13. QUESTION 13

To elucidate the difference in the paediatric studies whereby more suicide related behaviours were seen in the depression studies while more hostility events were seen in the OCD and social anxiety studies, the following information and analyses are requested:

13.1 Information about the age of children participating in all studies is requested per study. This includes means/median/mode and SD as well as the ages of the children involved in the events. In addition, stratified analysis by age bands should be performed. This should include at a minimum 2 age categories: 7-12, and 12-18.

13.2 Efficacy results for depression in young adults (18-29) and in children should be presented. The purpose of this analysis is to investigate whether the increase in suicidality is coupled with deterioration in other symptoms of depression and whether this occurs specifically in the first weeks of treatment. Therefore, the scores of depression scales over time should be presented and this should be done with and without exclusion of the suicide items.

The same analysis should be repeated for the other children indications and for adults in order to investigate whether such potential phenomenon is unique to depression and children.

Response

13.1. Information about the age of children in all studies

Information about the age of children participating in all studies is supplied as requested in Table 13.1 (Data source: Appendix 1, Table 1.21).

Table 13.1 Summary of Age (in years) by Treatment Group and Study Paediatric Placebo-Controlled Trials

		Treatment Group		
Study		**Paroxetine**	**Placebo**	**Total**
Overall	N	738	647	1385
	SD	2.97	3.01	2.99
	Mean	13.3	13.2	13.3
	Median	14	14	14
	Mode	15	14	14
	Minimum	6	6	6
	Maximum	19	18	19
Study 329	N	93	88	181
	SD	1.66	1.65	1.66
	Mean	14.8	15.1	15.0
	Median	15	15	15
	Mode	16	16	16
	Minimum	11	12	11
	Maximum	18	18	18
Study 377	N	181	95	276
	SD	1.63	1.6	1.62
	Mean	15.5	15.8	15.6
	Median	16	16	16
	Mode	17	17	17
	Minimum	12	13	12
	Maximum	19	18	19
Study 453	N	96	98	194
	SD	2.59	2.92	2.75
	Mean	11.8	11.7	11.8
	Median	11	12	12
	Mode	11	9	12
	Minimum	7	6	6
	Maximum	17	18	18
Study 676	N	165	157	322
	SD	2.83	2.72	2.77
	Mean	13.1	13.3	13.2
	Median	13	14	14
	Mode	14	14	14
	Minimum	7	7	7
	Maximum	17	17	17

Continued

Table 13.1 Summary of Age (in years) by Treatment Group and Study Paediatric Placebo-Controlled Trials (continued)

		Treatment Group		
Study		**Paroxetine**	**Placebo**	**Total**
Study 701	N	104	102	206
	SD	3	2.95	2.97
	Mean	11.9	12.2	12.1
	Median	12	12	12
	Mode	9	10	10
	Minimum	7	7	7
	Maximum	17	17	17
Study 704	N	99	107	206
	SD	3.02	2.98	3.0
	Mean	11.1	11.6	11.3
	Median	11	11	11
	Mode	7	11	11
	Minimum	6	6	6
	Maximum	17	17	17

In addition, stratified analysis by age bands were requested. Incidences of possibly suicide-related events by treatment group, indication and age band are presented in Table 13.2.

Table 13.2 Incidence of Possibly Suicide-Related Events by Treatment Group, Indication and Age Group
Paediatric Placebo-Controlled Trials (On therapy)

Indication and Age Group	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall				
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.07
<12 years	0/205 (0.0%)	0/194 (0.0%)		
12-15 years	10/329 (3.0%)	5/269 (1.9%)	1.66 (0.56, 4.90)	0.44
≥16 years	8/204 (3.9%)	2/184 (1.1%)	3.71 (0.78, 17.72)	0.11
Depression				
Overall	14/378 (3.7%)	7/285 (2.5%)	1.53 (0.61, 3.84)	0.50
<12 years	0/51 (0.0%)	0/46 (0.0%)		
12-15 years	7/184 (3.8%)	5/120 (4.2%)	0.91 (0.28, 2.93)	1.00
≥16 years	7/143 (4.9%)	2/119 (1.7%)	3.01 (0.61, 14.77)	0.19
OCD				
Overall	1/195 (0.5%)	0/205 (0.0%)		0.49
<12 years	0/107 (0.0%)	0/103 (0.0%)		
12-15 years	1/66 (1.5%)	0/76 (0.0%)		0.46
≥16 years	0/22 (0.0%)	0/26 (0.0%)		
Social Anxiety Disorder				
Overall	3/165 (1.8%)	0/157 (0.0%)		0.25
<12 years	0/47 (0.0%)	0/45 (0.0%)		
12-15 years	2/79 (2.5%)	0/73 (0.0%)		0.50
≥16 years	1/39 (2.6%)	0/39 (0.0%)		1.00

The large majority of possibly suicide-related events occurring on therapy in paediatric trials were observed in patients with depression, both for patients treated with paroxetine (14/18) and for patients treated with placebo (7/7). Possibly suicide-related events were not observed during treatment in patients aged < 12 years. A similar incidence of having a possibly suicide-related event was observed in depressed patients aged 12-15 years treated with paroxetine or placebo. Patients aged ≥ 16 years in depression studies who were treated with paroxetine had a higher incidence of having a possibly suicide-related event than patients receiving placebo.

Incidences of hostility events by treatment group, indication and age band are presented in Table 13.3.

Table 13.3 Incidence of Hostility Events by Treatment Group, Indication and Age Group
Paediatric Placebo-Controlled Trials (On therapy)

Indication and Age Group	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall				
Overall	27/738 (3.7%)	4/647 (0.6%)	6.10 (2.12, 17.54)	<0.001
<12 years	15/205 (7.3%)	1/194 (0.5%)	15.24 (1.99, 116.5)	<0.001
12-15 years	10/329 (3.0%)	3/269 (1.1%)	2.78 (0.76, 10.20)	0.16
≥16 years	2/204 (1.0%)	0/184 (0.0%)		0.50
Depression				
Overall	7/378 (1.9%)	1/285 (0.4%)	5.36 (0.66, 43.80)	0.15
<12 years	1/51 (2.0%)	0/46 (0.0%)		1.00
12-15 years	5/184 (2.7%)	1/120 (0.8%)	3.32 (0.38, 28.81)	0.41
≥16 years	1/143 (0.7%)	0/119 (0.0%)		1.00
OCD				
Overall	15/195 (7.7%)	1/205 (0.5%)	17.00 (2.22, 130.0)	<0.001
<12 years	11/107 (10.3%)	1/103 (1.0%)	11.69 (1.48, 92.25)	0.005
12-15 years	4/66 (6.1%)	0/76 (0.0%)		0.04
≥16 years	0/22 (0.0%)	0/26 (0.0%)		
Social Anxiety Disorder				
Overall	5/165 (3.0%)	2/157 (1.3%)	2.42 (0.46, 12.67)	0.45
<12 years	3/47 (6.4%)	0/45 (0.0%)		0.24
12-15 years	1/79 (1.3%)	2/73 (2.7%)	0.46 (0.04, 5.13)	0.61
≥16 years	1/39 (2.6%)	0/39 (0.0%)		1.00

There was a statistically significant, greater incidence of hostility events in the paroxetine treatment group compared to the placebo group overall and in the <12 year age group. In the 12-15 year age group, there was also a higher incidence of hostility events in the paroxetine group compared to the placebo group although the difference was not statistically significant. There was no statistically significant difference in the incidence of a hostility event in the ≥16 years age group.

The majority of on-therapy hostility events in the paroxetine treated group were in patients with OCD (15 of 27 patients, 56%) even though OCD patients only made up 26% (195/738) of the total paediatric population treated with paroxetine. The difference between treatment groups in the incidence of hostility in OCD patients was more pronounced in younger patients, particularly in those aged <12 years.

13.1.1. Conclusion

In placebo-controlled paediatric studies, possibly suicide-related events and hostility were observed more in patients treated with paroxetine than placebo. Possibly suicide-related events in both treatment groups were reported predominantly in adolescents with depression. The excess of reports of hostility on paroxetine was noticed particularly in younger patients with OCD.

13.2. Efficacy of paroxetine in young adults (aged 18–29 inclusive) and children with depression

The stated aim of the request for analyses of the efficacy results for depression in young adults and children is to investigate whether the potential increase in suicidality (presumably in children and young adults) is coupled with deterioration in other symptoms of depression and whether this occurs specifically in the first weeks of treatment. To this end it was requested to present the scores of depression scales over time, presenting with and without exclusion of the suicide items.

The same analysis for the other childen indications and for adults was requested in order to investigate whether any phenomenon observed was unique to depression and children. Similar presentations of data will be provided for adults with depression, but for the other children's indications it is not possible to provide such information. Rating scales for those other indications do not have "suicide" items that can be excluded in the say way as suicide items can be removed from HAM-D and MADRS depression rating scores. When depression rating scales have been used in studies in children, it has only been at baseline and at end of study treatment. Hence changes over time cannot be plotted

13.2.1. Efficacy of paroxetine in children and adolescents with depression

- Controlled clinical studies did not establish the efficacy of paroxetine in the treatment of children and adolescents with MDD.
- Results of post-hoc analyses indicated that older adolescents (≥15 years of age) with MDD may derive benefit from paroxetine administration.

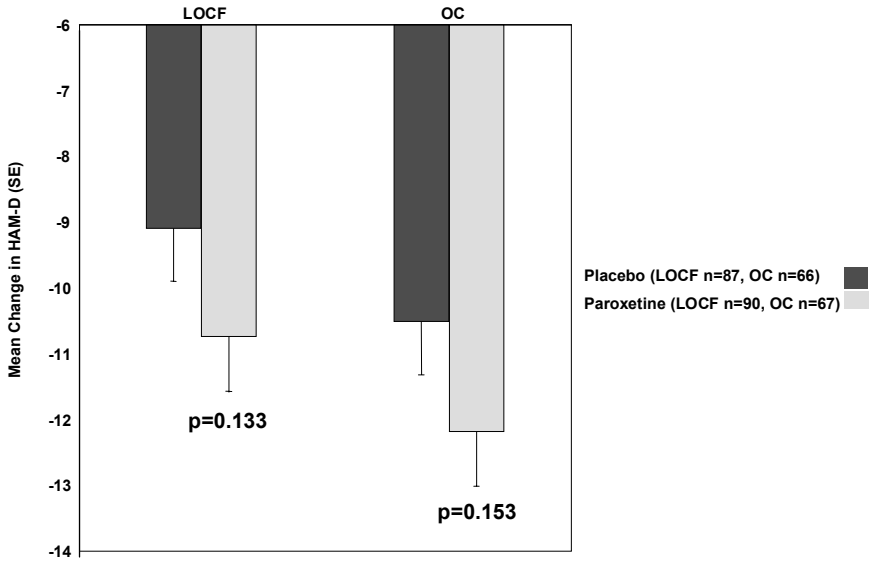
Three short-term, double-blind, placebo controlled studies were conducted in children and adolescents with MDD (701, 329 and 377). Study 329 included a 6 month double-blind extension phase. These data were provided to European regulatory agencies in June 2003 as part of a safety labelling variation for use in children and adolescents. The duration of treatment (8-12 weeks) was sufficient to assess efficacy in MDD. Patients fulfilled DSM-III-R/IV defined diagnostic criteria for MDD and had to meet pre-determined minimum scores relating to severity. The major criteria used to determine efficacy were the HAM-D (329), Children's Depression Rating Scale-revised (CDRS-R) (701), MADRS (377) and the clinical global impression (CGI) for severity of illness and global improvement (377 and 701).

The three acute double-blind, placebo-controlled studies included 654 children and adolescents with major depression (376 received paroxetine 10-50mg/day)

Demographic characteristics were generally well balanced between the two treatment groups in each of the studies. Studies 329 and 377 had slightly more females than males and recruited older adolescents (in accordance with the protocol). Study 701 recruited children and adolescents (age 7-17 years).

No statistically significant differences were observed for paroxetine compared with placebo on any of the primary efficacy variables (example, see Figure 13.1, study 329).

Figure 13.1 Study 329: Mean Change from Baseline in HAM-D Total Score



However, all three studies had high placebo response rates (>50%) which made it difficult to discern a treatment effect. Placebo-controlled, paroxetine studies in depressed adults have typically had a response of 30-40% in the placebo groups. From a clinical standpoint these studies in children can perhaps more appropriately be regarded as failed studies than negative studies, because it would be more difficult to achieve statistical separation from placebo under such circumstances. Although paroxetine did not achieve statistically significant separation from placebo on the primary efficacy variable, there was some suggestion of efficacy from secondary measures (example, see Table 13.4, study 329).

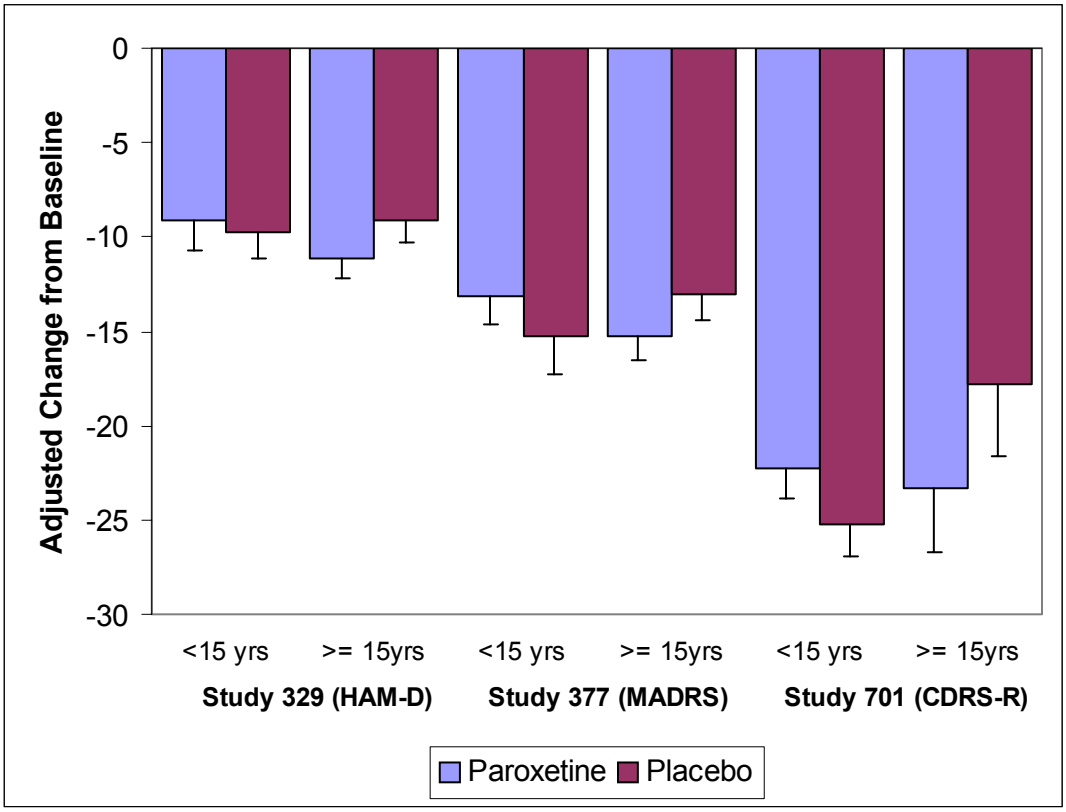
Table 13.4 Study 329 – Key Efficacy Results

MEASURE	Paroxetine			Placebo			Treatment Comparisons			
								95% CI		
	n	mean	SE	n	mean	SE	Diff	Lower Limit	Upper Limit	p-value
Δ HAM-D Total	90	-10.7	0.81	87	-9.1	0.83	-1.7	-3.9	0.6	0.133
Δ K-SADS-L Dep. sub-scale	83	-11.7	0.84	85	-9.6	0.83	-2.1	-4.4	0.2	0.065
Δ HAM-D Dep. Mood Item	90	-2.0	0.14	87	-1.3	0.14	-0.7	-1.1	-0.3	0.001
Δ K-SADS-L Dep. Mood Item	83	-2.2	0.18	85	-1.7	0.18	-0.5	-1.0	0.0	0.049
Measure	**n**	**N**	**%**	**n**	**N**	**%**	**Diff (%)**	**Lower Limit**	**Upper Limit**	**p-value**
50% ↓ HAM-D and/or HAM-D ≤ 8	60	90	66.7	48	87	55.2	11.5	-2.8	25.7	0.112
HAM-D ≤ 8	57	90	63.3	40	87	46.0	17.3	2.8	31.8	0.019
CGI-I Score of 1 or 2	59	90	65.6	42	87	48.3	17.3	2.9	31.7	0.02

13.2.1.1. Post hoc Analyses

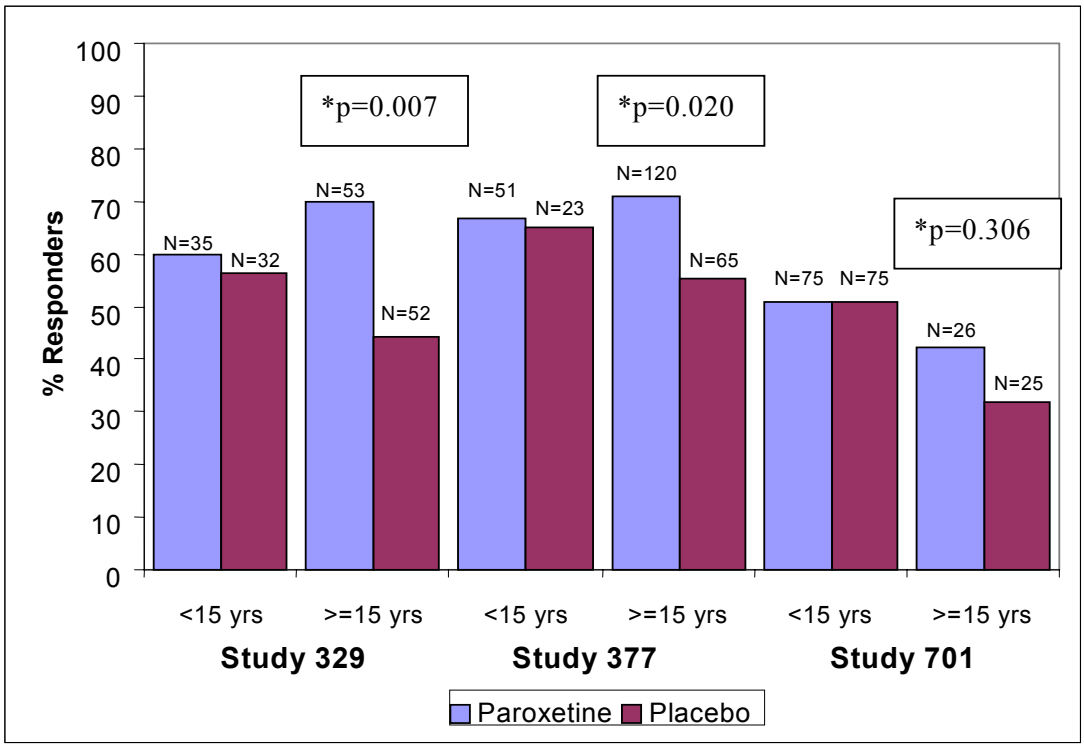
Post hoc analyses were performed on the primary efficacy variables and CGI Global Improvement data from the 3 short-term MDD studies (individually and where possible pooled) to determine if there was a statistically significant treatment difference when considering an older adolescent age subgroup (≥15 years). Patients were grouped into the following age ranges; <12, ≥12 years; <15, ≥15 years. Post-hoc analyses of the change from baseline data for the study specific primary efficacy variables, HAM-D, MADRS, and CDRS-R by age subgroup (<15 years, ≥15 years) suggested that for each efficacy variable, patients ≥15 years of age had greater symptom reduction than patients <15 years of age, however, these differences were not statistically significant, (Figure 13.2). There was, however, a statistically significant treatment by age group (<15 years, ≥15 years) interaction in Study 701.

Figure 13.2 Summary of Analysis of Change from Baseline by Treatment, Age Group and Study (LOCF Endpoint)



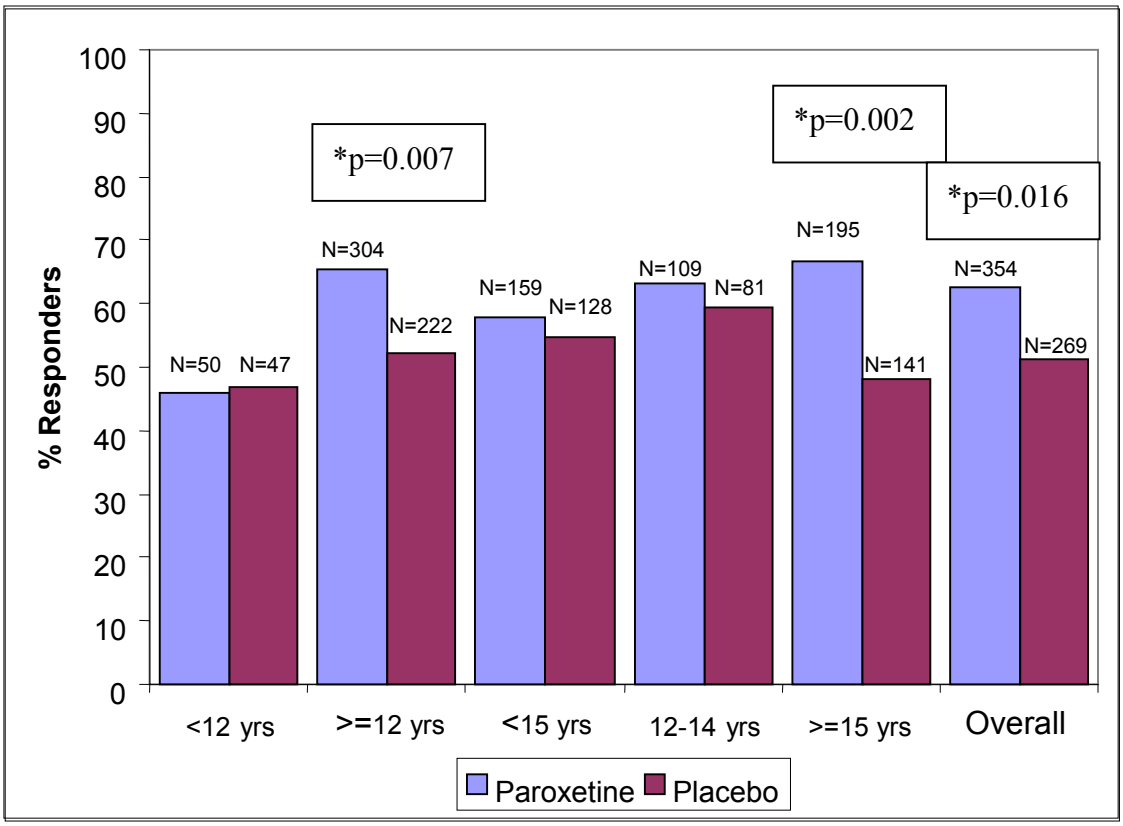
Post-hoc analyses based on the odds of being a responder on CGI Global improvement scale (score of 1 or 2) showed that the odds of responding on paroxetine were significantly higher than those on placebo for older adolescents (≥15 years of age) in studies 329 (OR 3.42 (95% CI: [1.40. 8.34], p=0.007)) and 377 (OR 2.21 (95% CI: [1.13, 4.30], p=0.020)), (Figure 13.3). Results in study 701 followed the same trend as those in studies 329 and 377 with more responders in patients treated with paroxetine than placebo in the ≥15 years age group, but the difference between treatment groups was not statistically significant. (The number of patients aged ≥15 years in study 701 was much lower than in the other two studies).

Figure 13.3 Summary of Analysis of Response based on CGI Improvement by Treatment, Age Group and Study (LOCF Endpoint)



In addition, a pooled analysis of the 3 short-term MDD studies showed that the odds of responding based on CGI improvement on paroxetine were statistically significantly different from the odds of responding on placebo (1.51, 95% CI: [1.08, 2.11], p = 0.016), (Figure 13.4).

**Figure 13.4 Summary of Analysis of Response based on CGI Improvement by Treatment and Age Group
Pooled MDD studies (329, 377, 701) – LOCF Endpoint**



A statistically significant treatment by age group (<15 years, ≥15 years) interaction was again observed. The odds of responding on paroxetine compared with placebo were statistically significantly higher in the ≥15 years age group but not in the <15 years age group. Comparison of the response rate in patients aged <12 years, 12-14 years and ≥15 years indicates a progression with age towards higher response on paroxetine than placebo in the oldest age group.

Results of these post-hoc analyses indicate that older adolescents (≥15 years of age) with MDD may derive some benefit from paroxetine administration.

13.2.2. Efficacy of paroxetine in young adults (18-29 years) with depression

In adult placebo-controlled depression trials, depressed patients aged 18-29 years (inclusive) had a significantly greater reduction in HAM-D total score at study endpoint (LOCF) than placebo (difference -1.76, 95% C.I. [-0.60, -2.93], p=0.003), (Table 13.5, Data Source Appendix 1, Table 1.45).

Table 13.5 Change from Baseline in HAMD Total Score in Young Adults (aged 18-29 years inclusive) by Treatment Group Adult Placebo Controlled Trials, Depression Studies Only Randomised Phase, LOCF

Treatment	N	Least Square Mean Change from Baseline (S.E.)	Treatment Comparison		
			Difference	95% CI	P value
Paroxetine	427	-10.1 (0.36)	-1.76	-0.60, -2.93	0.003
Placebo	245	-8.3 (0.47)			

The above data demonstrate that paroxetine is an effective antidepressant in young adults.

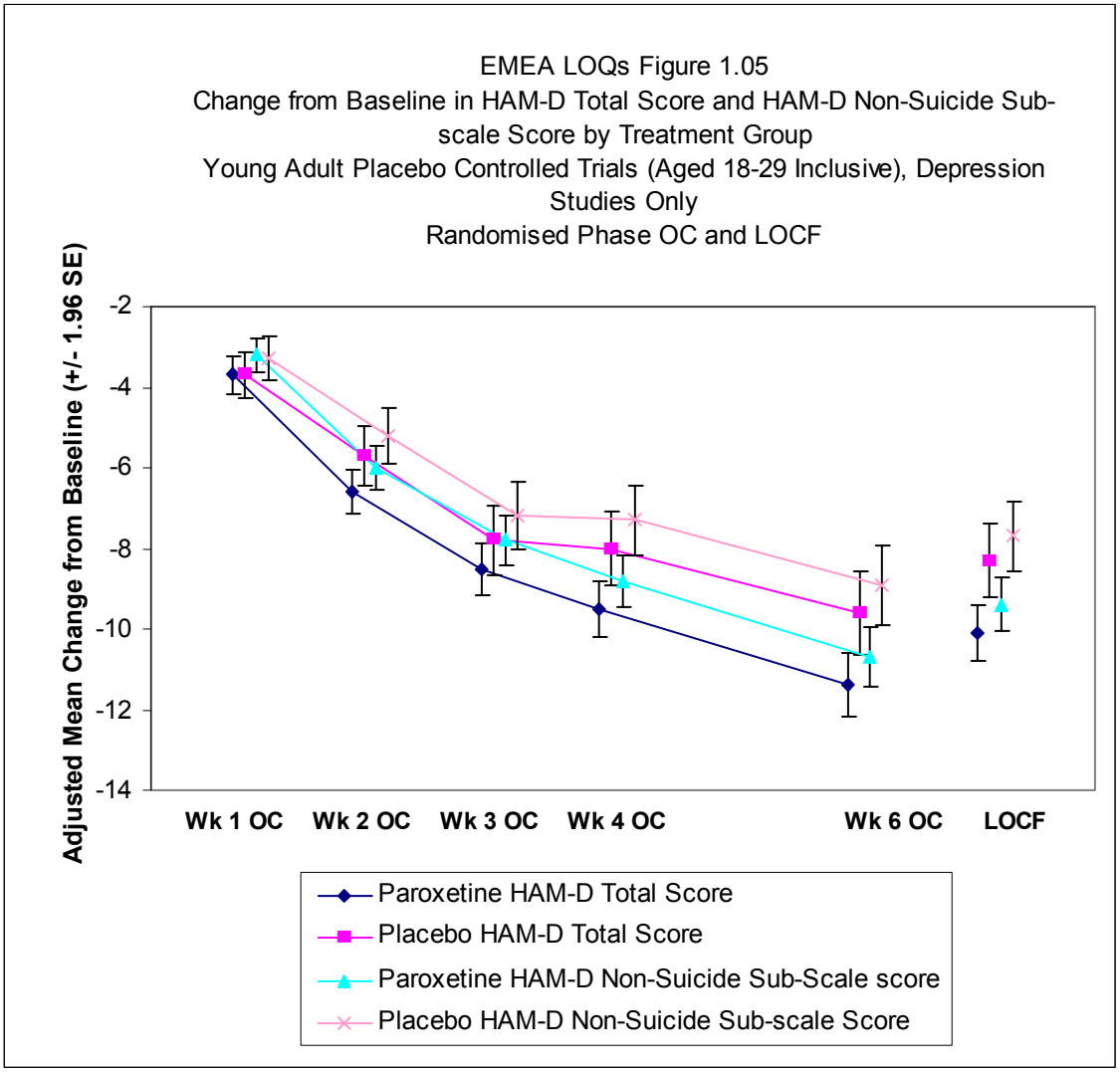
In adult placebo-controlled depression trials using the MADRS, depressed patients aged 18-29 years (inclusive) had a greater reduction in MADRS at study endpoint (LOCF) than placebo (difference -1.86, 95% C.I. [-3.96, 0.23], p=0.081), (Data Source: Appendix 1, Table 1.48).

13.2.3. Is suicidality coupled with deterioration in other symptoms of depression?

To address the above, and to assess whether any such association may occur specifically in the first weeks of treatment,the scores of depression scales over time were requested, with and without exclusion of suicide items.

The requested information is given below in Figure 13.5 and Figure 13.6 for young adults aged 18-29 years in placebo-controlled depression studies in which depressive symptoms were assessed using the HAM-D and MADRS rating scales, respectively. To give scores excluding suicide items, item 3 was excluded from the HAM-D total score, and item 10 was excluded from the MADRS score.

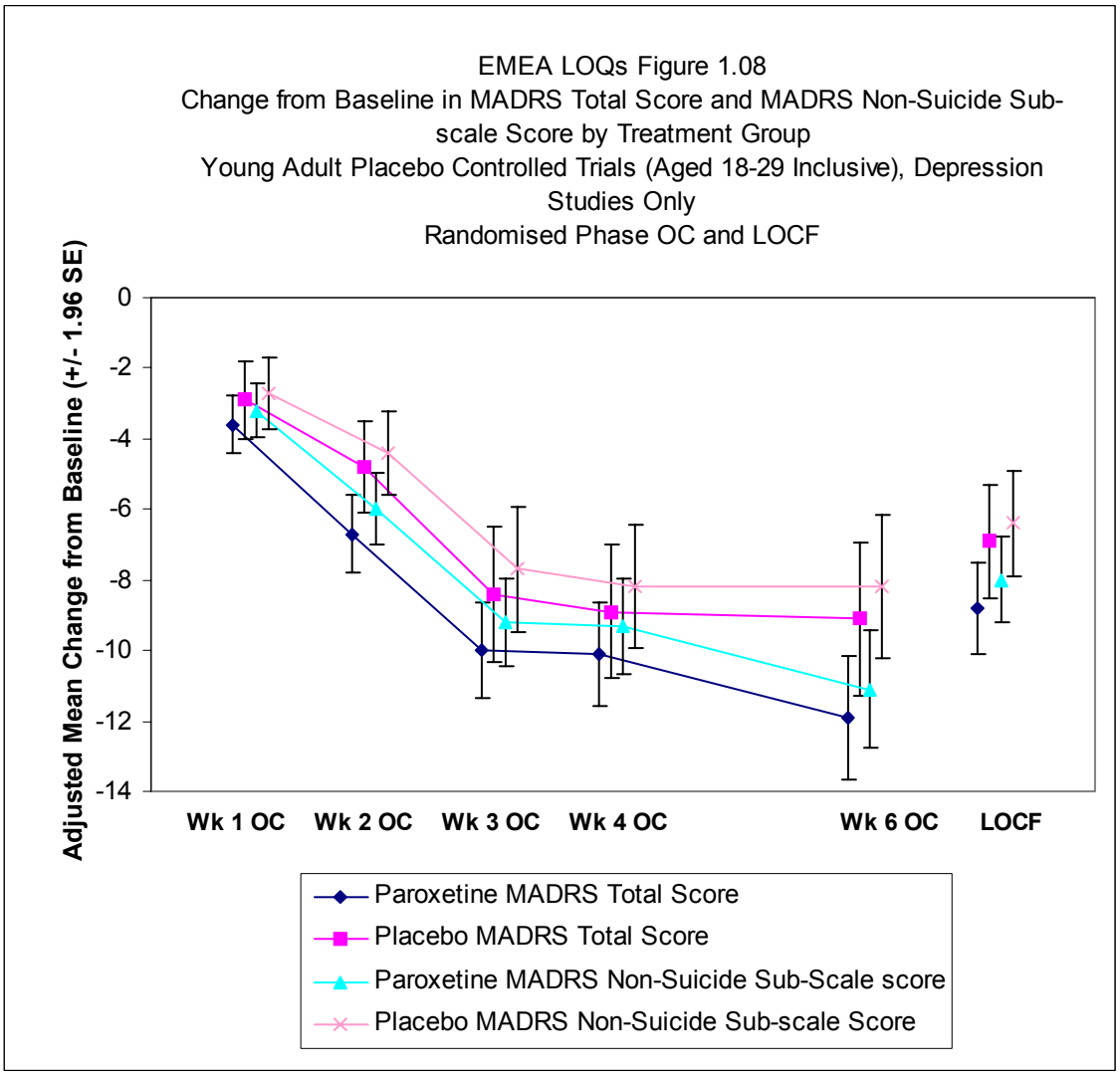
**Figure 13.5 Change from Baseline in HAM-D Total Score and HAM-D Non-Suicide Subscale Score by Treatment Group
Young Adult Placebo Controlled Trials (Aged 18-29 Inclusive), Depression Studies Only
Randomised Phase OC and LOCF**



(Data Source: Appendix 1, Table 1.45).

Please note: Most studies did not have a separate week 5 assessment and data at this timepoint are, therefore, sparse. Hence week 5 assessments are not shown in the graphs.

**Figure 13.6 Change from Baseline in MADRS Total Score and MADRS Non-Suicide Subscale Score by Treatment Group
Young Adult Placebo Controlled Trials (Aged 18-29 Inclusive), Depression Studies Only
Randomised Phase OC and LOCF**



(Data Source: Appendix 1, Table 1.48).

The shape of the change from baseline plots, and the difference between the paroxetine and placebo plots, appear very similar whether the suicide item is included or not. The similarity of the plots including and excluding suicide item scores was at all time points, including the first weeks of treatment.

Presumably, if paroxetine patients had increased suicide item scores during treatment compared to placebo patients, omitting the suicide score would increase the separation between the paroxetine and placebo plots compared to the plots of scores that included the suicide item. However, that was not observed at any time, and in light of the data below it would not be expected.

In patients aged 18-29 in placebo-controlled studies, the incidence of possibly suicide related events was low in both the paroxetine and the placebo groups, 1.8% (31/1727) and 1.4% (17/1204), respectively, but this difference was not statistically significant (OR 1.28, 95% CI 0.70, 2.32, P=0.46). Emergent suicidal ideation (as assessed by a HAM-D item 3 score of ≥ 3 on treatment, having had a score of 0 or 1 at baseline) was also low in young adults (aged 18-29): 1.8% (7/383) in paroxetine, and 1.1% (3/262) in placebo treated patients (odds ratio 1.61, 95% CI [0.41, 6.27], p=0.75). In addition, in placebo-controlled studies, the change (mean reduction) from baseline in the HAM-D and MADRS suicide items was greater in young adults treated with paroxetine than placebo, (Table 13.6). The mean reduction in MADRS item 10 was significantly greater in young adults (aged 18-29) treated with paroxetine (-0.35) than placebo (-0.20), (treatment difference of –0.15, 95% CI [-0.24, -0.05], p<0.01).

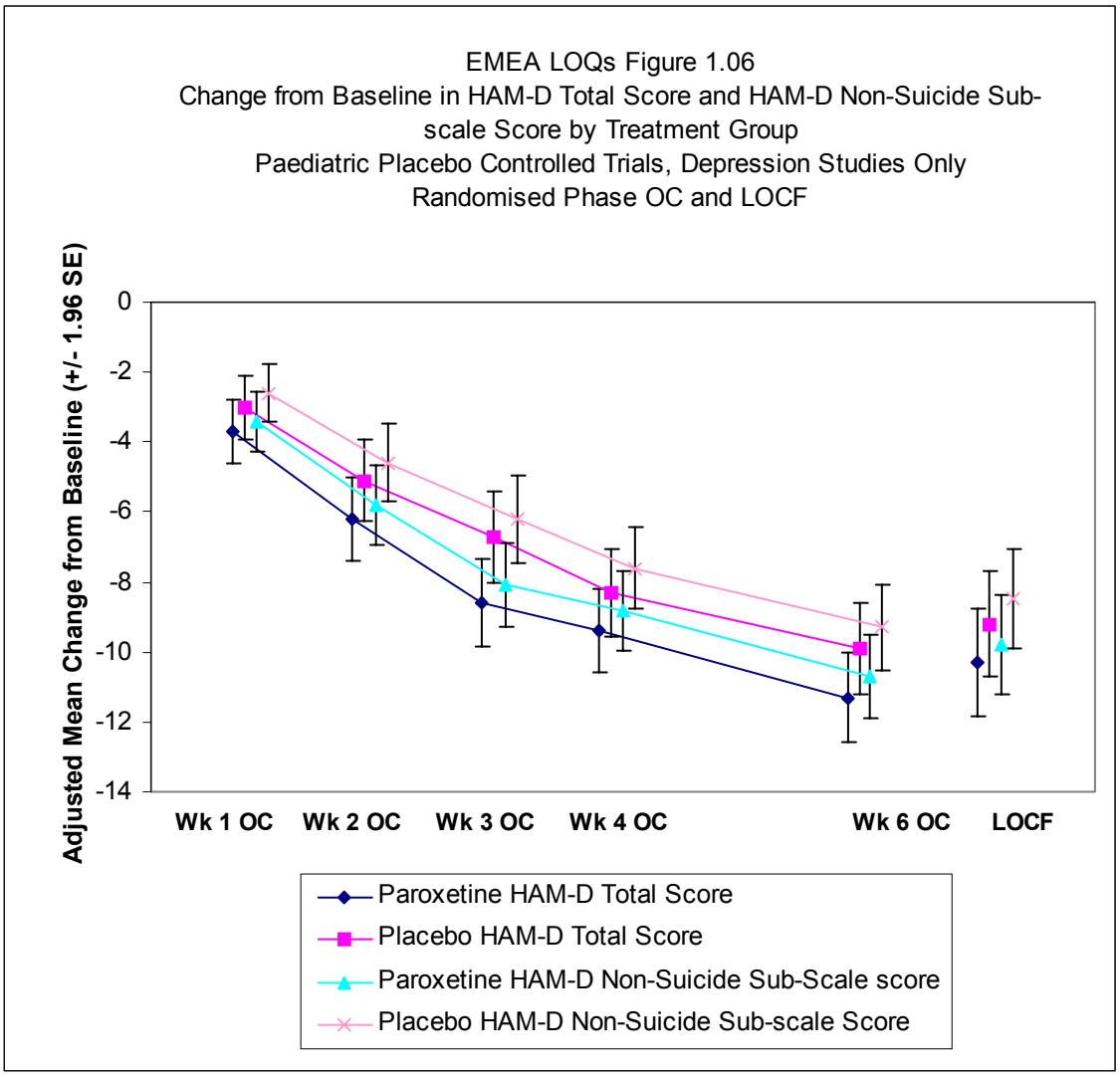
Table 13.6 Change from Baseline in HAM-D Item 3 and MADRS Item 10 in Young Adults (aged 18-29 years inclusive) by Treatment Group Adult Placebo Controlled Trials Randomised Phase LOCF

	Treatment	N	Least Square Mean Change from Baseline (S.E.)	Treatment Comparison		
				Difference	95% CI	P value
HAM-D Item 3	Paroxetine	528	-0.50 (0.03)	-0.07	-0.16, 0.02	0.12
	Placebo	349	-0.43 (0.04)			
MADRS Item 10	Paroxetine	676	-0.35 (0.03)	-0.15	-0.24, -0.05	<0.01
Placebo	Placebo	466	-0.20 (0.47)			

Hence with little or no difference to detect, it is not surprising than nothing was observed in this examination. The method used to examine the question is far from sensitive. The difference between approaches (i.e. omitting or including the suicide items of rating scales) is small. The suicide item scores make a relatively small contribution to the total rating scale scores.

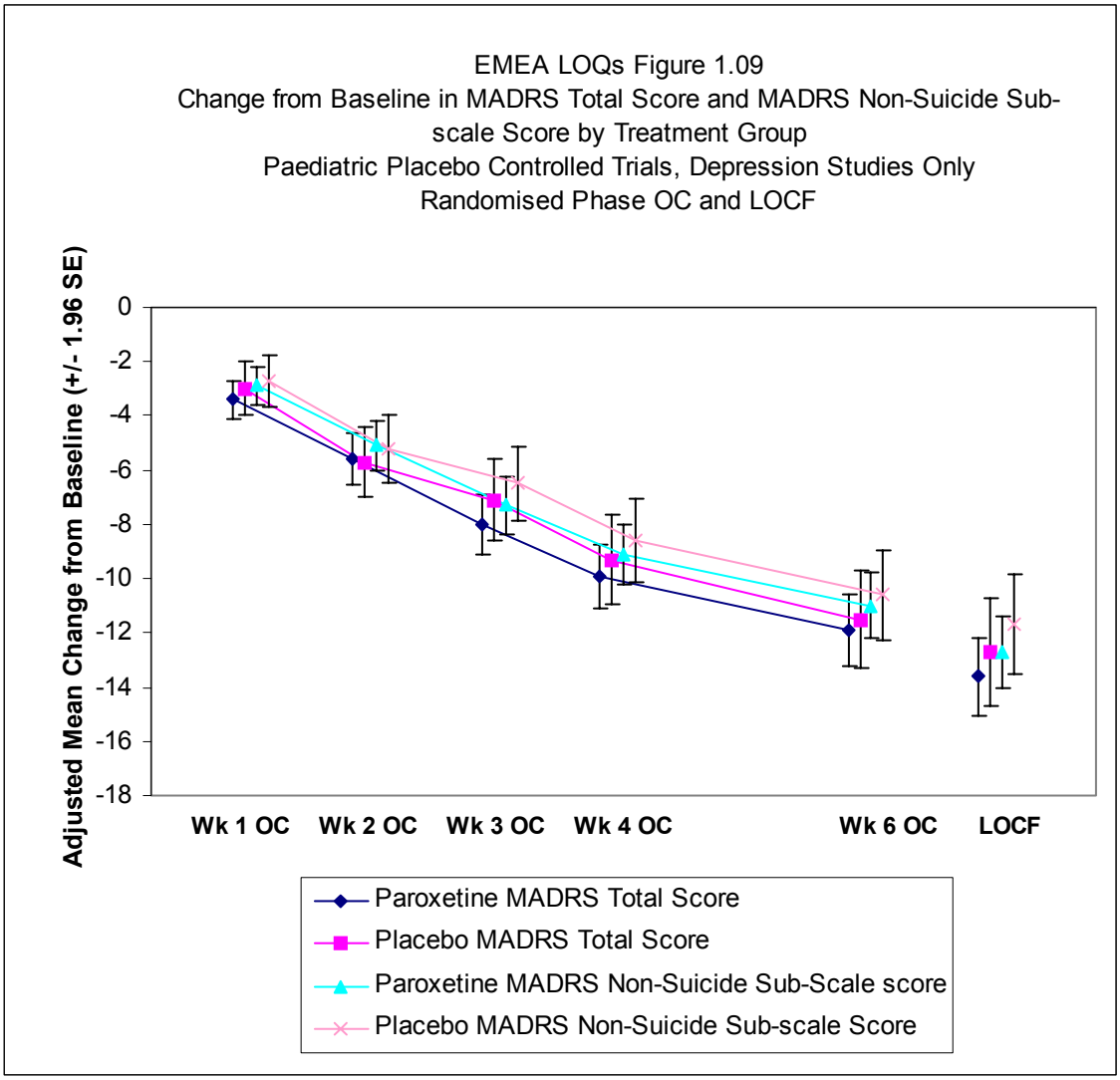
Scores including and excluding the suicide items of the HAM-D and MADRS from paediatric placebo-controlled depression studies are provided below. Figures 13.7, 13.8, and 13.9 show plots of data from studies 329, 377 and 701, respectively, that used the HAM-D, the MADRS, and CDRS-R rating scales, respectively. In the non-suicide subscales, the items omitted from the full rating scale were item 3 from the HAM-D, item 10 from the MADRS, and item 13 from the CDRS-R. Excluding the suicide item from the rating scale score had little impact and did not help in investigating whether increase in suicidality is coupled with deterioration in other symptoms of depression.

Figure 13.7 Change from Baseline in HAM-D Total Score and HAM-D Non-Suicide Subscale Score by Treatment Group Paediatric Placebo Controlled Trials, Depression Studies Only Randomised Phase OC and LOCF



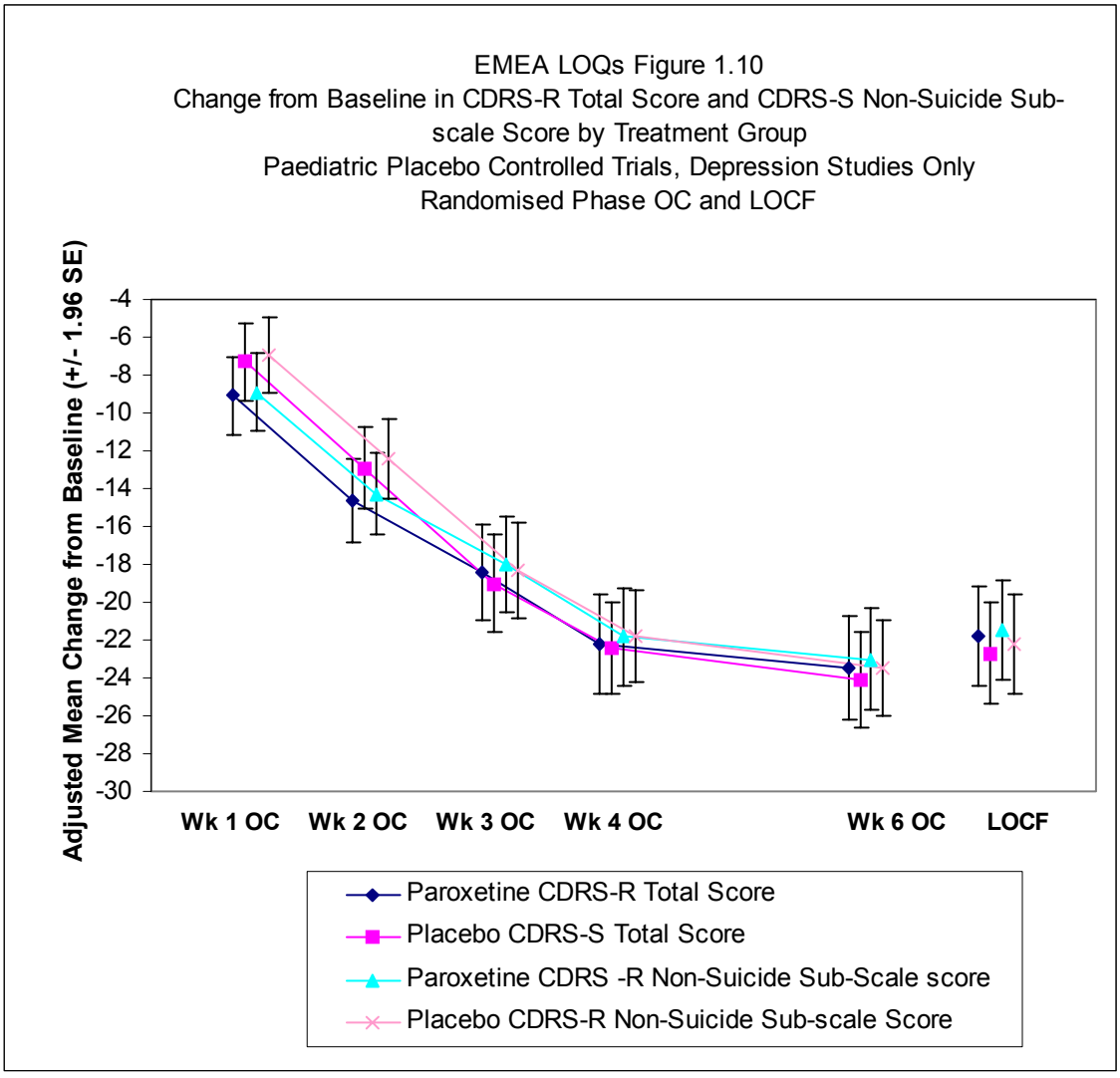
(Data Source: Appendix 1, Table 1.46).

Figure 13.8 Change from Baseline in MADRS Total Score and MADRS Non-Suicide Subscale Score by Treatment Group Paediatric Placebo Controlled Trials, Depression Studies Only Randomised Phase OC and LOCF



(Data Source: Appendix 1, Table 1.49).

Figure 13.9 Change from Baseline in CDRS-R Total Score and CDRS-R Non-Suicide Subscale Score by Treatment Group Paediatric Placebo Controlled Trials, Depression Studies Only Randomised Phase OC and LOCF



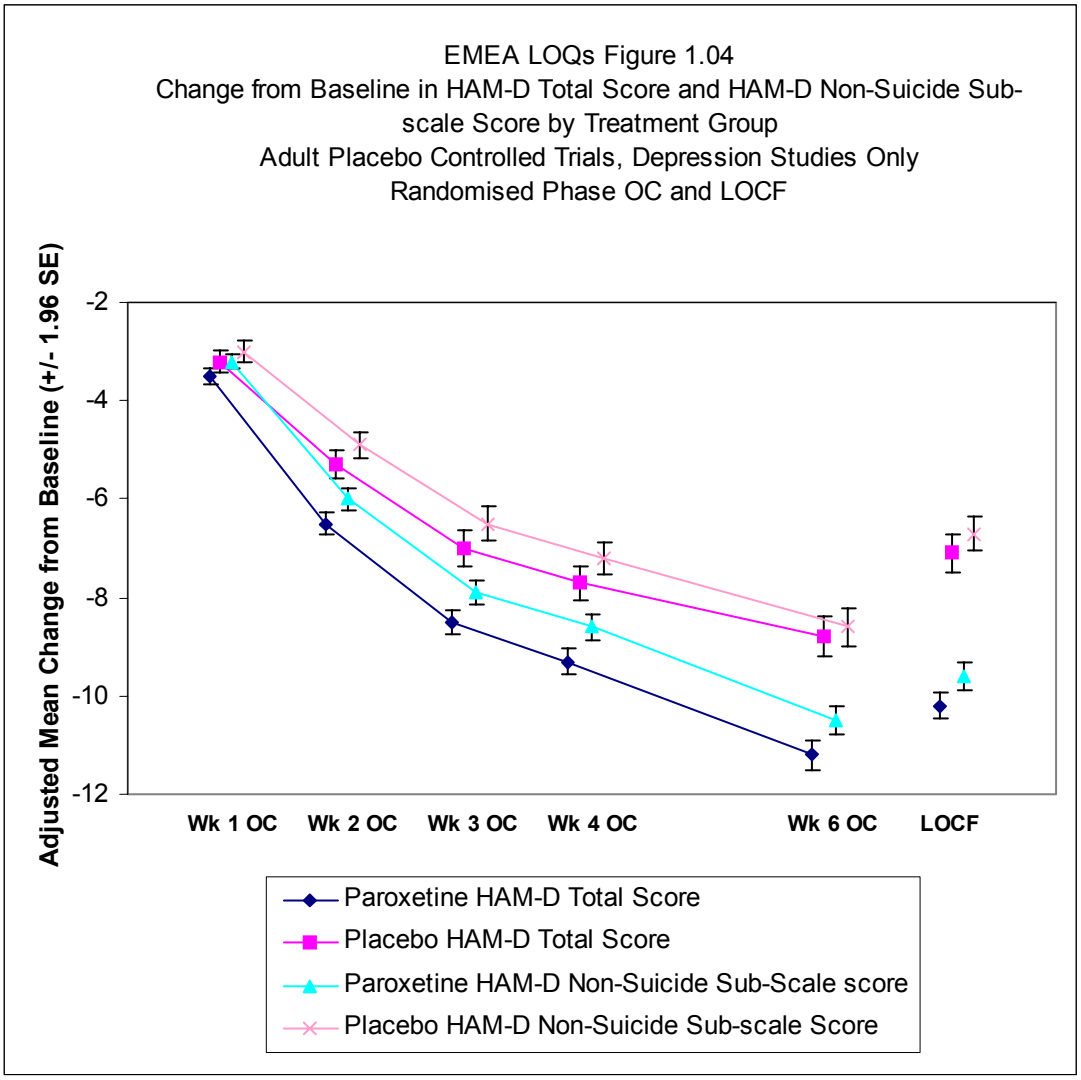
(Data Source: Appendix 1, Table 1.50).

As mentioned previously, the same analysis was requested for the other children's indications, but this was not possible as rating scales including a suicide item were not included in all of those studies, and where they were included they were only employed before the start and at the end of the study treatment period.

The same analysis was also requested in adults, and the plots obtained are shown in Figure 13.10 and

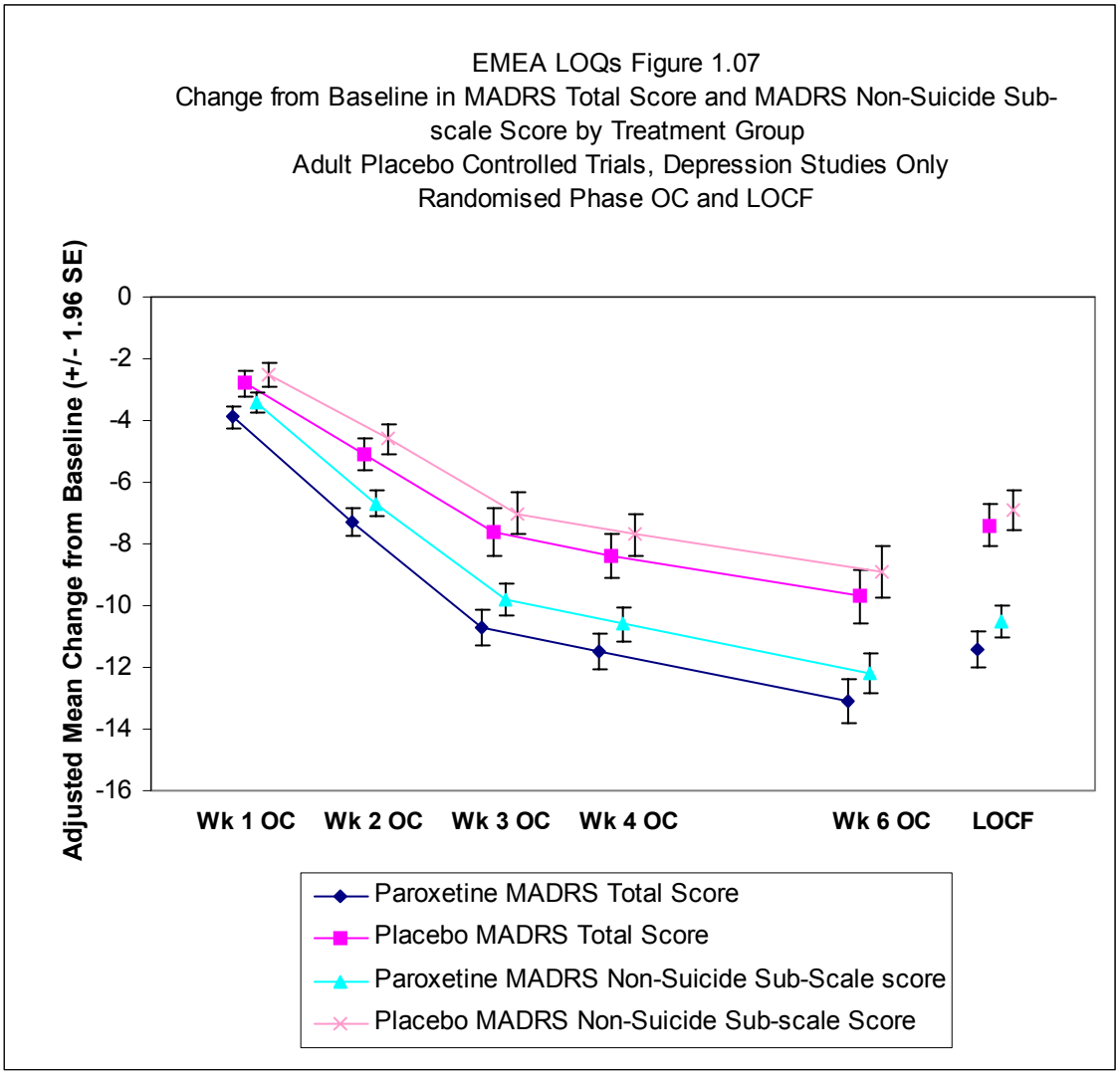
Figure 13.11. Again, omitting the suicide item had little effect on the shape of the plots or the difference over time between the paroxetine and placebo plots.

Figure 13.10 Change from Baseline in HAM-D Total Score and HAM-D Non-Suicide Subscale Score by Treatment Group Adult Placebo Controlled Trials, Depression Studies Only Randomised Phase OC and LOCF



(Data Source: Appendix 1, Table 1.44).

**Figure 13.11 Change from Baseline in MADRS Total Score and MADRS Non-Suicide Subscale Score by Treatment Group
Adult Placebo Controlled Trials, Depression Studies Only
Randomised Phase OC and LOCF**



(Data Source: Appendix 1, Table 1.47).

13.2.4. Conclusion

Paroxetine is an effective antidepressant in young adults, and further analyses of paediatric studies show that paroxetine produces a higher response rate than placebo in adolescents aged 15 – 18. In young adults there is a larger mean improvement in suicide item scores in patients treated with paroxetine than placebo, and emergent suicidal ideation was low in young adults (<2% on both paroxetine and placebo). With little or no evidence to suggest increase in suicidality in young adults, it is not surprising that

analyses conducted including and excluding rating scale suicide items did not detect any evidence of deterioration in other symptoms of depression.

Using data from paediatric depression studies, analyses including and excluding the suicide item scores again revealed no evidence of deterioration in other symptoms.