11. QUESTION 11

It is not clear why no analysis of emergent suicidal ideation was performed using the MADRS scale. This information should be provided.

Response

11.1. Suicidal ideation assessed by MADRS item 10 score

Item 3 of the Hamilton Depression Rating Scale (HAM-D) relates to suicide and is rated on a scale of 0 to 4 as follows: a score of 0 on Item 3 indicates that suicidal ideas or gestures are absent in the patient; a score of 1 indicates that the patient "feels life is not worth living"; a score of 2 indicates that the patient "wishes he/she were dead" or that the patient has "any thoughts of possible death to self"; a score of 3 indicates that the patient has "suicide ideas or gestures" and a score of 4 is given if the patient has made "attempts at suicide". Emergent suicidal ideation was examined based on Item 3 of the HAM-D in studies where this scale was utilised, and was defined as a baseline score of 0 or 1 on Item 3 changing to a score of ≥3 post-baseline, i.e.suicidal ideation emerging on treatment, having been absent at baseline.

In studies that used the Montgomery Asberg Depression Rating Scale (MADRS) rather than the HAM-D it was not so straightforward to define a criterion for emergent suicidal ideation based on the "suicide" item of the MADRS scale.

Item 10 of the MADRS concerns suicidal thoughts. It differs from item 3 of the HAM-D in that suicidal attempts should not in themselves influence the rating, and is rated on a seven point scale as follows:

0 = Enjoys life or takes it as it comes

1

2 = Weary of life. Only fleeting suicidal thoughts

3

4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention

5

6 = Explicit plans for suicide when there is an opportunity. Active preparation for suicide.

Note that descriptions are given for points 0, 2, 4 and 6 on the scale to serve as anchor points. Without a description for each term it is therefore difficult to assess exactly those scores that would correspond to the presence or absence of suicidal ideation e.g. whether the MADRS item 10 score that would correspond to "suicide ideas or gestures" on the HAM-D item 3 is "2", "3" or "4". In fact a score of ≥ 3 in the MADRS item 10 was used in the original responses as an indication of the presence of suicidal ideation, i.e. something more than a score of "2", "only fleeting suicidal thoughts." The cut-off score for absence of suicidal ideation is more difficult to assess from the anchor points. A score of "0" is described as "enjoys life or takes it as it comes". A score of "1" has no description, and a score of "2" is described as "weary of life, only fleeting suicidal thoughts". Hence the question arises as to whether the intermediate score of "1" on MADRS item 10 indicates the absence of suicidal ideation, or whether only a score of "0" indicates absence.

Without a firm cut-off for "absence" of suicidal ideation, it was therefore considered difficult to define "emergent suicidal ideation" using MADRS item 10 scores.

Nevertheless, "emergent suicidal ideation" based on a MADRS item 10 score of 3 or greater, having been absent at baseline, as defined by a score of 0 or 1 at baseline, has been calculated. Findings are shown in Tables 11.1 – 11.3 for adult placebo-controlled, adult active control and paediatric placebo-controlled trials. (Data source: Appendix 1, Tables 1.29 – 1.31).

Table 11.1 Emergent Suicidal Ideation (MADRS item 10) by Treatment Group. Adult Placebo Controlled Trials, Randomised Phase

Treatment Group	n/N	%	Odds ratio	95% CI	p-value
Paroxetine	44/2387	1.8	0.64	[0.43, 0.97]	0.03
Placebo	52/1834	2.8			

Table 11.2 Emergent Suicidal Ideation (MADRS item 10) by Treatment Group. Adult Active Control Trials, Randomised Phase

Treatment Group	n/N	%	Odds ratio	95% CI	p-value
Paroxetine	22/1111	2.0			
Comparator	25/1044	2.4	1.21	[0.68, 2.17]	0.51

Table 11.3 Emergent Suicidal Ideation (MADRS item 10) by Treatment Group. Paediatric Placebo Controlled Trials, Randomised Phase

Treatment Group	n/N	%	Odds ratio	95% CI	p-value
Paroxetine	4/82	4.9	0.41	[0.10, 1.61]	0.20
Placebo	5/45	11.1			

In the adult placebo-controlled trials there was a statistically significant difference in the emergence of suicidal ideation between treatment groups. There was significantly less emergent suicidal ideation in the paroxetine group (44/2387, 1.8%) than in the placebo group (52/1834, 2.8%) [odds ratio 0.64, 95%C.I. 0.43, 0.97; p=0.03].

In adult active control trials, a greater proportion of patients treated with active comparator (25/1044, 2.4%) had emergent suicidal ideation than for patients treated with paroxetine (22/1111, 2.0%), but the difference between groups was not significant.

In the paediatric placebo-controlled trials, 4.9% of patients in the paroxetine treatment group met the definition of emergent suicidal ideation compared to 11.1% in the placebo group but the numbers involved are small (paroxetine 4/82, placebo 5/45) and statistically this difference was not significant (odds ratio 0.41, 95% CI 0.10, 1.61; p=0.20).

These results for emergent suicidal ideation assessed by changes from baseline in MADRS item 10 score were compared with emergent suicidal ideation assessed by changes in HAM-D item 3 score. Emergent suicidal ideation as assessed by HAM-D item 3 score in adult placebo-controlled, adult active control and paediatric placebo-controlled trials is shown in Table 11.4.

Table 11.4 Emergent Suicidal Ideation (HAM-D Item 3) by Treatment Group Randomised Phase

Population	Paroxetine		Placebo or Comparator		Odds Ratio	95% CI	P-value
	n/N	(%)	n/N	(%)			
Adult Placebo-Controlled	31/2325	1.3	18/1515	1.2	1.12	(0.63, 2.02)	0.77
Adult Active Control	31/2737	1.1	24/1974	1.2	0.93	(0.54, 1.59)	0.79
Paediatric Placebo-Controlled	5/154	3.2	1/146	0.7	4.87	(0.56, 42.16)	0.22

Denominators are the number of patients without suicidal ideation at baseline and with at least one post-baseline efficacy assessment.
The OR represents the odds of emergent suicidal ideation on paroxetine compared to subjects on placebo/comparator

In studies using the HAM-D item 3 definition of emergent suicidal ideation, in adult placebo-controlled and active control trials there were no differences in the percentage of patients meeting the definition of emergent suicidal ideation in the paroxetine treatment group compared to the placebo or comparator groups. In the paediatric placebo-controlled trials, 3.2% of patients in the paroxetine treatment group met the definition of emergent suicidal ideation compared to 0.7% in the placebo group but the numbers involved are small (paroxetine 5/154, placebo 1/146) and statistically this difference was not significant (OR 4.87, 95% CI 0.56, 42.16, P=0.22).

There were few studies that employed both the HAM-D and MADRS as measures of depressive symptoms, and therefore there is very little overlap in the studies contributing to the measures of suicidal ideation by change in MADRS item 10 or change in HAM-D item 3. However, although the populations studied by the two methods were different, it can be seen that the MADRS item 10 definition of emergent suicidal ideation produced higher proportions of patients with emergent suicidal ideation than the HAM-D-based definition (Tables 11.1 – 11.4).

11.2. Overall Conclusion

Comparing the results obtained by the two methods, whereas there was little difference between emergent suicidal ideation in adult patients treated with paroxetine and placebo when emergence was based on the HAM-D definition (as reported in the original response, Sep 2003), there was significantly less suicidal ideation in patients treated with paroxetine when emergent suicidal ideation was assessed by the MADRS definition. In addition, in paediatric placebo-controlled studies, whereas when emergent suicidal ideation was assessed by HAM-D item 3 there was more emergent suicidal ideation in paroxetine than placebo treated patients (as reported in the original response, Sep 2003), the opposite was found when emergent suicidal ideation was assessed by MADRS item 10. However, the numbers involved in the paediatric studies that employed HAM-D and MADRS were small, and differences observed between paroxetine and placebo were not statistically significant.