641, a fixed dose design was employed in which patients were randomized in a 1:1:1 ratio to receive either 20 mg/day of paroxetine, 40 mg/day of paroxetine or placebo. Paroxetine patients initiated treatment at 10 mg/day and increased their dose in weekly increments of 10 mg until they reached their assigned dose.

A schedule of study assessments and procedures is presented in Table 2.1.1 below.

Table 2.1.1: Outline of Study Procedures for 29060/641

	Scrn Visit Day	**Base Line Visit Day 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 8**
Screen/Baseline Evaluation								
Informed Consent	X							
MINI	X							
GAD Criteria (DSM-IV)	X							
Inclusion/Exclusion Criteria	X	X						
Patient Randomization		X						
Efficacy Parameters								
HAM-A	X	X	X	X	X	X	X	X
CGI (Severity of Illness)		X	X	X	X	X	X	X
CGI (Global Improvement)			X	X	X	X	X	X
HAD		X	X	X	X	X	X	X
COVI Anxiety Scale		X				X	X	X
Sheehan Disability Scale (SDS)		X				X	X	X
MADRS	X	X						X
Quality of Life (EuroQol)		X						X
Dispense Study Medication								X

Study 642 has an extra visit at Week 5.

In studies 637 and 642, a flexible dose design was employed in which patients were randomized in a 1:1 ratio to receive either paroxetine in a range of 20-50 mg once daily, or placebo. In study 637, patients initiated paroxetine treatment at 20 mg/day, while in study 642, the starting dose of paroxetine was 10 mg/day. Both trials permitted doses up to 50 mg/day in weekly increments of 10 mg.

All three protocols required a taper phase at the completion of the 8-week treatment period. During this phase, the paroxetine patients who were receiving doses of 30 mg or higher were titrated down at decrements of 10 mg/week to the 20 mg regimen. The taper phase was followed by a follow-up phase of 2-6 weeks duration. In study 641, patients assigned to the 20 mg regimen remained on the 20 mg daily regimen during the taper phase, in studies 637 and 642 patients receiving 20 mg per day did not participate in the taper phase.

2.2 Efficacy Variables

The outcome measures employed were identical in all three studies. Each protocol defined a single primary efficacy measure, the mean change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) Total score. The HAM-A is a reliable and validated measure of anxiety that is commonly employed in anxiety studies. Details are provided in Appendix 1.

The protocol described several secondary and global assessments of improvements as well as various symptom rating scales, the COVI, HAD and MADRS. Also defined by the protocols were assessment of the target symptoms, (HAM-A psychic anxiety and tension items), a functional disability scale (Sheehan Disability Scale), and health and economic and quality of life instruments (Job status and EURoQol).

COVI anxiety scale measures severity of anxiety. In particular, this secondary efficacy variable is an assessment of to what extent does the subject evidence anxiety in verbal report, behavior and somatic complaints. Each of these three components are evaluated in to five categories: 1=Not at all; 2=Some what; 3=Moderately; 4=Considerably; 5= Very much. The variable COVI ranges from 3 to 15.

Another secondary efficacy variable is the Clinical Global Impression (CGI) – Global Improvement score. This score was an answer to: Compared with his/her condition on admission to the study, how much has he/she changed? There were eight possible answers/scores: 0=Not assessed; 1=Very much improved; 2=Much improved; 3=Minimally improved; 4=No change; 5=Minimally worse; 6=Much worse; 7=Very much worse.

2.3 Statistical Consideration

The primary comparison of interest for efficacy was paroxetine versus placebo in the intent to treat population at the endpoint. The change from baseline of efficacy variables was analyzed by the general linear models (SAS/GLM) procedure. Type III sums of squares were used. Non-parametric methods were used for treatment comparisons when the data suggested that the underlying assumptions of the proposed parametric analysis were violated.

Categorical efficacy variables were analyzed, via categorical modeling procedure (CATMOD) of the SAS System or Cochran-Mantel-Haenszel (CMH) using the FREQ procedure of the SAS System.

All hypotheses were tested at an overall two-tailed alpha level of 0.05. In the fixed dose study, 641, Dunnett's test was used to maintain the overall experiment-wise error rate. Testing of hypothesis of significance of interactions (e.g., treatment-by-site, treatment-by-covariate) was performed at an alpha level of 0.1.

The intent to treat (ITT) population for analyses included all patients who received any double-blind medication and for who at least one valid post-baseline efficacy evaluation was conducted. This population constituted the primary population of interest for efficacy. Patients were included in the population regardless of whether the entry criteria were fulfilled or the protocol was otherwise violated.

Two data sets were used to analyze the efficacy results: last observation carried forward data set (LOCF) and observed case data set (OC). In the LOCF data set, the last available on-therapy (treatment phase) observation for each patient was used to estimate missing data points. In the OC data set, efficacy data were evaluated only for the time point when they were collected; i.e., no data were carried forward to estimate missing data points. The LOCF data set was thus generated from the OC data set.

3. SPONSOR'S ANALYSES AND CONCLUSIONS

3.1 Sponsor's data analyses results

The change from baseline of efficacy variables was analyzed by the general linear models procedure, in SAS version 6.12. Type III sums of squares were used. About the model choics, the sponsor writes (for example, in BRL-029060/RSD-101336/1/CPMS-641): The statistical model adopted for all change from baseline efficacy variables was determined by analyzing HAM-A Total at endpoint. A full model was tested using effects for treatment, investigational site, and treatment-by-site interaction. The interaction term was not significant and therefore dropped from the final analysis model. The model determined from the assessment at endpoint was used for all other time-points. All other change from baseline secondary efficacy variables were analyzed via the model determined by HAM-A Total at endpoint. The sponsor's results are reproduced in Tables 3.1.1 through 3.1.3. The sponsor claims that the *mean change* shown in these tables is the adjusted mean. These results are based on the analysis of variance with factors site and treatment without the interaction term.

Table 3.1.1*: **HAM-A Total Score Mean Baseline and Mean Change from Baseline (All Studies) (ITT Population)**

Study 641 (Fixed Dose)

	Placebo			20 mg			40 mg		
	N	Mean Change	SE	N	Mean Change	SE	N	Mean Change	SE
Baseline	180	23.9	0.3	188	23.8	0.3	197	23.3	0.3
LOCF Wk 8	180	-9.6	0.7	188	-12.5	0.6	197	-12.2	0.6
OC Wk 8	140	-10.7	0.7	141	-13.8	0.6	146	-13.9	0.6

* Source: NDA Supplement for Efficacy, Volume 001 (p. 000085)

Table 3.1.1 continued..

Study 641: Treatment Difference

	20 mg vs. Placebo		40 mg vs. Paroxetine	
	Difference (CI)+	**p-value**	**Difference (CI)+**	**p-value**
Baseline	-0.0 (-0.8, 0.7)	0.901	-0.5 (-1.3, 0.2)	0.103
LOCF Wk 8	-2.9 (-4.6, -1.2)	< 0.001*	-2.6 (-4.0, -0.6)	0.008*
OC Wk 8	-3.0 (-4.8, -1.2)	< 0.001*	-2.5 (-4.3, -0.7)	0.006*

Table 3.1.1 continued...

Study 642 (Flexible Dose)

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	**Mean**	**SE**	**N**	**Mean**	**SE**	**Diff (CI)++**	**p-value**
Baseline	163	23.6	0.3	161	23.9	0.3	0.3 (-0.5, 1.0)	0.472
LOCF Wk 8	163	-9.5	0.7	161	-11.8	0.7	-2.3 (-4.0, -0.6)	0.008*
OC Wk 8	133	-10.7	0.8	127	-13.3	0.8	-2.5 (-4.3, -0.7)	0.006*

Study 637 (Flexible Dose)

	Placebo			Paroxetine			Placebo vs. Paroxetine	
	N	**Mean**	**SE**	**N**	**Mean**	**SE**	**Diff (CI)++**	**p-value**
Baseline	183	25.9	0.4	181	26.0	0.4	0.1 (-0.7, 1.0)	0.7888
LOCF Wk 8	183	-11.3	0.8	181	-12.4	0.8	-1.1 (-2.8, 0.5)	0.171
OC Wk 8	163	-12.5	0.8	149	-14.8	0.8	-2.3 (-3.9, -0.7)	0.005*

Table 3.1.2*: **Overview of Secondary Efficacy Variables at Week 8 LOCF (ITT Population)**

Fixed Dose Study 641

Secondary variable	**20 mg**			**40 mg**		
	Diff	(C.I)	p-value	Diff	(C.I)	p-value
Mean Change in HAM-A Item 1[+]	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.7, -0.2)	< 0.001
Mean Change in HAM-A Item 2[++]	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.8, -0.3)	< 0.001
Mean CGI Severity Score	-0.5	(-0.8, -0.3)	< 0.001	-0.5	(-0.8, -0.2)	< 0.001
Responder CGI Score 1 & 2	16.1	(4.5, 27.8)	0.002	22.5	(11.0, 33.9)	<0.001
Mean Change in COVI	-1.0	(-1.6, -0.4)	<0.001	-0.9	(-1.5, -0.3)	<0.001
[+]Item 1: Anxiety Item; [++]Item 2: Tension Item						

* Source: NDA Supplement for Efficacy, Volume 001 (p. 000085)

Table 3.1.3: **Overview of Secondary Efficacy Variables at Week 8 LOCF (ITT Population)**

Flexible Dose Studies

Secondary variable	Study 642			Study 637		
	Diff	(C.I)	p-value	Diff	(C.I)	p-value
Mean Change in HAM-A Item 1*	-0.4	(-0.6, -0.2)	0.001	-0.3	(-0.5, -0.1)	0.041
Mean Change in HAM-A Item 2**	-0.3	(-0.5, -0.1)	0.005	-0.2	(-0.4, 0.0)	0.071
Mean CGI Severity Score	-0.3	(-0.5, 0.0)	0.042	-0.3	(-0.5, 0.0)	0.027
Responder CGI Score 1 & 2	14.9	(4.0, 25.7)	0.007	13.3	(3.1, 23.4)	0.011
Mean Change in COVI	-0.6	(-1.2, 0.0)	0.058	-0.5	(-1.0, 0.0)	0.059
*Item 1: Anxiety Item; **Item 2: Tension Item						

3.2 Sponsor's Efficacy Summary and Conclusions

In summary, the results from these well-controlled clinical trials provide convincing evidence that paroxetine is effective in the treatment of Generalized Anxiety Disorder. Collectively the results derived from the primary and secondary measures clearly demonstrate that the effects of paroxetine are robust and clinically meaningful. In addition, the results allow clear recommendation for the dosing of paroxetine in the treatment of Generalized Anxiety Disorder.

4. REVIEWER'S ANALYSES AND COMMENTS

The protocol defined the primary efficacy variable as the change from baseline in the total HAM-A score at the week 8 endpoint for all three studies. Technically, HAM-A Total score ranges from 0 to 56. Lower HAM-A Total score means that the subject is close to *normal*. The protocol defined primary efficacy variable- change from baseline in the Week 8 HAM-A Total score which is abbreviated as HMA_DTOT, as used in this review, is

HMA_DTOT = Week 8 HAM-A Total - Baseline HMA-A Total .

Analysis of covariance (ANCOVA) that includes the terms treatment and site is the protocol specified method of analysis for all three studies.

4.1 Study 641- Fixed dose study

Demographics

The LOCF population of this study consisted of 314 (55.6%) females and 251 (44.4%) males. There were 476 (84.2%) Caucasians, 26 (4.6%) Blacks, 10 (1.8%) Orientals. The remaining 53 (9.4%) belonged to other races. The youngest of these patients was 18 years old and the oldest was 74. The average age was 40.5 years.

Baseline comparison

- The data from Baseline Visit contained 162, 172 and 179 observations on the HAM-A Total score under placebo, Paxil 20 mg and Paxil 40 mg groups, respectively. The

mean baseline HAM-A Totals for placebo, 20 mg and 40 mg of paroxetine were 24.42, 24.06 and 23.92, respectively. One way analysis of variance indicated that there is no significant differences among these three treatment groups (p-value = 0.4197).

- One-way analysis of variance on the baseline HAM-A Total indicated that the three treatment groups- placebo, paroxetine 20mg and paroxetine 40mg are not significantly different (p-value = 0.404). The data from Baseline Visit contained 185 and 187 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.914) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT

LOCF analysis

The LOCF data contain a total of 565 observations. Of these 565, the treatment groups placebo, Paxil 20 mg, and Paxil 40 mg had 180, 188 and 197 observations, respectively. The SAS output for the analysis of variance model on the primary efficacy variable that includes the terms for treatment and site is presented below. The data provide sufficient evidence to claim that each of the two paroxetine groups is statistically significantly different from placebo and that the two paroxetine- groups 20 mg/day and 40 mg/day are not significantly different with respect to the change from baseline in the Week 8 HAM-A Total scores. The LOCF observed means of the protocol defined primary efficacy variable for placebo, paroxetine 20 mg and paroxetine 40 mg are –9.74, -12.56 and –12.23, respectively.

SAS OUTPUT: STUDY 641- LOCF DATA

General Linear Models Procedure

Dependent Variable: HMA_DTOT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	4170.8230165	94.7914322	1.80	0.0017
Error	520	27441.0884879	52.7713240		
Corrected Total	564	31611.9115044			

R-Square	C.V.	Root MSE	HMA_DTOT Mean
0.131938	-62.90236	7.2643874	-11.548673

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	42	3326.6346188	79.2055862	1.50	0.0251
TRT	2	861.1286804	430.5643402	8.16	0.0003

General Linear Models Procedure
Least Squares Means

TRT	HMA_DTOT LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
0	-9.7362504	1	.	0.0002	0.0010
20	-12.5621739	2	0.0002	.	0.6592
40	-12.2317917	3	0.0010	0.6592	.

OC analysis

The OC data contain a total of 427 observations on the protocol defined primary efficacy variable.. Of these 427, the treatment groups placebo, Paxil 20 mg, and Paxil 40 mg had 180, 188 and 197 observations, respectively. The SAS output for the analysis of variance model that includes the terms for treatment and site is presented below. The data provide sufficient evidence to claim that each of the two paroxetine groups is statistically significantly different from placebo and that the two paroxetine- groups 20 mg/day and 40 mg/day are not significantly different with respect to the change from baseline in the Week 8 HAM-A Total scores. The adjusted means of the primary efficacy variable for placebo, paroxetine 20 mg and 40 mg are –11.0, -13.94 and –14.06, respectively.

SAS OUTPUT: STUDY 641- OC DATA
General Linear Models Procedure

Dependent Variable: HMA_DTOT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	4632.4176899	105.2822202	2.44	0.0001
Error	382	16475.3434342	43.1291713		
Corrected Total	426	21107.7611241			

R-Square	C.V.	Root MSE	DIFF Mean
0.219465	-50.72773	6.5672804	-12.946136

Source	DF	Type III SS	Mean Square	F Value	Pr > F
BLOCK	42	3792.9175351	90.3075604	2.09	0.0002
TRT	2	811.1196013	405.5598006	9.40	0.0001

General Linear Models Procedure
Least Squares Means

TRT	DIFF	Pr > |T| HO: LSMEAN(i)=LSMEAN(j)		
	LSMEAN	i/j 1	2	3
0	-10.9969062	1 .	0.0003	0.0001
20	-13.9394710	2 0.0003	.	0.8828
40	-14.0561945	3 0.0001	0.8828	.

Secondary efficacy variable HMA_DIT1
LOCF analysis

HMA_DIT1 is the change from baseline in the Week 8 Hamilton Rating Scale Item 1 (Anxiety Item). The LOCF data contain 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms treatment and site yields adjusted means of –0.93, -1.46 and –1.40, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value < 0.001). There is no significant difference between the two paroxetine groups- 20 mg and 40 mg (p-value = 0.547).

Secondary efficacy variable HMA_DIT1
OC analysis

The OC data contain 140, 141 and 146 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms treatment and site yields adjusted means of –1.13, -1.63 and –1.63, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value = 0.0001). There is no significant difference between the two paroxetine groups- 20 mg and 40 mg (p-value = 0.9906).

Secondary efficacy variable HMA_DIT2

LOCF analysis

HMA_DIT2 is the change from baseline in the Week 8 Hamilton Rating Scale Item 2 (Tension Item). The LOCF data contain 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –0.89, -1.42 and –1.42, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value < 0.001). There is no significant difference between the two paroxetine groups (p-value = 0.976).

Secondary efficacy variable HMA_DIT2

OC analysis

The OC data contain 140, 141 and 146 observations under placebo, Paxil 20 mg and Paxil 40 mg, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –1.06, -1.57 and –1.71, respectively for placebo and Paxil 20 mg and Paxil 40 mg, respectively. Furthermore, these data provide sufficient evidence to claim that each of the paroxetine groups is significantly different from placebo (p-value = 0.0001). There is no significant difference between the two paroxetine groups (p-value = 0.2353).

Secondary efficacy variable COV_DTOT

LOCF analysis

The secondary efficacy variable COV_DTOT represents the change from baseline in the Week 8 COVI Anxiety scale. That is,

COV_DTOT = Week 8 COVI Total score – Baseline COVI Total score.

The LOCF data on COV_DTOT has 163, 173 and 179 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively, with observed means of –2.4, -3.31 and –3.29. The normality assumption for any (one-way or two-way) analysis of variance model for the change from baseline in the Week 8 COVI anxiety scale COV_DTOT (for treatment comparison) does not hold good (p-value < 0.05). However, the Wilcoxon rank-sum test for these data indicates the three treatment groups are significantly different (p-value = 0.0002). Results of pair-wise analyses of COV_DTOT are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0003). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0005). (c) The two paroxetine groups are not significantly different (p-value = 0.7862).

Secondary efficacy variable COV_DTOT

OC analysis

The OC data on COV_DTOT has 140, 141 and 144 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively, with observed means of –2.55, -3.69 and –3.54. The Wilcoxon rank-sum test for these data indicates the three treatment groups are significantly different (p-value = 0.0001). Results of pair-wise analyses of COV_DTOT

are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0003). (c) The two paroxetine groups are not significantly different (p-value = 0.645).

Secondary efficacy variable CGI_DSEV

LOCF analysis

The secondary efficacy variable CGI_DSEV represents the change from baseline in the Week 8 Illness Severity. That is,

CGI_DSEV = Week 8 Illness Severity – Baseline Illness Severity.

The LOCF data on CGI_DSEV has 180, 188 and 197 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively. One-way analysis of variance yields a mean of –1.06, -1.56 and –1.55 for placebo, Paxil 20 mg and Paxil 40 mg, respectivley. Results of pair-wise analyses of CGI_DSEV are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0001). (c) The two paroxetine groups are not significantly different (p-value = 0.9314).

Secondary efficacy variable CGI_DSEV

OC analysis

The LOCF data on CGI_DSEV has 140, 140 and 146 observations under placebo, Paxil 20 mg and Paxil40 mg, respectively. One-way analysis of variance yields a mean of –1.2, -1.77 and –1.87 for placebo, Paxil 20 mg and Paxil 40 mg, respectivley. Results of pair-wise analyses of CGI_DSEV are as follows. (a) Paroxetine 20 mg is significantly different from placebo (p-value = 0.0001). (b) Paroxetine 40 mg is significantly different from placebo (p-value = 0.0001). (c) The two paroxetine groups are not significantly different (p-value = 0.4798).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that both paroxetine groups are significantly different from placebo. However, the data for the subgroup of males (only) indicated that only the paroxetine 40 mg is significantly different from placebo.

4.2 Study 642- Flexible dose study

Demographics

The LOCF population of this study consisted of 206 (63.6%) females and 118 (36.4%) males. There were 271 (83.6%) Caucasians, 12 (3.7%) Blacks, 2 (0.6%) Orientals. The remaining 39 (12%) belonged to other races. The youngest of these patients was 19 years old and the oldest was 80. The average age was 40.5 years.

Baseline comparison

- The data from Baseline Visit contained 164 and 162 observations on the HAM-A Total (HMA_RTOT) under placebo and Paxil groups, respectively. The means for placebo and Paxil groups were 24.13 and 24.26, respectively. One-way analysis of variance indicates that there was no significant difference among the two treatment groups (p-value = 0.7434) with respect to the HAM-A Total score.

- The data from Baseline Visit contained 164 and 162 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.4965) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT
LOCF analysis

As mentioned earlier, the sponsor analyzes the primary efficacy variable by the general linear models (SAS/GLM). This reviewer pooled all the small sites with less than 5 patients. The data contain 163 and 161 observations under placebo and Paxil, respectively. The analysis of variance model that includes terms for treatment and site indicates that Paxil and placebo are significantly different (p-value = 0.0077). The adjusted mean changes for placebo and Paxil are –9.53 and –11.81, respectively. That is, the reduction in the Week 8 HAM-A under paroxetine is significantly larger compared to placebo.

Protocol defined Primary efficacy endpoint HMA_DTOT
OC analysis

The OC data contains 133 and 127 observations under placebo and Paxil, respectively. Once again, This reviewer pooled all the small sites with less than 5 patients. The analysis of variance model that includes terms for treatment and site yields adjusted means of –10.66 and –13.23 for placebo and Paxil, respectively. The OC data do provide sufficient evidence to conclude that the test drug is significantly different from placebo (p-value = 0.0044). That is, the reduction in the Week 8 HAM-A under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT1
LOCF analysis

The LOCF data contain 163 and 161 observations under placebo, and Paxil, respectively. The analysis of variance model that includes terms for treatment yields adjusted means of –0.91, and –1.31, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0007). That is, the reduction in the Week 8 Hamilton Item 1 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT1

OC analysis

The OC data contain 140 and 132 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.11, and –1.54, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0008). In other words, the reduction in the Week 8 Hamilton Item 1 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT2

LOCF analysis

The LOCF data contain 163 and 161 observations under placebo, and Paxil, respectively. The analysis of variance model that includes terms for treatment and site yields adjusted means of –0.88, and –1.20, respectively for placebo and Paxil, respectively. These data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0043). That is, the reduction in the Week 8 Hamilton Item 2 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable HMA_DIT2

OC analysis

The LOCF data contain 140 and 132 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.02, and –1.43, respectively for placebo and Paxil, respectively. These data do provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0016). In other words, the reduction in the Week 8 Hamilton Item 2 score under paroxetine is significantly larger compared to placebo.

Secondary efficacy variable COV_DTOT

LOCF analysis

The LOCF analysis of data on COV_DTOT contains 154 and 152 observations under placebo and Paxil, respectively. The analysis of variance model with terms for treatment and site gives adjusted means of –2.53 and –3.1 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.0576).

Secondary efficacy variable COV_DTOT

OC analysis

The OC analysis of data on COV_DTOT contains 133 and 125 observations under placebo and Paxil, respectively. The analysis of variance model with terms for comparing treatments gives adjusted means of –2.8 and –3.41 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.059).

Secondary efficacy variable CGI_DSEV

LOCF analysis

The LOCF analysis of data on CGI_DSEV contains 163 and 161 observations under placebo and Paxil, respectively. The one-way analysis of variance gives estimated means of –1.07 and –1.27 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.1499).

Secondary efficacy variable CGI_DSEV

OC analysis

The OC analysis of data on CGI_DSEV contains 140 and 132 observations under placebo and Paxil, respectively. The analysis of variance (with factors- sites and treatment) gives adjusted means of –1.26 and –1.51 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0838).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that Paxil is not significantly different from placebo. This was also the case for males.

4.3 Study 637- Flexible dose study

Demographics

The LOCF population of this study consisted of 256 (70.3%) females and 108 (29.7%) males. Almost all, 262 (99.5%) patients were Caucasians and only 2 belonged to other racial groups. The youngest of these patients was 18 years old and the oldest was 78. The average age was 46.1 years.

Baseline comparison

- The data from Baseline Visit contained 185 and 187 observations on the HAM-A Total (HMA_RTOT) under placebo and Paxil groups, respectively. The means for placebo and Paxil groups were 25.64 and 25.64, respectively. One-way analysis of variance indicates that there was no significant difference among the two treatment groups (p-value = 0.9975) with respect to the HAM-A Total score.

- The data from Baseline Visit contained 185 and 187 observations on severity of illness (CGI_RSEV) under placebo and Paxil groups, respectively. The median observation was 4 in both treatment groups. The Wilcoxon rank-sum test indicates that there was no significant difference among the two treatment groups (p-value = 0.914) with respect to severity of illness.

Protocol defined Primary efficacy endpoint HMA_DTOT

LOCF analysis

The LOCF data contain 183 and 181 observations in placebo and paroxetine, respectively. There were 23 sites (out of 45) with less than 4 subjects. Seven sites had just 1 subject each. Therefore, this reviewer kept the site factor out of analysis. The one-way analysis of variance model to compare the treatments shows that paroxetine and placebo are not significantly different (p-value = 0.2808). The mean change from baseline in Week 8 HAM-A total score under paroxetine and placebo are -13.52 and –12.52, respectively. That is, the reduction in the Week 8 HAM-A total score under paroxetine is not significantly different from placebo.

Protocol defined Primary efficacy endpoint HMA_DTOT

OC analysis

The OC data at Week 8 contained 163 and 149 observations under placebo and paroxetine groups, respectively. The one-way analysis of variance model to compare the treatments shows that paroxetine and placebo are significantly different (p-value = 0.0262). The mean change from baseline in Week 8 HAM-A score under paroxetine and placebo are –15.4 and –13.37, respectively. In other words, the reduction in the Week 8 HAM-A total score under paroxetine is significantly higher compared to placebo.

Secondary efficacy variable HMA_DIT1

LOCF analysis

The LOCF data contain 183 and 181 observations under placebo, and Paxil, respectively. The analysis of variance model to compare the treatments yields adjusted means of –1.10, and –1.38, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0114). That is, the LOCF data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT1

OC analysis

The OC data contain 163 and 149 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.21, and –1.54, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.0031). In other words, the OC data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT2

LOCF analysis

The LOCF data contain 183 and 181 observations under placebo, and Paxil, respectively. The analysis of variance mode to compare treatments yields adjusted means of –1.08, and –1.27, respectively for placebo and Paxil, respectively. Furthermore, these data do not

provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.071). That is, the LOCF data on Hamilton Item 1 score do not support the efficacy of Paxil Tablets.

Secondary efficacy variable HMA_DIT2

OC analysis

The OC data contain 163 and 149 observations under placebo, and Paxil, respectively. The analysis of variance model to compare treatments yields adjusted means of –1.24, and –1.56, respectively for placebo and Paxil, respectively. Furthermore, these data provide sufficient evidence to claim that Paxil is significantly different from placebo (p-value = 0.004). In other words, the OC data on Hamilton Item 1 score support the efficacy of Paxil Tablets.

Secondary efficacy variable COV_DTOT

LOCF analysis

The LOCF analysis of data on COV_DTOT contains 178 and 175 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –2.74 and –3.16 for placebo and Paxil, respectively. The LOCF data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.1461).

Secondary efficacy variable COV_DTOT

OC analysis

The OC analysis of data on COV_DTOT contains 163 and 149 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –2.94 and –3.46 for placebo and Paxil, respectively. The OC data do not provide sufficient evidence to indicate that the two treatment groups are significantly different (p-value = 0.081).

Secondary efficacy variable CGI_DSEV

LOCF analysis

The LOCF analysis of data on CGI_DSEV contains 183 and 181 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –1.17 and –1.45 for placebo and Paxil, respectively. The LOCF data provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0271).

Secondary efficacy variable CGI_DSEV

OC analysis

The OC analysis of data on CGI_DSEV contains 163 and 149 observations under placebo and Paxil, respectively. The one-way analysis of variance gives adjusted means of –1.3 and –1.7 for placebo and Paxil, respectively. The LOCF data provide sufficient evidence to conclude that the two treatment groups are significantly different (p-value = 0.0047).

Subgroup analysis – by sex (LOCF)

Analysis of variance shows that the two gender groups were not significantly different with respect to the change from baseline in the Week 8 HAM-A Total score. The data for the subgroup of females (only) indicated that Paxil is not significantly different from placebo. This was also the case for males.

4.4 Efficacy results- in tabular form

Table 4.4.1: Reviewer's Summary of efficacy results

Study	Efficacy Endpoint	LOCF analysis	OC analysis
637	**Primary**	Not significant (p-value 0.281)	Significant (p-value 0.0262)
	Secondary HMA_Item 1 HMA_Item2	Significant (p-value = 0.0114) **Not** significant (p-value = 0.127)	Significant (p-value = 0.0031) Significant (p-value = 0.0083)
641	**Primary**	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01)	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01)
	Secondary HMA_Item1 HMA_Item2	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01) *	Both Paxil groups 20 mg and 40 mg are significantly different from placebo (p-value < 0.01) *
642	**Primary**	Significant (p-value 0.0077)	Significant (p-value = 0.0044)
	Secondary HMA_Item1 HMA_Item2	Significant (p-value = 0.0007) Significant (p-value = 0.0043)	Significant (p-value = 0.0008) Significant (p-value = 0.0016)

* for both secondary efficacy variables..

Table 4.4.2: **Endpoint (WK-8) HMA_DTOT adjusted means**

ITT Population-LOCF analyses

Study 637		**Study 641**		**Study 642**	
Treatment	Mean	Treatment	Mean	Treatment	Mean
Placebo	-12.52	Placebo	-9.74	Placebo	-9.53
Paroxetine	-13.52	Paxil 20 mg	-12.56	Paroxetine	-11.81
		Paxil 40 mg	-12.23		

Table 4.4.3: Adjusted Mean Differences and Standard Errors

Study 641- LOCF data

	Paxil 20mg-Placebo	Paxil 40 mg-Placebo	Paxil 20mg-Paxil 40m
Difference	-2.826	-2.496	-0.33
Standard Error	0.759	0.751	0.742

Table 4.4.4: Adjusted Mean Difference: Paxil-Placebo

LOCF data

Study 642		Study 637	
Difference	Standard Error	Difference	Standard Error
-2.28	0.706	-1.0	0.921

5. OVERALL CONCLUSIONS

- The data from **Study 641** provide sufficient evidence to claim that the change from baseline in the Week 8 Hamilton Anxiety scale under paroxetine is significantly larger than that of under placebo. That is, Study 641 data on the protocol defined primary efficacy indicate that paroxetine is effective in the treatment of Generalized Anxiety Disorder. The Study 641 data on several secondary efficacy variables are supportive of this conclusion.

- The efficacy data from **Study 642** also provide sufficient evidence to claim that paroxetine is effective in the treatment of Generalized Anxiety Disorder. That is, the change from baseline in the Week 8 Hamilton Anxiety scale under paroxetine is significantly larger than that of under placebo. The Study 642 data on several secondary efficacy variables support the efficacy of the study drug.

- However, the efficacy data from **Study 637** do not provide sufficient evidence to claim that paroxetine is effective in the treatment of Generalized Anxiety Disorder.

/S/

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6. APPENDIX

HAMILTON ANXIETY RATING SCALE (HAM-A): They are based on the following fourteen items.

1. **Anxious Mood** (worries, anticipation of the worst, fearful anticipation, irritability).
2. **Tension** (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax).
3. **Fears** (of dark, of strangers, of being left alone, of animals of traffic, of crowds).
4. **Insomnia** (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors).
5. **Intellectual** (difficulty in concentration, poor memory).
6. **Depressed mood** (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing).
7. **Somatic-Muscular** (pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone).
8. **Somatic-Sensory** (tinnitus, blurring of vision, hot and cold flashes, feelings of weakness, prickling sensation).
9. **Cardiovascular symptoms** (tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat).
10. **Respiratory symptoms** (pressure or constriction in chest, choking feelings, sighing, dyspnea).
11. **Gastrointestinal symptoms** (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation).
12. **Genitourinary Symptoms** (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence).
13. **Autonomic symptoms** (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, rising of hair).
14. **Behavior at Interview** (fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos).

Each had five possible response levels:

0 = Not present; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe.