6. QUESTION 6

Provide the narratives of the case reports for the suicide that occurred during clinical trials and an expert report discussing these cases (see also question 14).

Response

6.1. Completed suicides

Patient identifiers for patients who completed suicide during clinical trials that are included in the paroxetine central R&D aggregated database are listed below, (Table 6.1). Patients who committed suicide during a pre-treatment run-in or screening period are not included in this report, nor are. patients committing suicide while receiving placebo in a screening/run-in period.

Table 6.1 Patient Identifiers of Patients who Completed Suicide during Paroxetine Clinical Trials

Patient Number	Study	Study Treatment
083.003.1090	29060/083	Paroxetine
1 13 126	MDUK 13 Wade	Paroxetine
2206 005	Belgian MC Open	Paroxetine
2406.149	German MC Comparative	Paroxetine
245.161.0163	29060/245	Paroxetine
502.037.05146	29060/502	Paroxetine
6 47 003	HP 82 47a Vervarcke	Paroxetine
650.307.06282	29060/650	Paroxetine
7124.012	DFG 124 P32	Paroxetine
057.012.1217	29060/057	Placebo
627.605.01012	29060/627	Placebo
785.721.00716	29060/785	Placebo
197.045.0322	29060/197	Comparator – Imipramine
237I 054	MDF 1727 MC Comparative	Comparator –Clomipramine
6 67 002	HP 83 67 Margo	Comparator – Amitriptyline
7124 023	DFG 124 P32	Comparator – Imipramine
7124 060	DFG 124 P32	Comparator – Imipramine

There have been 17 completed suicides in total (patient narratives for each of these cases are included in Appendix 6). All were in adult studies. Ten were in active control trials, 4 in placebo-controlled trials and 3 in uncontrolled trials. A thorough review of information pertaining to these cases, including review of Case Record Forms and any additional information provided by the investigators, has provided nothing to suggest that these completed suicides, whether by patients receiving paroxetine, active comparators or placebo, were directly attributable to study medication.

Nine of the cases were patients that had received paroxetine, 5 had received active comparator treatment, and three had had placebo. Viewing the results by study type, there is no increased risk of completed suicide on paroxetine in comparison to control treatment. In adult placebo controlled studies, completed suicide occurred in 1/8481 (0.01%) patients treated with paroxetine, and in 3/5808 (0.05%) patients treated with placebo. In adult, active control studies, 5/6522 (0.08%) paroxetine, and 5/4969 (0.10%) active control patients committed suicide (Table 6.2).

Table 6.2 Completed Suicide by Treatment Group and Study Category

Number of Completed Suicides		
Study Treatment	**Paroxetine**	**Placebo / Comparator**
Study Category	**n/N (%)**	**n/N (%)**
Placebo-Controlled	1/8481 (0.01%)	3/5808 (0.05%)
Active Control	5/6522 (0.08%)	5/4969 (0.10%)

Of the nine suicides in patients that received paroxetine, three were in males. The ages at suicide were: female – 18, 42, 56, 58 (two) and 67 years old; males – 23, 35 and 50 years.

Most cases of suicide were in patients treated for depressive disorders, although one patient (502.037.05146) was receiving paroxetine for Social Anxiety Disorder, and two patients (627.605.01012 receiving placebo, and 650.307.06282 receiving paroxetine) were in studies of Post Traumatic Stress Disorder (PTSD).

Whether the suicide occurred while the patient was on-therapy or post-therapy is recorded in Table 6.3. [Patients were considered "on-therapy" if the date of last dose of study medication was on the day of suicide, or the preceding day]. The suicides occurred at a variety of times after starting study medication, (Table 6.3). The nine suicides in patients receiving paroxetine occurred at day 2, day 7, day 8, day 11, 5 weeks, 6 weeks, approximately 4 months and approximately 6 months after starting paroxetine, and in one case 6 days after stopping study medication. The suicides in patients receiving active comparators (imipramine, amitriptyline or clomipramine depending on the study) occurred on: day 18, day 22, day 26 and at 2 weeks and 4 weeks after stopping study mediaction. All suicides in patients who received placebo in the studies, occurred after study medication had been stopped: 17 days, 19 days and 33 days after stopping placebo.

Table 6.3 Completed Suicide – On Therapy / Post Therapy

Number of Completed Suicides				
Study Treatment	**Paroxetine**		**Placebo / Comparator**	
	On Therapy	**Post Therapy**	**On Therapy**	**Post Therapy**
Study Category				
Active Control	4	1	3	2
Placebo-Controlled	1	0	0	3
Uncontrolled	3	0	NA*	NA*
TOTAL	8	1	3	5

* Not applicable

It was of interest to see three post-therapy suicides in patients who had received placebo during study. This obviously cannot be attributed to withdrawal effects and suggests a suppression of suicidality during the course of the study that is then released when study treatment is discontinued. The narratives of the cases did not suggest these events were associated with starting new pharmacotherapy.

There was no apparent link to previous or concomitant medication use, the duration of the patients' conditions, nor to the maximum dose of study medication taken. Of the nine paroxetine cases, the maximum daily dose of paroxetine taken was 20mg (3 cases), 30mg (5 cases) and 50mg (in one). A variety of methods of suicide was used. The nine cases in patients who received paroxetine during studies used hanging (3), overdose (3), shooting, drowning and jumping out of a window.

The patients who committed suicide had various levels of suicidal ideation at entry to the studies. Five patients (one on paroxetine, two each on comparator treatment and placebo) had suicidal ideation (defined as a score of 3 or more on item 3 of the HAM-D scale, or on item 10 of the MADRS) already present at baseline.

In no case did the investigator consider the suicide related to treatment with study medication. From reviewing the Case Record Forms, it is apparent that the majority of patients who had received paroxetine and committed suicide had made suicide attempts or expressed suicidal intentions previously, had family members who had committed suicide, or had adverse family circumstances (e.g. recent deaths of partners).

In conclusion, from review of the cases of completed suicide in our clinical studies with paroxetine, there is no evidence of an increased risk of completed suicide with paroxetine compared to control treatment, nor that paroxetine (or other study medication) was the direct cause of the suicides recorded.