Report Synopsis

Study Title

A Double-blind, Multicentre Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression

Investigator(s) and Center(s)

The study was carried out in 33 centres in Belgium, Italy, Spain, United Kingdom, Holland, Canada, South Africa, United Arab Emirates, Argentina and Mexico.

Publication

None published as of August 1998.

Study Dates

26th April 1995 to 15th May 1998.

Objective(s)

The primary objective of the study was to compare the efficacy of paroxetine and placebo in the treatment of adolescents with unipolar, major depression.

The secondary objective of this study was to assess the safety and tolerability of paroxetine in adolescents with unipolar, major depression.

Study Design

This was a multicentre, double-blind, randomised, parallel group, placebo controlled study to compare the efficacy and safety of paroxetine (20-40mg daily, flexible dose) and placebo in the treatment of adolescents with unipolar, major depression as defined by DSM-IV criteria. After Screening patients entered a 2 week, single-blind, placebo run-in period. Eligible patients were then randomised to receive paroxetine (20-40mg daily, flexible dose) or placebo (2:1 randomisation) for a period of 12 weeks. Patients returned to the clinic at the end

of Weeks 1, 2, 3, 4, 6, 8 and 12 for assessments of efficacy, safety, concomitant medications and general compliance with study procedures. Patients withdrawing prematurely from the study received 2 week run out medication. At the end of the study all patients were down-titrated off study medication over a period of 2 weeks and returned to the clinic for a last assessment of safety at the end of Week 14.

Study Population

Male or female patients aged between 13 years and 18 years 11 months at Screening, with a current diagnosis of unipolar, major depression as defined by DSM IV criteria, a C-GAS score <69 and a MADRS score ≥16 were eligible to enter the study.

Treatment and Administration

Study medication was formulated as capsules for oral administration twice a day. Batch numbers: paroxetine 10mg – M94002 and M96328; paroxetine 15mg – M94003; paroxetine 20mg – M94004, M95004 and M96330; placebo – CT2/4301 and M96332

Evaluation Criteria

Efficacy Parameters

The primary efficacy parameters were the proportion of patients with a 50% or greater reduction in MADRS score between baseline and study endpoint, and the change from baseline to study endpoint in K-SADS-L depression subscale. The secondary efficacy variables were: change from baseline in MADRS total score; change from baseline in CGI severity of illness score; CGI global improvement score; change from baseline in BDI and change from baseline in MFQ. All primary and secondary variables were analysed at Weeks 6, 8 and study endpoint. Please note: the protocol states analysis of the secondary variables at week 6 and endpoint only. An amendment to the reporting and analysis plan prior to database freeze added week 8 as a time point for analysis, this should have been reflected in the protocol as a protocol modification.

Safety Parameters

Safety parameters consisted of adverse experiences and assessment of vital signs and laboratory data.

Statistical Methods

The proportion of patients responding (≥50% reduction in MADRS total score) was analysed using logistic regression (PROC LOGISTIC of SAS). The model included treatment group, country group, and covariates of age and baseline score. Odds ratios and 95% confidence intervals were presented. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \geq 0.1$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The mean change from baseline in K-SADS-L depression subscale score, MADRS, BDI and MFQ total scores were analysed using analysis of covariance (PROC GLM of SAS) with factors treatment, country group, age and baseline score. Least squares means were compared at the 5% level and 95% confidence intervals presented for treatment differences. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \geq 0.1$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The changes from baseline in the CGI severity of illness (an ordered categorical rating scale) were analysed non parametrically using the Wilcoxon Rank Sum test (PROC NPAR1WAY of SAS). No adjustment was made for country grouping or covariates. The CGI global improvement scores were compared using Cochran-Mantel-Haenszel chi-square tests (stratifying by country group) at the 5% level using PROC FREQ of SAS.

Patient Disposition and Key Demographic Data

Patient disposition and key demographic data are shown below.

Patient Disposition and Key Demographic Data

	Treatment group		Total
	Paroxetine	**Placebo**	
Number of patients:			
Screened	-	-	324
Randomized	187	99	286
ITT populations	182	93	275
Per-protocol population	130	68	198
Completed the study (ITT)	127	69	196
Demography (ITT population)			
Females: number (%)	122 (67.0)	61 (65.6)	-
Mean age (sd): years	15.5 (1.6)	15.8 (1.6)	-
Age range: years	*12 - 19	13 – 18	-
Caucasian: number (%)	126 (69.2)	61 (65.6)	-

* Patients 377.026.00200, 377.029.00040, and 377.057.00532 were 12 years old when recruited into the study and were excluded from the per-protocol population as protocol violators.

A total of 324 patients were screened and 286 patients were randomised to study medication, 187 to paroxetine and 99 to placebo. The treatment groups were well matched for all demographic parameters. Eleven patients were not eligible to be included in the ITT population, 5 in the paroxetine group (2 due to AEs, 1 protocol violator, 1 lost to follow-up and 1 centre 007 patient) and 6 in the placebo group (2 centre 007 patients, 1 protocol violator, 1 lost to follow-up, 1 due to lack of efficacy and 1 for another reason). Of all randomised patients, similar numbers of patients withdrew during the study, 60 out of 187 in the paroxetine group (32.1%) and 30 out of 99 in the placebo group (30.3%), 55 (30.2%) and 24 (25.8%) respectively in the ITT population. Slightly more patients withdrew due to adverse experiences in the paroxetine group, 11.8% compared with 7.1% in the placebo group (11.0% and 7.5% respectively in the ITT population).

Please note that the data from the centre 007 patients was not included in the efficacy analyses due to clinical concerns over the validity of the data from this centre. The decision to exclude this data in the efficacy analysis was made prospectively, prior to database freeze.

Efficacy Results

Data Sets

Two sets of efficacy data were used, observed cases (OC) and last observation carried forward (LOCF). The OC dataset consisted of each patient's observations at each visit. The LOCF dataset was generated from the OC dataset whereby missing data were estimated by extending forward the data from the previous visit. The primary analysis population for the study was the intention-to-treat population using the LOCF dataset with the primary timepoint of interest being the Week 12 LOCF timepoint. A confirmatory analysis based on the per-protocol analysis was carried out on the primary efficacy variables.

Primary Efficacy Variable(s)

No clinically or statistically significant differences were detected between paroxetine and placebo in either of the primary efficacy variables.

The results are summarised below:-

Proportion of patients with a 50% or greater reduction from baseline in MADRS total score

Dataset	**Treatment groups**						
Timepoint	**Paroxetine**		**Placebo**		**Adjusted Odds Ratio**	**95% CI (Paroxetine/ Placebo**	**P-value**
	n/N	**%**	**n/N**	**%**			
LOCF dataset							
Week 12	107/177	60.45	53/91	58.24	1.109	(0.653,1.884)	0.702
OC dataset							
Week 12	94/126	74.60	47/66	71.21	1.161	(0.590, 2.285)	0.666

No statistically significant treatment differences were observed at any time point. At the week 12 endpoint in the ITT LOCF population, 60.5% of the paroxetine patients and 58.2% of the placebo patients had responded. These findings were confirmed by the OC dataset and in the per protocol population.

The only statistically significant interaction found was treatment by age ($p=0.002$). The results from re-analysis of the dataset split by age group (≤ 16 and > 16 years old) showed that in the younger group the proportion of responders was

higher in the placebo group, although this was not statistically significant. In the older age group, the proportion of responders was higher in the paroxetine group.

Proportion of Patients with a ≥ 50% reduction in MADRS Total Score by Age Group at Week 12:

Age Group ≤ 16 years Old

Dataset	Paroxetine Responders	Placebo Responders	Adjusted Odds Ratio	95% CI (Paroxetine /Placebo)	P-value
LOCF	65/118 (55.08%)	37/57 (64.91%)	0.609	(0.309,1.201)	0.153
OC	56/80 (70.00%)	33/45 (73.33%)	0.815	(0.355,1.870)	0.629

Age Group > 16 years Old

Dataset	Paroxetine Responders	Placebo Responders	Adjusted Odds Ratio	95% CI (Paroxetine /Placebo)	P-value
LOCF	42/59 (71.19%)	16/34 (47.06%)	-	-	-
OC	38/46 (82.61%)	14/21 (66.67%)	-	-	-

NB – Model could not be fitted due to lack of responders per treatment group.country group combination.

The odds ratios, confidence intervals and p-values were obtained using logistic regression adjusting for country group, baseline MADRS total score and age (in years).

The per-protocol population confirmed the ITT LOCF results i.e. that there was no overall evidence of treatment differences. However, the statistically signficant treatment by age interaction confirmed that there appeared to be differences between treatment groups depending on the patients age.

Kiddie-SADS-Lifetime Schedule depression subscale Score at Week 12:

Dataset	Treatment groups				
	Paroxetine N, adjusted mean, (S.E.)	**Placebo N, adjusted mean, (S.E.)**	**Difference in Adjusted Means**	**95% CI (Paroxetine/ Placebo**	**P-value**
LOCF	171, -9.330 (0.54)	88, -8.923 (0.70)	-0.408	(-2.007,1.192)	0.616
OC	126, -10.824 (0.49)	66, -10.167 (0.63)	-0.657	(-2.126,0.812)	0.379

The P-values were obtained using analysis of covariance adjusting for country group, baseline K-SADS-L depression subscale score and age (in years). The confidence intervals were obtained using adjusted means.

At Endpoint, the difference between the treatment groups in the adjusted means (see appendix I) of –0.41 in the ITT LOCF population did not achieve clinical or statistical significance. This was confirmed by the ITT OC dataset and the per protocol population.

Again, the only statistically significant interaction found was treatment by age (p=0.020 ITT LOCF). The dataset was re-analysed, split by age group. As with the other primary parameter, although there was no evidence of overall treatment differences, in the older age group, the mean change from baseline was larger in the paroxetine group.

Change from Baseline in K-SADS-L Depression Subscale Score by Age Group at Week 12:

Age Group ≤ 16 years Old

Dataset	Paroxetine N, Adjusted Mean (S.E.)	Placebo N, Adjusted Mean (S.E.)	Difference in Adjusted Means	95% CI (Paroxetine /Placebo)	P-value
LOCF	113, -8.416 (0.61)	55, -9.384 (0.83)	0.968	(-0.954, 2.891)	0.321
OC	80, -10.081 (0.61)	45 -9.797 (0.77)	-0.285	(-2.141, 1.571)	0.762

Age Group > 16 years Old

Dataset	Paroxetine N, Adjusted Mean (S.E.)	Placebo N, Adjusted Mean (S.E.)	Difference in Adjusted Means	95% CI (Paroxetine /Placebo)	P-value
LOCF	58, -11.163 (1.25)	33, -8.438 (1.47)	-2.725	(-5.641,0.192)	0.067
OC	46, -12.060 (0.93)	21, -10.899 (1.20)	-1.161	(-3.681,1.358)	0.360

The p-values were obtained using analysis of covariance adjusting for country group, baseline K-SADS-L depression subscale score and age (in years). The confidence intervals were obtained using adjusted means.

Results from the per protocol analyses confirmed those obtained from the ITT population.

Secondary Efficacy Variable(s)

No overall treatment differences between paroxetine and placebo were detected for any of the secondary efficacy variables. However, there did appear to be some evidence of treatment by age interactions as seen for the primary efficacy variables (See Appendix I), and hence for consistency all variables were additionally analysed by age group.

Safety Results

Adverse Experiences

Similar proportions of patients from both treatment groups experienced adverse events (65.4% of paroxetine patients compared with 59.1% of placebo patients; ITT population).

Serious Adverse Experiences

Twenty two (12.1%) patients in the paroxetine group and 6 (6.5%) patients in the placebo group experienced serious emergent adverse events in the ITT population. None of the SAEs were fatal.

Withdrawals Due to Adverse Experiences

For all randomised patients, 22 out of 187 (11.8%) patients in the paroxetine group withdrew due to adverse experiences compared to 7 out of 99 (7.1%) in the placebo group. This difference was not statistically significant.

Vital Signs

Changes in mean vital signs values between baseline and week 12 were small for both treatment groups and of no clinical concern, and there were no differences between the treatment groups regarding vital signs values meeting sponsor-defined clinical concern criteria.

Laboratory Tests

Similar proportions of patients in the two treatment groups had one or more laboratory value meeting sponsor-defined clinical concern criteria (paroxetine 29.1%, placebo 33.3%).

Conclusion(s)

The results failed to show any superiority for paroxetine over placebo in the treatment of adolescent depression. A significant age by treatment interaction was detected in both of the primary efficacy variables and most of the secondary, indicating evidence of a different treatment effect dependent on age. Therefore conclusions drawn on the data presented overall should be treated with caution.

Paroxetine was well tolerated with no unexpected finding regarding adverse experiences, vital signs or laboratory values.