27. QUESTION 27

Comment on the possibility that at the time of the early clinical trials with paroxetine suicide related events may have been considered as lack of efficacy, and as such may not have been recorded as adverse events.

Response

27.1. Introduction

The above question was examined by looking at the incidence of possibly suicide-related AEs in depression studies according to study start date. If possibly suicide-related events were considered as lack of efficacy (in treating depression) and not recorded as adverse events in early clinical trials, a lower incidence of such events would be expected in the earlier depression studies. The incidence of possibly suicide-related AEs by treatment group and study was listed with studies ordered by study start date (Appendix 1, Table 1.32, 1.33, 1.34).

The incidence of suicidality in depression studies according to study start date was also examined using a composite definition of suicidality: patients having a possibly suicide-related AE and/or emergent suicidal ideation (as defined by increasing HAM-D item 3 or MADRS item 10 scores to ≥ 3) on treatment. As this measure depends less on AE reporting, by comparing with incidences of possibly suicide-related AEs in studies, it should allow a better assessment as to whether reporting of possibly suicide-related events has changed over time.

27.1.1. Adult placebo controlled depression studies

The start dates of the 26 placebo-controlled paroxetine depression studies on the central R&D aggregated database range from 02 Dec 1982 to 28 Aug 2001. Two studies, studies 057 and 106 (that both started in May/June 1990), both in patients with brief intermittent depression, had particularly high incidences of possibly suicide-related events in both the paroxetine and placebo treatment groups. Study 057, which required patients to have had a recent episode and a history of suicidal behaviour for entry, had an incidence of 20.6% (27/131) for patients receiving paroxetine, and 21.3% (29/136) in patients treated with placebo. In study 106, the incidence of events was 38.9% (7/18) and 27.8% (5/18) in patients receiving paroxetine and placebo, respectively. As 12 placebo-controlled studies had start dates prior to the start dates of these two atypical studies, and 12 started after them, it was decided to categorise the placebo-controlled studies into those starting before and after studies 057 and 106. The incidence of possibly suicide-related events by treatment group and study start date category are shown in Table 27.1.

Table 27.1 Incidence of Possibly Suicide-Related Events by Treatment Group and Study Start Date Category
Adult Placebo-Controlled Depression Trials

Study Start Dates	Paroxetine % (n/N)	Placebo % (n/N)
Overall (26 studies)	1.7% (58/3421)	1.9% (41/2117)
Overall (omitting studies 057 & 106)	0.73% (24/3272)	0.36% (7/1963)
02 Dec 82 to 04 Jul 89 (12 studies)	0.38% (4/1066)	0.29% (2/693)
19 May 90 to 25 Jun 90 (2 studies*)	22.8% (34/149)	22.1% (34/154)
20 Mar 91 to 28 Aug 01 (12 studies)	0.91% (20/2206)	0.39% (5/1270)

* studies 057 and 106

The incidence of possibly suicide-related events from adult placebo-controlled depression trials was very low in both treatment groups when studies 057 and 106 were omitted. There was a suggestion of higher reporting from paroxetine treated patients in the later study start date category (0.91%, vs. 0.38% in the earlier start date category). The later study start category was sub-divided to see whether a trend for greater reporting of events was maintained in the more recent studies, (Table 27.2).

Table 27.2 Incidence of Possibly Suicide-Related Events by Treatment Group and Study Start Date – Further Analysis of Later Study Start Category
Adult Placebo-Controlled Depression Trials

Study Start Dates	Paroxetine % (n/N)	Placebo % (n/N)
Overall (12 studies)	0.91% (20/2206)	0.39% (5/1270)
20 Mar 91 to 05 Apr 94 (6 studies)	1.06% (10/942)	0.69% (4/578)
10 Sep 96 to 28 Aug 01 (6 studies)	0.79% (10/1264)	0.14% (1/692)

Again, the incidence of possibly suicide-related events was very low in both treatment groups and in both study start time categories. If anything, the incidences in the studies with the more recent start dates were lower than the incidences in studies with earlier start dates.

The incidence of suicidality (as defined by patients having possibly suicide-related events or emergent suicidal ideation) by study start date category is shown in Table 27.3. In comparison with Table 27.1, it can be seen that the incidence of suicidality is higher in both treatment groups by this definition than by possibly suicide-related events alone. In addition, incidences in both treatment groups are similar in the earlier and later study start date categories.

Table 27.3 Incidence of Suicidality (by Composite Definition) by Treatment Group and Study Start Date Category Adult Placebo-Controlled Depression Trials

Study Start Dates	Paroxetine % (n/N)	Placebo % (n/N)
Overall (26 studies)	3.0% (104/3421)	3.8% (81/2117)
Overall (omitting studies 057 & 106)	1.8% (60/3272)	1.8% (36/1963)
02 Dec 82 to 04 Jul 89 (12 studies)	1.6% (17/1066)	1.9% (13/693)
19 May 90 to 25 Jun 90 (2 studies*)	29.5% (44/149)	29.2% (45/154)
20 Mar 91 to 28 Aug 01 (12 studies)	1.9% (43/2206)	1.8% (23/1270)

* studies 057 and 106

27.1.2. Adult active control depression studies

Adult active control depression studies were categorised into similar start date groups as for the adult placebo-controlled depression studies. The incidence of possibly suicide-related events by study start date category in these studies is shown in Table 27.4.

Table 27.4 Incidence of Possibly Suicide-Related Events by Treatment Group and Study Start Date Category Adult Active Control Depression Trials

Study Start Dates	Paroxetine % (n/N)	Comparator % (n/N)
Overall (75 studies)	0.89% (54/6040)	1.29% (59/4589)
17 Oct 80 to 31 Mar 90 (61 studies)	0.95% (22/2325)	0.92% (21/2288)
01 Oct 90 to 11 Apr 01 (14 studies)	0.86% (32/3715)	1.65% (38/2301)

The incidence of events in patients treated with paroxetine was very similar in studies in the two study start categories (of approximately 10 years each). This suggests that reporting practice was consistent over time, but again the incidence of events was very low. Reporting in the active comparator group appeared to be greater in more recent times but that does not necessarily imply a change in reporting practice as a change would then also be expected for paroxetine treated patients. The apparent increase over time in the comparator group more likely reflects the different comparators studied in the later period than in the earlier period.

The data using the composite suicidality measure lead to similar conclusions, (Table 27.5). There was no evidence of increased suicidality over time in the paroxetine studies, but there was an apparent increase in the comparators group.

**Table 27.5 Incidence of Suicidality (by Composite Definition) by Treatment Group and Study Start Date Category
Adult Active Control Depression Trials**

Study Start Dates	Paroxetine % (n/N)	Comparator % (n/N)
Overall (75 studies)	1.6% (94/6040)	2.0% (94/4589)
17 Oct 80 to 31 Mar 90 (61 studies)	1.9% (44/2325)	1.7% (39/2288)
01 Oct 90 to 11 Apr 01 (14 studies)	1.3% (50/3715)	2.4% (55/2301)

27.1.3. Paediatric placebo-controlled depression studies

There have been only three paediatric placebo-controlled depression studies, and all have been conducted relatively recently in comparison with the adult studies in depression. Consequently the incidence of possibly suicide-related events in each study is shown individually in Table 27.6.

**Table 27.6 Incidence of Possibly Suicide-Related Events by Treatment Group and Study Start Date
Paediatric Placebo-Controlled Depression Trials**

Study Start Dates	Paroxetine % (n/N)	Placebo % (n/N)
Overall (3 studies)	3.7% (14/378)	2.5% (7/285)
Study 329 (20 Apr 94)	6.5% (6/93)	2.3% (2/88)
Study 377 (18 May 95)	3.9% (7/181)	4.2% (4/95)
Study 701 (20 Mar 00)	1.0% (1/104)	1.0% (1/102)

The paediatric studies appear to show less reporting of possibly suicide-related events over time. However to assign the lower reporting to when the study was performed would be an over-simplification and ignores other more important factors that affect the incidence of reporting possibly suicide-related events. As in the other types of studies, variations in entry criteria and study population from study to study will affect the reporting of possibly suicide related events. The inclusion of adolescents only in studies 329 and 377 but children and adolescents in study 701 is a much more likely cause of the higher reporting in studies 329 and 377. The apparent difference between studies 329 and 377 with regard to the incidences of possibly suicide-related events on paroxetine in comparison to placebo are accentuated by the incidences of suicidality (by the composite definition), (Table 27.7).

Table 27.7 Incidence of Suicidality (by Composite Definition) by Treatment Group and Study Start Date
Paediatric Placebo-Controlled Depression Trials

Study Start Dates	Paroxetine % (n/N)	Placebo % (n/N)
Overall (3 studies)	5.8% (22/378)	4.6% (13/285)
Study 329 (20 Apr 94)	10.8% (10/93)	3.4% (3/88)
Study 377 (18 May 95)	6.1% (11/181)	9.5% (9/95)
Study 701 (20 Mar 00)	1.0% (1/104)	1.0% (1/102)

27.2. Conclusion

There is the possibility that possibly suicide related events may be considered as lack of efficacy in depression studies and under-reported as adverse experiences. However reporting of such events is low and has remained low even in more recent times. There is little evidence to suggest an appreciably lower rate of reporting of such events in early clinical trials with paroxetine, and therefore little to support the hypothesis that cases considered as lack of efficacy in the past are now more properly described as suicide related events. Even if the hypothesis of AE under reporting (due to regarding as lack of efficacy) is true, there is no evidence of a drug effect over placebo when looking at both efficacy and AE data for suicidal behaviour.