1. QUESTION 1

The analysis of suicidal related behaviours in the clinical trial data set is lacking the necessary detail and therefore there is a concern that potentially existing associations might be diluted or masked. Therefore the following analyses and information are requested:

1.1 As most suicidal behaviours occur during the first month of treatment and more during the first 2 weeks, an analysis in which only these time periods are considered is requested. Note that in the analysis, the denominators should be the number of patients at risk during the first 2 weeks and during the first month and not total exposure time.

1.2 To address the issue of baseline suicidal risk, two analyses are requested. In the first, studies should be grouped according to the exclusion criteria used with respect to suicidal risk so that studies that excluded patients with suicidal risk are analysed separately from those that did not. The grouping of studies should be done once globally (i.e. suicidal risk excluded/ not excluded regardless of method used to define this) and once more refined (i.e. taking into account the method used). The second analysis should stratify patients by level of suicidal risk at baseline. This should be defined based on item 3 in the HAM-D and any other information that is available about suicidality.

1.3 A stratified analysis by dose should be performed.

1.4 A stratified analysis by previous exposure to paroxetine and, separately, by previous exposure to any SSRI should be performed. In addition, simultaneous stratification by previous SSRI/paroxetine experience and age bands (including children and adolescents) should be performed.

1.5 In order to increase the transparency of the analyses outlined above, please provide a table in which all clinical trials in the company's database concerning paroxetine are indicated including the following information for each trial: type of trial, duration, age of patients included, dosing, in/excluding criteria with respect to suicide (this should include specific information about how suicide risk was defined and measured) baseline level of suicidal risk, information about previous exposure to paroxetine and/or other SSRIs.

Response

1.1. Introduction

It is stated that most suicidal behaviours occur during the first month of treatment and more during the first two weeks. While it is true that approximately 50% of possibly suicide-related events occurred during the first four weeks of treatment in the adult placebo-controlled trials, and more than 50% occurred within the first four weeks of treatment in the adult active control studies, this may reflect the duration of the studies rather than implying a particular issue in this regard in the first weeks of treatment. The adult placebo-controlled trials were generally of 8-12 weeks duration, and the adult active controlled studies largely 6-8 weeks. As the time of first onset of events is recorded, it is perhaps not surprising that 50% or more of patients reporting such events did so within the first four weeks of study. There was no suggestion from the adult studies that possibly suicide-related events in patients treated with paroxetine occurred at a higher incidence, or sooner after starting treatment than in patients treated with placebo.

It should be noted, however, that there was no suggestion from the paediatric placebo-controlled studies that most possibly suicide-related events that were observed occurred in the first four weeks of treatment. Indeed, as included in the original response, examination of the time to first onset of such events in the paediatric placebo-controlled studies revealed no excess of reports in either the paroxetine or placebo treated patients in the first weeks of treatment (Table 1.1). As for the adult studies, there was no difference between the paroxetine treatment group and placebo group with respect to the time to first occurrence of these events in the paediatric trials.

Table 1.1 Time to First Onset of Possibly Suicide-Related Events by Treatment Group
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Time Period	Paroxetine (N=738)	Placebo (N=647)
Total number of patients with event	18	7
Week 1	0 (0.0%)	1 (14.3%)
Week 2	2 (11.1%)	0 (0.0%)
Week 3	0 (0.0%)	0 (0.0%)
Week 4	3 (16.7%)	0 (0.0%)
Week 5-6	6 (33.3%)	2 (28.6%)
Week 7-8	1 (5.6%)	1 (14.3%)
Week 9-12	4 (22.2%)	1 (14.3%)
Week 13+	2 (11.1%)	2 (28.6%)

1.1.1. Definition of "possibly suicide-related events" and "self-harm"

This section describes the method used to establish adverse events occurring in paroxetine clinical trials which could possibly be related to suicide and includes events ranging from completed suicides and suicide attempts through to mild acts of self harm and through to suicidal thoughts/ideation. As such, it is an inclusive definition of events. Most of the possibly suicide-related events code to a preferred term of "emotional lability" which also encompasses events such as "crying" and "mood changes". Therefore, in order to establish a definition of events that is sensitive and specific, the following strategy was employed across the central R&D aggregated database to search for adverse event terms that met the definition of "possibly suicide-related":

1. Patients were included in the "possibly suicide-related" category if they met any of the following criteria:

a Preferred term was "Emotional lability" *and* the verbatim term contained any of the following text strings: "asphyxia", "attempt", "burning", "car exhaust", "carbon monoxide", "cut", "drown", "dsh", "d.s.h", "electrocut", "firearm", "gas", "gun", "hang", "hung", "immolat", "jump", "lacerat", "mutilat", "o/d", "o.d.", "overdos", "over-dos", "over dos", "poison", "plastic bag", "railway", "rifle", "self damag", "self harm", "self inflict", "self injur", "self-damag", "self-harm", "s.i.", "self-inflict", "self-injur", "s.h.", "shoot", "shot", "slash", "suffocat", "suic".

b Preferred term was "Intentional overdose" or "Overdose". (Specifically, "Accidental overdose" was excluded.)

c Any other cases where the verbatim term contained the text string "overdos", "over-dos", "over dos", or "suic".

d Patients successfully completing suicide were included in the "possibly suicide-related" category. These cases were obtained from a computer search of the cause of death. Where the cause of death included the text string "suic" or "overdos" then the patient was included in the "possibly suicide-related" category, with the exception of any case where the cause of death *also* included the text string "accident". Additionally a manual review of all deaths was undertaken to identify any additional cases.

e Any terms found through this search which were clearly erroneous were agreed and removed by senior members of Biomedical Data Sciences, GSK and Clinical Development and Medical Affairs, GSK.

2. Terms identified above to be used in computer searches were *not* case-sensitive.

By employing this search strategy, the definition of possibly suicide-related events was largely objective with limited requirement for subjective manual interpretation. It must be noted that if all adverse events terms (regardless of preferred term coding) had been searched, this would have led to the inclusion of more erroneous terms and resulted in a less specific definition with more "noise".

The definition of "self harm" adhered to in this section follows the definition of possibly suicide-related but removes events that are ideas or thoughts. Therefore, the definition of self harm is restricted to those events that involve an action. But, as for the possibly suicide-related events, this definition still includes cases of mild self harm such as face slapping.

The following strategy was employed across the central R&D aggregated database to search for adverse event terms that meet the definition of self-harm:

1. Patients were included in the "self-harm" category if they met any of the following criteria:

a Preferred term was "Emotional lability" *and* the verbatim term contained any of the following text strings: "asphyxia", "attempt", "burning", "car exhaust", "carbon monoxide", "cut", "drown", "dsh", "d.s.h", "electrocut", "firearm", "gas", "gun", "hang", "hung", "immolat", "jump", "lacerat", "mutilat", "o/d", "o.d.", "overdos", "over-dos", "over dos", "poison", "plastic bag", "railway", "rifle", "self damag", "self harm", "self inflict", "self injur", "self-damag", "self-harm", "s.i.", "self-inflict", "self-injur", "s.h.", "shoot", "shot", "slash", "suffocat", "suic".

b Preferred term was "Intentional overdose" or "Overdose". (Specifically, "Accidental overdose" was excluded.)

c Any other cases where the verbatim term contained the text string "overdos", "over-dos", "over dos", or "suic".

d Any of the cases identified from the searches specified above were removed if the verbatim term contained any of the following text strings: "idea", "intent", "plan", "tendency", "think", "thought", "threat", or "wish". Additionally, any cases where the verbatim term contained only the text "suicidal" or "suicidality" were *not* included as "self-harm".

e Patients successfully completing suicide were included in the "self-harm" category. These cases were obtained from a computer search of the cause of death. Where the cause of death included the text string "suic" or "overdos" then the patient was included in the "self-harm" category, with the exception of any case where the cause of death *also* included the text string "accident". Additionally a manual review of all deaths was undertaken to identify any additional cases.

f Any terms found through this search which were clearly erroneous were agreed and removed by senior members of Biomedical Data Sciences, GSK and Clinical Development and Medical Affairs, GSK. This also applied to erroneous terms identified for exclusion in 1d above.

2. Terms identified above to be used in computer searches were *not* case-sensitive.

The above methodology for identifying cases of possibly suicide related events in clinical studies was based on examination of adverse events reported. It is recognised that other search modalities may detect different cases. In paediatric studies, a wider search algorithm, applied at the request of the FDA (search of all preferred terms for the target text strings), identified two additional patients (both had received paroxetine) making a total of 39 patients with potential events of interest (paroxetine n=27, imipramine n=4, placebo n=8). In addition to these programmed searches, a recent thorough "manual" review of all serious adverse event (SAE) forms and narratives in the 6 paediatric studies in question was undertaken to identify any potential additional cases which were not identified by the algorithms. This review identified an additional eight events potentially suggestive of intentional self-injury, suicidal ideation, or suicide attempt. All eight patients in question had received paroxetine, and were from the MDD studies. The manner in which these events were recorded/reported by the investigator and/or how these verbatim terms were subsequently coded were such that these events would not have been identified by the algorithms, and have therefore not been included in the analyses for the responses related to possibly suicide related adverse events in paediatric patients.

1.1.2. Reports of suicidal behaviour within the first two and four weeks of treatment

The incidence of possibly suicide-related events and self-harm events that occurred within the first 2 weeks and the first 4 weeks of starting treatment overall (and by indication) in adult placebo-controlled, adult active control, and paediatric placebo-controlled studies are tabulated in Appendix 1, Tables 1.01 – 1.12. The denominators used are the number of patients receiving the drug at any time during the first two or four weeks of treatment (i.e. the total number of patients receiving the drug) and are not corrected for exposure time.

1.1.2.1. Possibly suicide-related events in adult placebo controlled trials

Overall, in adult placebo-controlled studies, the incidence of possibly suicide-related events during the first two weeks of treatment was 0.2% (13/7892) and 0.3% (17/5207) in patients randomised to paroxetine and placebo, respectively, (Table 1.2). The incidence of such events in patients with depression was 0.4% in both treatment groups (paroxetine 12/3360; placebo 9/2053). The incidence was no higher on paroxetine than placebo in any of the indications studied (depression, generalised anxiety disorder, obsessive compulsive disorder, premenstrual dysphoric disorder, post traumatic stress disorder, panic disorder and social anxiety disorder). All but one (12/13) of the events observed during the first two weeks of treatment with paroxetine were reported in depression studies, whereas approximately half (9/17) of such events in patients treated with placebo were from depression studies. The incidence of possibly suicide-related events during the first two weeks of treatment in indications other than depression was 0.02% (1/4532) in patients treated with paroxetine, and 0.25% (8/3154) in patients treated with placebo, (Table 1.2).

Table 1.2 Incidence of Possibly Suicide-Related Adverse Events During the First 2 and 4 Weeks of Treatment by Treatment Group and Indication (Excluding Relapse Prevention Studies)
Adult Placebo Controlled Trials
On-Therapy

	2 Weeks			4 Weeks		
Indication	**Paroxetine n/N (%)**	**Placebo n/N (%)**	**P value**	**Paroxetine n/N (%)**	**Placebo n/N (%)**	**P value**
Overall	13/7892 (0.2%)	17/5207 (0.3%)	0.06	35/7892 (0.4%)	28/5207(0.5%)	0.44
Depression	12/3360 (0.4%)	9/2053 (0.4%)	0.66	33/3360 (1.0%)	18/2053 (0.9%)	0.77
GAD	0/904 (0.0%)	0/697 (0.0%)	-	0/904 (0.0%)	1/697 (0.1%)	0.44
OCD	0/542 (0.0%)	3/265 (1.1%)	0.04	0/542 (0.0%)	3/265 (1.1%)	0.04
PMDD	0/760 (0.0%)	0/379 (0.0%)	-	0/760 (0.0%)	0/379 (0.0%)	-
PTSD	1/698 (0.1%)	2/510 (0.4%)	0.58	2/698 (0.3%)	3/510 (0.6%)	0.66
Panic	0/920 (0.0%)	2/780 (0.3%)	0.21	0/920 (0.0%)	2/780 (0.3%)	0.21
SAD	0/708 (0.0%)	1/523 (0.2%)	0.42	0/708 (0.0%)	1/523 (0.2%)	0.42

The incidence of possibly suicide-related events during the first four weeks of treatment in adult placebo-controlled studies again showed similar incidences overall in paroxetine treated (0.4%, 35/7892) and placebo treated patients (0.5%, 28/5207), (Table 1.2). In depression studies the incidences were 1.0% (33/3360) and 0.9% (18/2053) in patients taking paroxetine and placebo, respectively. A large proportion of the possibly suicide-related events in patients with depression occurred in study 057, a study that required patients to have a recent episode and a history of suicidal behaviour for entry. Omitting study 057, the incidence of possibly suicide-related events during the first four weeks of treatment in depression studies was 0.6% (19/3229) and 0.4% (7/1917) in patients treated with paroxetine and placebo, respectively (Appendix 1, Table 1.02a). The incidence of possibly suicide-related events during the first four weeks of treatment in studies in indications other than depression was 0.04% (2/4532) in patients treated with paroxetine, and 0.32% (10/3154) in patients treated with placebo.

1.1.2.2. Possibly suicide-related events in adult active control trials

Overall, the incidence of possibly suicide-related events during the first 2 weeks of treatment in adult active control studies was 0.3% (18/6522) in paroxetine and 0.5% (24/4969) in active comparator treated patients, (Table 1.3). In studies in comparison with other SSRIs, the incidence in patients receiving paroxetine was again 0.3% (4/1200), and in patients receiving other SSRIs was 1.1% (13/1218), an odds ratio of 0.31 (95% CI 0.1, 0.95, p=0.05), (Appendix 1, Table 1.03). Overall, the incidence of events in the first 4 weeks of treatment was 0.6% (38/6522) and 0.9% (44/4969) in patients treated with paroxetine and active comparator, respectively. In studies comparing paroxetine and other SSRIs, 0.8% (10/1200) of paroxetine patients and 1.5% (18/1218) of patients treated with other SSRIs reported possibly suicide-related events during the first four weeks of treatment (Table 1.3).

**Table 1.3 Incidence of Possibly Suicide-Related Adverse Events During First 2 and 4 weeks of Treatment by Treatment Group and Control Medication Class (Excluding Relapse Prevention Studies)
Adult Active Control Trials
On-Therapy**

	2 Weeks			4 Weeks		
Control Medication Class	Paroxetine n/N (%)	Comparator n/N (%)	P value	Paroxetine n/N (%)	Comparator n/N (%)	P value
Overall	18/6522 (0.3%)	24/4969 (0.5%)	0.09	38/6522 (0.6%)	44/4969 (0.9%)	0.06
Benzo-diazepine	0/76 (0.0%)	0/77 (0.0%)	-	0/76 (0.0%)	0/77 (0.0%)	-
SSRI	4/1200 (0.3%)	13/1218 (1.1%)	0.05	10/1200 (0.8%)	18/1218 (1.5%)	0.18
Tetracyclic	0/527 (0.0%)	0/518 (0.0%)	-	2/527 (0.4%)	3/518 (0.6%)	0.68
Tricyclic	9/2953 (0.3%)	10/2754 (0.4%)	0.82	17/2953 (0.6%)	21/2754 (0.8%)	0.42
Other	5/1766 (0.3%)	1/402 (0.2%)	1.00	9/1766 (0.5%)	2/402 (0.5%)	1.00

1.1.2.3. Possibly suicide-related events in paediatric placebo controlled trials

In paediatric placebo controlled trials 0.3% (2/642) of patients receiving paroxetine and 0.2% (1/549) of patients receiving placebo reported possibly suicide-related AEs during the first 2 weeks of treatment (Table 1.4). In those studies the incidence of possibly suicide-related events during the first 4 weeks of treatment was 0.9% (6/642) and 0.4% (2/549) in patients receiving paroxetine and placebo, respectively. The incidences in paediatric depression trials during the first 4 weeks of treatment were 1.1% (4/378) for paroxetine treated patients and 0.7% (2/285) for placebo treated patients.

**Table 1.4 Incidence of Possibly Suicide-Related Adverse Events During First 2 and 4 weeks of Treatment by Treatment Group and Indication (Excluding Relapse Prevention Studies)
Paediatric Placebo Controlled Trials
On-Therapy**

	2 Weeks			4 Weeks		
Indication	Paroxetine n/N (%)	Placebo n/N (%)	P value	Paroxetine n/N (%)	Placebo n/N (%)	P value
Overall	2/642 (0.3%)	1/549 (0.2%)	1.00	6/642 (0.9%)	2/549 (0.4%)	0.30
Depression	2/378 (0.5%)	1/285 (0.4%)	1.00	4/378 (1.1%)	2/285 (0.7%)	0.70
OCD	0/99 (0.0%)	0/107 (0.0%)	-	1/99 (1.0%)	0/107 (0.0%)	0.48
SAD	0/165 (0.0%)	0/157 (0/0%)	-	1/165 (0.6%)	0/157 (0.0%)	1.00

1.1.2.4. Self harm events

The incidence of self-harm during the first two, and first four weeks of treatment in adult placebo controlled, adult active control trials, and paediatric placebo-controlled trials are given in Appendix 1, Tables 1.07 – 1.12 and are broadly similar to the findings for possibly suicide-related events. [Table 1.5 shows the findings in adult placebo controlled trials].

The incidence of self-harm was low and there was no greater incidence of self-harm in the first two and four weeks of treatment in patients treated with paroxetine in the adult studies than patients receiving placebo or active comparator. Similarly, there was little to suggest that the incidence of self-harm in the first weeks of treatment was greater in paediatric patients receiving paroxetine than in those receiving placebo. The incidence of self harm during the first four weeks of treatment in the paediatric placebo-controlled trials was 0.6% (4/642) and 0.4% (2/549) in patients receiving paroxetine and placebo, respectively (Appendix 1, Table 1.12). All events of self harm reported during the first four weeks of treatment in the paediatric placebo-controlled trials were from depression studies.

Table 1.5 Incidence of Self Harm During First 2 and 4 weeks of Treatment by Treatment Group and Indication (Excluding Relapse Prevention Studies)
Adult Placebo Controlled Trials
On-Therapy

	2 Weeks			4 Weeks		
Indication	**Paroxetine n/N (%)**	**Placebo n/N (%)**	**P value**	**Paroxetine n/N (%)**	**Placebo n/N (%)**	**P value**
Overall	8/7892 (0.1%)	11/5207 (0.2%)	0.16	23/7982 (0.3%)	17/5207 (0.3%)	0.75
Depression	7/3360 (0.2%)	7/2053 (0.3%)	0.41	22/3360 (0.7%)	13/2053 (0.6%)	1.00
GAD	0/904 (0.0%)	0/697 (0.0%)	-	0/904 (0.0%)	0/697 (0.0%)	-
OCD	0/542 (0.0%)	1/265 (0.4%)	0.33	0/542 (0.0%)	1/265 (0.4%)	0.33
PMDD	0.760 (0.0%)	0.379 (0.0%)	-	0/760 (0.0%)	0/379 (0.0%)	-
PTSD	1/698 (0.1%)	1/510 (0.2%)	1.00	1/698 (0.1%)	1/510 (0.2%)	1.00
Panic	0/920 (0.0%)	1/780 (0.1%)	0.46	0/920 (0.0%)	1/780 (0.1%)	0.46
SAD	0/708 (0.0%)	1/523 (0.2%)	0.42	0/708 (0.0%)	1/523 (0.2%)	0.42

It can be assumed that the difference between reports of possibly suicide-related behaviour and reports of self-harm, are reports of suicidal ideation. It was noted in adult studies comparing paroxetine and other SSRIs (Appendix 1, Table 1.09 and Table 1.10) that the excess of possibly suicide-related AEs reported during the first weeks of treatment in other SSRIs compared to paroxetine was not due to self harm, and was therefore likely due to more reports of suicidal ideation in patients treated with the other SSRIs than with paroxetine. For example, in the first two weeks of treatment, the incidences of possibly suicide-related events were 0.3% (4/1200) and 1.1% (13/1218) in patients treated with paroxetine and other SSRIs, respectively, and the incidences of self-harm were 0.2% (2/1200) and 0.1% (1/1218) in patients taking paroxetine and other SSRIs, respectively (Appendix 1, Tables 1.03 and 1.09). Similarly, in the first four weeks of treatment, the incidences of possibly suicide-related events were 0.8% (10/1200) and 1.5% (18/1218) in patients treated with paroxetine and other SSRIs, respectively, and the incidences of self-harm were 0.3% (4/1200) and 0.3% (4/1218) in patients taking paroxetine and other SSRIs, respectively (Appendix 1, Tables 1.04 and 1.10).

1.1.3. Conclusions

From review of the data from the first two and four weeks of treatment in clinical studies, there is no evidence that paroxetine causes suicidal behaviour or self harm in adults. Indeed, paroxetine may reduce the risk of suicidality in adults compared to other antidepressants. In paediatric studies, the incidence of possibly suicide-related events during the first two and four weeks of treatment was low, and did not suggest that the higher rate of such events observed in paroxetine patients in paediatric placebo-controlled trials overall, occurred early during treatment.

1.2. Introduction

The request was for analyses grouping studies according to the exclusion criteria used with respect to suicidal risk so that studies that excluded patients with suicidal risk are analysed separately from those that did not. However, the analyses provided cannot be as straightforward as requested above. The paroxetine studies did not have exclusion criteria that assured the exclusion of patients with suicidal risk. It cannot be assumed that patients enrolled in these studies (especially patients with depression) had no risk of suicide, regardless of the exclusion criteria. Consequently, for most studies, the exclusion criterion regarding suicidal risk based exclusion on severity or degree of risk, or on known, established or current risk. Various exclusion criteria were used (see response to Question 1.5 for exclusion criteria with respect to suicide risk employed in each study). These ranged from a study that required a recent episode and a history of suicidal behaviour (to investigate prevention of recurrent suicidal behaviour in patients with intermittent brief depression) to early studies in which no criteria regarding risk of suicide was specified. From a review of these criteria it was decided that the most appropriate categories in which to group studies were studies in which:

1. Suicidal behaviour was required
2. No specific criteria regarding suicidal behaviour were given
3. Patients with severe or serious risks were excluded
4. Patients with known, established or current risk were excluded

Generally, the decision regarding risk of suicide was based on the investigator's opinion. However, in some studies, HAM-D item 3 (the suicide item) score was used to determine eligibility, patients with a score of 4 (described as "attempts at suicide (any serious attempts rate 4)") being excluded.

Therefore studies are assessed "globally" (in the four categories outlined above) in section 1.2.1. Further, a more "refined" analysis of studies, by specific method used to determine eligibility, is assessed in section 1.2.1. [However the only more "refined" analysis that was possible was by sub-category of category 3 ("Patients with severe or serious risks") for adult active control studies. The only studies to assess suicidal risk by anything other than the investigator's opinion were some adult active control trials in which eligibility regarding severe or serious suicidal risk was determined by HAM-D item 3 score]. The "second analysis", that stratified patients by level of suicidal risk at baseline, is outlined in section 1.2.2.

1.2.1. Suicide related behaviours in studies with different suicidality design criteria

The incidence of possibly suicide-related events and self harm occurring during treatment in adult placebo controlled trials, in adult active control trials and in paediatric placebo controlled trials are given in Appendix 1, Tables 1.13 – 1.18.

1.2.1.1. Possibly suicide-related events – Adult placebo-controlled trials

Overall, in adult placebo controlled studies (Table 1.6), the incidence of possibly suicide-related events was 0.8% (66/8481) in patients that received paroxetine and 0.9% (55/5808) in patients that took placebo. The vast majority of the patients in the adult placebo controlled studies participated in studies in which severe or serious risks of suicide were excluded, or in which known, established or current risk was excluded. In both types of study, the incidence of possibly suicide-related behaviour was the same in the paroxetine and placebo groups. In studies in which severe or serious risk was excluded, the incidence in paroxetine patients was 0.6% (34/6180), and was 0.6% (22/3984) in placebo patients. In studies in which known, established or current risk of suicide was excluded, the incidence in both the paroxetine and placebo groups was 0.2% (paroxetine 5/2149, placebo 4/1678). In the other categories, incidences were again remarkably similar in the paroxetine and placebo groups. For patients in the study in which a recent episode of suicidal behaviour was required, the incidence of possibly suicide-related behaviour was 20.6% (27/131) in the paroxetine group and 21.3% (29/136) in the placebo group. For patients in studies with no specific entry criteria regarding suicidal behaviour, no possibly suicide-related events were observed (paroxetine 0/21, placebo 0/10), (Table 1.6); (Data Source: Appendix 1, Table 1.13). There was no adult placebo-controlled study that assessed entry on grounds other than the investigator's opinion of suicidal risk. Hence a "refined" analysis, based on different methods used to define eligibility, was not possible in this population of studies.

Table 1.6 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Suicidality Design Criteria
Adult Placebo Controlled Trials
On-Therapy

Suicidality Design Criteria	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
'Global' Criteria				
Suicidal behaviour required	27/131 (20.6%)	29/136 (21.3%)	0.96 (0.53, 1.73)	1.00
No specific criteria	0/21 (0.0%)	0/10 (0.0%)	-	-
Severe or serious risks excluded	34/6180 (0.6%)	22/3984 (0.6%)	1 (0.58, 1.71)	1.00
Known, established or current risk excluded	5/2149 (0.2%)	4/1678 (0.2%)	0.98 (0.26, 3.64)	1.00

1.2.1.2. Possibly suicide-related events – Adult active control trials

There was no study amongst the adult active control trials that required suicidal behaviour for entry and so studies in this group were split only into those in which there were no specific exclusion criteria regarding suicidality, those in which severe or serious risk of suicide was excluded, and those in which known, established or current risk was excluded (Table 1.7). This group of trials also included studies that excluded patients with a baseline HAM-D item 3 score of 4. Hence, the studies in which severe or serious risk was excluded contain studies that assessed the risk by different methods, most by the investigator's opinion, and some by HAM-D item 3 score. Two analyses have been performed on the data from this set of studies. One that groups studies according to the suicidality design criteria, and another that takes into account the method used to assess entry to those studies that excluded patients with severe or serious suicidal risk. Overall, the incidence of possibly suicide-related events in the adult active control studies was 0.8% (55/6522) in patients receiving paroxetine and 1.3% (63/4969) in patients receiving active comparators. There was little difference in the relative incidences (paroxetine compared to active comparator) reported in the different categories of studies. In studies with no specific criteria, the incidence of possibly suicide-related events was 0.4% (3/857) for paroxetine and 0.6% (5/850) for active comparator patients. In patients from studies in which severe or serious risk of suicide was excluded the incidences were 0.9% (37/4318) and 1.3% (35/2790) for paroxetine and active comparator patients, respectively, and the corresponding incidences for patients from studies in which known, established or current suicidal risk was excluded were 1.1% (15/1347) and 1.7% (23/1329), (Table 1.7); (Data Source: Appendix 1, Table 1.14).

Table 1.7 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Suicidality Design Criteria
Adult Active Controlled Trials
On-Therapy

Suicidality Design Criteria	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.03
'Global' Criteria				
No specific criteria	3/857 (0.4%)	5/850 (0.6%)	0.59 (0.14, 2.49)	0.51
Severe or serious risks excluded	37/4318 (0.9%)	35/2790 (1.3%)	0.68 (0.43, 1.08)	0.11
Known, established or current risk excluded	15/1347 (1.1%)	23/1329 (1.7%)	0.64 (0.33, 1.23)	0.19

In the "refined" analysis of the adult active controlled study population, it was unfortunate that the number of patients enrolled into studies that excluded patients with severe or serious suicidal risk based on a HAM-D item 3 score of 4 was relatively low in comparison to the number enrolled in studies in which a similar exclusion (severe or serious suicidal risk) was assessed by the investigator's opinion. However, the incidences of possibly suicide-related events were similar for the two methods used to define entry. In patients from studies that based entry on the HAM-D item 3 score, incidences were 0.8% (1/126) in patients treated with paroxetine, and 0.8% (1/125) in patients treated with active comparator. In studies that relied on the investigator's opinion of suicidal risk, the

incidence in the paroxetine group was 0.9% (36/4192) and 1.3% (34/2665) in the active comparator group.

1.2.1.3. Possibly suicide-related events – Paediatric placebo-controlled trials

The entry criteria for the paediatric placebo controlled trials were such that the studies could be grouped into those in which severe or serious suicidal risk was excluded, and those in which known, established or current risk was excluded (Table 1.8). In these paediatric placebo controlled trials, the overall incidence of possibly suicide-related events during the on therapy period was 2.4% (18/738) in paroxetine patients and 1.1% (7/647) in placebo patients. The incidences in studies where severe or serious suicidal risks were excluded were 3.0% (16/535) and 1.4% (6/438) in paroxetine and placebo patients, respectively. In studies that excluded known, established or current suicidal risk, the incidence was 1.0% (2/203) in paroxetine treated patients, and 0.5% (1/209) in patients taking placebo (Data Source: Appendix 1, Table 1.15).

Table 1.8 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Suicidality Design Criteria Paediatric Placebo Controlled Trials On-Therapy

Suicidality Design Criteria	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.07
'Global' Criteria				
Severe or serious risks excluded	16/535 (3.0%)	6/438 (1.4%)	2.22 (0.86, 5.72)	0.13
Known, established or current risk excluded	2/203 (1.0%)	1/209 (0.5%)	2.07 (0.19, 23)	0.62

To summarise, the incidence of possibly suicide-related events varied depending on the criteria regarding suicidal risk used to determine entry to studies. However, in adult placebo controlled studies the incidence of events was similar for paroxetine and placebo within each grouping of studies. In the adult active control studies, the incidence of possibly suicide-related events was lower on paroxetine compared to comparator, and in the paediatric placebo controlled studies the incidence of possibly suicide-related events was higher on paroxetine than placebo, but the relative incidences on paroxetine versus comparator/placebo were similar across the study grouping categories. There was no study group in both adult and paediatric datasets in which paroxetine produced an apparently different relative incidence of possibly suicide-related events in comparison with its comparator (placebo or active control).

1.2.1.4. Self harm events

Similar conclusions are drawn from reviewing the incidences of self harm in studies grouped by suicidality design criteria. An example, incidence of self-harm by suicidality design criteria in adult placebo-controlled studies, is given below, (Table 1.9); (Data Sorce: Appendix 1, Table 1.16 – 1.18). The only apparent inconsistency comes from the

paediatric studies. Overall, the incidence of self harm in the paediatric placebo controlled trials was 2.0% (15/738) for paroxetine and 0.8% (5/647) for placebo. The incidence of self harm in paediatric placebo controlled trials that excluded patients with known, established or current suicidal risk was similar for paroxetine and placebo patients (0.5% in both groups; paroxetine 1/203, placebo 1/209) whereas in studies that excluded patients with severe or serious suicidal risk it was 2.6% (14/535) for paroxetine and 0.9% (4/438) for placebo patients. However, the number of cases of self-harm was low, and so it cannot be concluded that patients in studies that excluded patients with severe or serious suicidal risk are more likely to have self harm events than those in studies that excluded patients with known, established or current risk of suicide.

Table 1.9 Incidence of Self Harm by Treatment Group and Suicidality Design Criteria
Adult Placebo Controlled Trials
On-Therapy

Suicidality Design Criteria	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	51/8481 (0.6%)	38/5808 (0.7%)	0.92 (0.6, 1.4)	0.75
'Global' Criteria				
Suicidal behaviour required	26/131 (19.8%)	28/136 (20.6%)	0.96 (0.53, 1.74)	1.00
No specific criteria	0/21 (0.0%)	0/10 (0.0%)	-	-
Severe or serious risks excluded	21/6180 (0.3%)	10/3984 (0.3%)	1.35 (0.64, 2.88)	0.47
Known, established or current risk excluded	4/2149 (0.2%)	0/1678 (0.0%)	-	0.14

1.2.2. Suicidal behaviour stratified by level of suicidal risk at baseline

As reported in the original response, the incidence of on-therapy possibly suicide-related events and self-harm by treatment group and baseline suicidal risk is summarised in the following section. The presence of suicidal risk at baseline is defined here as those patients with baseline suicidal ideation, (HAM-D Item 3 ≥3 or MADRS Item 10 ≥3 at baseline). Note that cases from studies where the HAM-D or the MADRS were not used or cases where Item 3 of the HAM-D or Item 10 of the MADRS were not assessed were classed as "absent". Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

1.2.2.1. Possibly Suicide Related Events - Adult Placebo Controlled Trials

Overall the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 0.9% in the placebo group (Table 1.10). Fifty one of the 66 (77%) events in the paroxetine group and 34 of the 55 (62%) events in the placebo group occurred in patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed. However, in this sub-group, there was no difference in the incidence of possibly suicide-related events between treatment groups (paroxetine 51/8037 (0.6%), placebo 34/5517 (0.6%), OR 1.03, 95% CI 0.67, 1.59, P=0.91). In the sub-group of patients who did have baseline suicidal ideation, there was a lower incidence of possibly suicide-related events in patients in the paroxetine treatment group

compared to the placebo group and this difference between treatment groups was statistically significant (paroxetine 15/444 (3.4%), placebo 21/291 (7.2%), OR 0.45, 95% CI 0.23, 0.89, P=0.023).

Table 1.10 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Risk
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
Absent*	51/8037 (0.6%)	34/5517 (0.6%)	1.03 (0.67, 1.59)	0.91
Present	15/444 (3.4%)	21/291 (7.2%)	0.45 (0.23, 0.89)	0.023

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.2. Possibly Suicide Related Events - Adult Active Control Trials

Overall the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 1.3% in the active comparator group (Table 1.11). Forty one (41) of the 55 (75%) events in the paroxetine group and 48 of the 63 (76%) events in the active comparator group occurred in patients with no baseline suicidal ideation or in cases where baseline suicidal ideation was not assessed. In this sub-group, there was a lower incidence of possibly suicide-related events in patients in the paroxetine treatment group compared to the active comparator group and this difference between treatment groups was statistically significant (OR 0.65, 95% CI 0.42, 0.98, P=0.041). There was no significant difference in the incidence of possibly suicide-related events between treatment groups in the sub-group of patients who did have baseline suicidal ideation, however, again the incidence appeared to be lower in the paroxetine group (paroxetine 1.9%, comparator 2.6%, OR 0.73, 95% CI [0.35, 1.53], P=0.45).

Table 1.11 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Risk
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.031
Absent*	41/5787 (0.7%)	48/4387 (1.1%)	0.65 (0.42, 0.98)	0.041
Present	14/735 (1.9%)	15/582 (2.6%)	0.73 (0.35, 1.53)	0.45

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.3. Possibly Suicide Related Events – Paediatric Placebo Controlled Trials

In paediatric placebo-controlled studies, overall, the incidence of on-therapy possibly suicide-related events was 2.4% in the paroxetine treatment group and 1.1% in the placebo group (Table 1.12). In patients with baseline suicidal ideation, there was no statistically significant difference in the incidence of possibly suicide-related events between treatment groups. Higher incidence rates were seen in patients with baseline suicidal ideation than in patients where baseline suicidal ideation was classed as "absent". However, the data for the cases where baseline suicidal ideation was classed as "absent" includes studies where suicidal ideation was not assessed and so does not provide a solid assessment of the incidence of possibly suicide-related events in paediatric patients without baseline suicidal ideation.

Table 1.12 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Risk
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.069
Absent*	12/680 (1.8%)	4/615 (0.7%)	2.74 (0.88, 8.55)	0.081
Present	6/58 (10.3%)	3/32 (9.4%)	1.12 (0.26, 4.80)	1.00

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.4. Self Harm Events – Adult Placebo Controlled Trials

Overall, in the adult placebo-controlled trials, the incidence of on-therapy self harm events was 0.6% in the paroxetine treatment group and 0.7% in the placebo group (Table 1.13). Forty of the 51 (78%) events in the paroxetine group and 20 of the 38 (53%) events in the placebo group occurred in patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed. However, in this sub-group, there was no difference in the incidence of self harm events between treatment groups (paroxetine 40/8037 (0.5%), placebo 20/5517 (0.4%), OR 1.37, 95% CI 0.80, 2.35, P=0.29). In the sub-group of patients who did have baseline suicidal ideation, there was a lower incidence of self harm events in patients in the paroxetine treatment group compared to the placebo group and this difference between treatment groups was statistically significant (paroxetine 11/444 (2.5%), placebo 18/291 (6.2%), OR 0.39, 95% CI 0.18, 0.83, P=0.019).

Table 1.13 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Risk
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	51/8481 (0.6%)	38/5808 (0.7%)	0.92 (0.60, 1.40)	0.75
Absent*	40/8037 (0.5%)	20/5517 (0.4%)	1.37 (0.80, 2.35)	0.29
Present	11/444 (2.5%)	18/291 (6.2%)	0.39 (0.18, 0.83)	0.019

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.5. Self Harm Events – Adult Active Control Trials

Overall the incidence of on-therapy self harm events was 0.4% in the paroxetine treatment group and 0.6% in the active comparator group in the adult sctive controoled studies dataset (Table 1.14). In both sub-groups (i.e. patients with baseline suicidal ideation and patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed), there was no statistically significant difference between the paroxetine treatment group and the active comparator group in terms of the incidence of self harm events. In the sub-group of patients who did have baseline suicidal ideation, there was a lower incidence of self-harm events in patients in the paroxetine treatment group compared to the active comparator group, however this difference between treatment groups was not statistically significant.

Table 1.14 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Risk
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	29/6522 (0.4%)	32/4969 (0.6%)	0.69 (0.42, 1.14)	0.16
Absent*	22/5787 (0.4%)	23/4387 (0.5%)	0.72 (0.40, 1.30)	0.29
Present	7/735 (1.0%)	9/582 (1.5%)	0.61 (0.23, 1.65)	0.45

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.6. Self Harm Events – Paediatric Placebo Controlled Trials

In paediatric placebo-controlled trials, overall, the incidence of on-therapy self harm events was 2.0% in the paroxetine treatment group and 0.8% in the placebo group (Table 1.15). In both sub-groups (i.e. patients with baseline suicidal ideation and patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed), there was a higher incidence of self harm events in the paroxetine treatment group than in the placebo group.

Table 1.15 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Risk
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Risk	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	15/738 (2.0%)	5/647 (0.8%)	2.66 (0.96, 7.37)	0.069
Absent*	9/680 (1.3%)	3/615 (0.5%)	2.74 (0.74, 10.15)	0.15
Present	6/58 (10.3%)	2/32 (6.3%)	1.73 (0.33, 9.12)	0.71

* Absent includes cases where baseline suicidal ideation was not assessed.

1.2.2.7. Conclusions

In this assessment of suicidal behaviour by suicidal risk at baseline, it is apparent that higher incidences of possibly suicide-related events and self harm are seen in patients displaying suicidal ideation at baseline than in those who are not. Paroxetine provided significant protection against suicidal behaviour in adults with suicidal ideation at baseline. The incidences of possibly suicide-related and self harm events were significantly less in patients with suicidal ideation at baseline that received paroxetine than in those that received placebo. Further, incidences of possibly suicide-related and self harm events were lower in patients with suicidal ideation at baseline that received paroxetine than in those that received active comparators, although these differences were not statistically significant.

No significant effect of paroxetine was detected for paediatric patients with suicidal ideation at baseline. However, the pooled paediatric placebo-controlled studies treated only approximately 10% of the number of patients included in the adult placebo controlled trials. It is therefore difficult to reach similar conclusions to those possible in the adult population from such relatively small paediatric experience. It was noted that suicidal ideation at baseline was present in 58/738 (7.9%) of paroxetine treated patients in the paediatric placebo controlled trials and in 32/647 (4.9%) of placebo treated patients. Given that the incidence of possibly suicide related events in patients with suicidal ideation at baseline was appreciably higher than in patients without baseline suicidal ideation or in whom baseline suicidal ideation was not assessed (paroxetine 10.3% vs 1.8%, placebo 9.4% vs 0.7%) it is possible that the greater proportion of higher risk patients in the paroxetine treatment group may have contributed to the overall apparent difference between paroxetine and placebo treatment in incidence of possibly suicide-related events observed in paediatric placebo controlled studies. However, given the extent of the difference between treatment groups (7.9% vs 4.9%), any contribution resulting would be expected to be very small.

1.3. Analyses of suicide related behaviours by dose

Stratified analyses of possibly suicide-related and self harm events were performed on fixed-dose, placebo-controlled studies and suggest no link between such events and

increasing doses of paroxetine. The analyses were performed including and excluding Study 057, in which the study population comprised suicidal patients. Study 057 compared a dose of 40mg paroxetine against placebo and accounted for all 27 possibly suicide-related events seen with the 40mg paroxetine dose. The results of Study 057 itself showed no difference in the incidence of on-therapy possibly suicide-related events in the paroxetine treatment group compared to the placebo group (paroxetine 27/131 (20.6%), placebo 29/136 (21.3%), Odds Ratio 0.96, 95% CI 0.53, 1.73, P=1.00). The incidence of possibly suicide-related events and self harm by treatment group and dose in adult placebo controlled trials including and excluding Study 057, are given in Tables 1.16 and 1.17, respectively, (Data Source: Appendix 1, Tables 1.19, 1.19a, 1.20 and 1.20a).

Table 1.16 Incidence of Possibly Suicide-Related Events by Treatment Group and Dose
Adult Fixed-Dose Placebo-Controlled Trials, Including and Excluding Study 057

Including Study 057					
Dose		**Paroxetine**	**Placebo**	**Odds Ratio (95% CI)**	**P-value**
5 mg	n/N (%)	0/11 (0.0%)	0/9 (0.0%)		
10 mg	n/N (%)	3/775 (0.4%)	1/737 (0.1%)	2.86 (0.30, 27.55)	0.62
20 mg	n/N (%)	9/1405 (0.6%)	9/1324 (0.7%)	0.94 (0.37, 2.38)	1.00
30 mg	n/N (%)	1/150 (0.7%)	0/101 (0.0%)		1.00
40 mg	n/N (%)	27/874 (3.1%)	32/810 (4.0%)	0.78 (0.46, 1.31)	0.36
50 mg	n/N (%)	0/57 (0.0%)	0/60 (0.0%)		
60 mg	n/N (%)	0/182 (0.0%)	1/184 (0.5%)		1.00
Excluding Study 057					
Dose		**Paroxetine**	**Placebo**	**Odds Ratio (95% CI)**	**P-value**
5 mg	n/N (%)	0/11 (0.0%)	0/9 (0.0%)		
10 mg	n/N (%)	3/775 (0.4%)	1/737 (0.1%)	2.86 (0.30, 27.55)	0.62
20 mg	n/N (%)	9/1405 (0.6%)	9/1324 (0.7%)	0.94 (0.37, 2.38)	1.00
30 mg	n/N (%)	1/150 (0.7%)	0/101 (0.0%)		1.00
40 mg	n/N (%)	0/743 (0.0%)	3/674 (0.4%)		0.11
50 mg	n/N (%)	0/57 (0.0%)	0/60 (0.0%)		
60 mg	n/N (%)	0/182 (0.0%)	1/184 (0.5%)		1.00

Table 1.17 Incidence of Self Harm by Treatment Group and Dose Adult Fixed-Dose Placebo-Controlled Trials, Including and Excluding Study 057

Including Study 057					
Dose		**Paroxetine**	**Placebo**	**Odds Ratio (95% CI)**	**P-value**
5 mg	n/N (%)	0/11 (0.0%)	0/9 (0.0%)		
10 mg	n/N (%)	1/775 (0.1%)	0/737 (0.0%)		1.00
20 mg	n/N (%)	9/1405 (0.6%)	5/1324 (0.4%)	0.94 (0.37, 2.38)	0.43
30 mg	n/N (%)	1/150 (0.7%)	0/101 (0.0%)		1.00
40 mg	n/N (%)	26/874 (3.0%)	28/810 (3.5%)	0.78 (0.46, 1.31)	0.58
50 mg	n/N (%)	0/57 (0.0%)	0/60 (0.0%)		
60 mg	n/N (%)	0/182 (0.0%)	0/184 (0.0%)		
Excluding Study 057					
Dose		**Paroxetine**	**Placebo**	**Odds Ratio (95% CI)**	**P-value**
5 mg	n/N (%)	0/11 (0.0%)	0/9 (0.0%)		
10 mg	n/N (%)	1/775 (0.4%)	0/737 (0.1%)		1.00
20 mg	n/N (%)	9/1405 (0.6%)	5/1324 (0.4%)	1.70 (0.57, 5.09)	0.43
30 mg	n/N (%)	1/150 (0.7%)	0/101 (0.0%)		1.00
40 mg	n/N (%)	0/743 (0.0%)	0/674 (0.0%)		
50 mg	n/N (%)	0/57 (0.0%)	0/60 (0.0%)		
60 mg	n/N (%)	0/182 (0.0%)	1/184 (0.5%)		

These analyses provides strong evidence of no link between possibly suicide-related events and increasing doses of paroxetine in adults.

All paediatric studies employed flexible dosing. Consequently it is not possible to perform similar analyses for children and adolescents and no determination of a dose dependent effect on the emergence or worsening of suicidality can be ascertained from these studies. Most of the 25 possibly suicide-related events reported in paediatric patients randomised to paroxetine occurred while subjects were on between 20 mg and 40mg daily. One event occurred at 50mg daily. Only four of the subjects on paroxetine had an escalation of 10mg in their daily dose within one week prior to the event indicating that such events were not related to increase in dose.

1.3.1. Conclusions

There is no compelling evidence that possibly suicide-related events observed during treatment with paroxetine are dose dependent.

1.4. Analyses by previous exposure to paroxetine and to any SSRI.

Stratified analyses of the occurrence of possibly suicide-related and self harm events by previous exposure to paroxetine, and to any SSRI have been performed. In some clinical studies, in particular those conducted in the early stages of the development of paroxetine, information on previous mediactions was not collected to the same extent as in later studies. Consequently, patients have been classified into two categories: those who had received paroxetine (or any SSRI) previously, and those who had not received paroxetine (or any SSRI) previously or in whom previous exposure to paroxetine (or any SSRI) was unknown. These categories are utilised for both sets of analyses i.e. i) previous exposure to paroxetine and ii) previous exposure to any SSRI.

Results are presented below examining the effect of previous exposure to paroxetine in adult placebo-controlled trials (Table 1.18), adult active control trials (Table 1.19) and paediatric placebo-controlled trials (Table 1.20), (Data Source: Appendix 1, Tables 1.81, 1.82 and 1.83). This could be considered a "worst case" examination of the data if previous exposure to an SSRI (including paroxetine) makes a patient more likely to have a possibly suicide-related event. However, if previous exposure to paroxetine (or any SSRI) makes a patient less likely to have possibly suicide-related events then including "unknowns" with those with no previous exposure would dilute the effect of having no previous exposure.

Table 1.18 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Paroxetine
Adult Placebo-Controlled Trials (On Therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
No/Unknown	66/7694 (0.9%)	51/5057 (1.0%)	0.85 (0.59, 1.23)	0.39
Yes	0/787 (0.0%)	4/751 (0.5%)		0.057

Table 1.19 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Paroxetine
Adult Active Control Trials (On Therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Comparator n/N (%)	Odds Ratio (95% CI)	P-value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.031
No/Unknown	55/6510 (0.8%)	63/4958 (1.3%)	0.66 (0.46, 0.95)	0.031
Yes	0/12 (0.0%)	0/11 (0.0%)		

**Table 1.20 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Paroxetine
Paediatric Placebo-Controlled Trials (On Therapy)**

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.069
No/Unknown	18/626 (2.9%)	7/535 (1.3%)	2.23 (0.93, 5.39)	0.071
Yes	0/112 (0.0%)	0/112 (0.0%)		

The number of patients with previous exposure to paroxetine was relatively small. However no patient who had previously been exposed to paroxetine who was treated with paroxetine in adult placebo or active control, or in paediatric placebo-controlled studies, reported a possibly suicide-related event.. Hence there was no evidence to suggest that patients that have taken paroxetine previously are more likely to have possibly suicide-related events when treated with paroxetine than placebo. In adult patients that have either not been exposed previously to paroxetine or for whom it is not known whether paroxetine had been taken previously, there is again no suggestion that they are more likely to have possibly suicide-related events when treated with paroxetine than placebo. Indeed they are less likely to have such events when treated with paroxetine than active comparators.

As was seen in the adult studies, in the paediatric studies there was no indication that patients previously exposed to paroxetine were more likely to develop possibly suicide-related events when treated with paroxetine than placebo. However, paediatric patients not previously exposed to paroxetine, or for whom previous exposure is unknown, appear more likely to experience possibly suicide-related events when treated with paroxetine than placebo.

Similar conclusions can be reached from examining the effect of previous exposure to any SSRI. Tables 1.21, 1.22 and 1.23 show the incidence of possibly suicide-related events by prior exposure to any SSRI in the paroxetine adult placebo-controlled, adult active control, and paediatric placebo-controlled trials, respectively, (Data Source: Appendix 1, Tables 1.84, 1.85 and 1.86).

Some patients who had previously been exposed to an SSRI did experience possibly suicide-related events when receiving paroxetine in the adult placebo-controlled studies, but again there was no suggestion that patients receiving paroxetine in the studies were more likely to experience such events than patients receiving placebo (Table 1.21). In addition, patients without previous exposure to an SSRI, or for whom previous exposure was unknown, were also no more likely to experience such events when treated with paroxetine than placebo.

**Table 1.21 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Any SSRI
Adult Placebo-Controlled Trials (On Therapy)**

Pre-randomisation SSRI use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	66/8481 (0.8%)	55/5809 (0.9%)	0.82 (0.57, 1.18)	0.31
No/Unknown	60/7134 (0.8%)	50/4652 (1.1%)	0.78 (0.54, 1.14)	0.20
Yes	6/1347 (0.4%)	5/1156 (0.4%)	1.03 (0.31, 3.38)	1.00

As for patients previously exposed to paroxetine, patients previously exposed to any SSRI were no more likely to experience possibly suicide-related events when treated with paroxetine than active comparators (although the number of patients for this assessment is very low), but patients with no recorded use of an SSRI previously were more likely to experience such events when treated with active comparators than with paroxetine (Table 1.22).

**Table 1.22 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Any SSRI
Adult Active Control Trials (On Therapy)**

Pre-randomisation SSRI use?	Paroxetine n/N (%)	Comparator n/N (%)	Odds Ratio (95% CI)	P-value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.031
No/Unknown	55/6438 (0.9%)	63/4898 (1.3%)	0.66 (0.46, 0.95)	0.031
Yes	0/84 (0.0%)	0/71 (0.0%)		

As for paediatric patients not previously exposed to paroxetine, or for whom previous exposure is unknown, patients with no recorded use of any SSRI appear more likely to experience possibly suicide-related events when treated with paroxetine than placebo (Table 1.23).

**Table 1.23 Incidence of Possibly Suicide-Related Events by Treatment Group and Prior Exposure to Any SSRI
Paediatric Placebo-Controlled Trials (On Therapy)**

Pre-randomisation SSRI use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.069
No/Unknown	17/587 (2.9%)	7/496 (1.4%)	2.08 (0.86, 5.07)	0.15
Yes	1/151 (0.7%)	0/151 (0.0%)		1.00

1.4.1. Analyses by age

The effect of previous exposure to paroxetine or any SSRI on the incidence of possibly suicide-related events was assessed by age. In the adult study populations, the age categories considered were <18 years, 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years and ≥70 years. In the paediatric placebo-controlled studies the age categories considered were < 12 years (children), 12-15 years (young adolescents) and >16 years. Tables 1.24, 1.25 and 1.26 show analyses regarding previous exposure to paroxetine by age category for the adult placebo-controlled, the adult active control, and the paediatric placebo-controlled studies populations, respectively, (Data Source: Appendix 1, Tables 9.08, 9.09 and 1.87).

In the adult placebo-controlled trials, no patient previously exposed to paroxetine reported a possibly suicide-related event when treated with paroxetine, although four patients previously exposed to paroxetine had possibly suicide-related events on placebo treatment, (Table 1.24). Hence the lower incidence (or lack) of possibly suicide-related events in paroxetine-treated patients with prior exposure to paroxetine was observed across all age categories.

Table 1.24 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Paroxetine and Age Group Adult Placebo-Controlled Trials (On therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	31/1727 (1.8%)	17/1204 (1.4%)	1.28 (0.70, 2.32)	0.46
30-39 years	18/2550 (0.7%)	18/1728 (1.0%)	0.68 (0.35, 1.30)	0.24
40-49 years	12/2270 (0.5%)	11/1515 (0.7%)	0.73 (0.32, 1.65)	0.52
50-59 years	3/1152 (0.3%)	9/807 (1.1%)	0.23 (0.06, 0.86)	0.03
60-69 years	0/530 (0.0%)	0/381 (0.0%)		
≥70 years	2/247 (0.8%)	0/172 (0.0%)		0.51
No/Unknown	66/7694 (0.9%)	51/5057 (1.0%)	0.85 (0.59, 1.23)	0.39
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	31/1591 (1.9%)	17/1080 (1.6%)	1.24 (0.68, 2.26)	0.55
30-39 years	18/2358 (0.8%)	17/1532 (1.1%)	0.69 (0.35, 1.33)	0.30
40-49 years	12/2046 (0.6%)	11/1300 (0.8%)	0.69 (0.30, 1.57)	0.40
50-59 years	3/996 (0.3%)	6/669 (0.9%)	0.33 (0.08, 1.34)	0.17
60-69 years	0/472 (0.0%)	0/318 (0.0%)		
≥70 years	2/226 (0.9%)	0/157 (0.0%)		0.51
Yes	0/787 (0.0%)	4/751 (0.5%)		0.06
18-29 years	0/136 (0.0%)	0/124 (0.0%)		
30-39 years	0/192 (0.0%)	1/196 (0.5%)		1.00
40-49 years	0/224 (0.0%)	0/215 (0.0%)		
50-59 years	0/156 (0.0%)	3/138 (2.2%)		0.10
60-69 years	0/58 (0.0%)	0/63 (0.0%)		
≥70 years	0/21 (0.0%)	0/15 (0.0%)		

Overall, in adult active control trials, there were significantly less possibly suicide-related events in patients receiving paroxetine than active comparator (paroxetine 0.8% (55/6522), comparator 1.3% (63/4969; odds ratio 0.66, 95% CI [0.46, 0.95], p=0.03), (Table 1.25). This difference was especially apparent in young adults (aged 18-29 years); (paroxetine 1.0% (10/969), comparator 2.6% (20/779; odds ratio 0.40, 95% CI [0.18, 0.85], p=0.02). There were only 23 patients (12 on paroxetine, 11 on placebo) in the adult active control studies with prior exposure to paroxetine and none had possibly suicide-related events during study treatment.

Table 1.25 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Paroxetine and Age Group Adult Active Control Trials (On therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Comparator n/N (%)	Odds Ratio (95% CI)	P-value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.03
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	10/969 (1.0%)	20/779 (2.6%)	0.40 (0.18, 0.85)	0.02
30-39 years	13/1544 (0.8%)	10/1146 (0.9%)	0.96 (0.42, 2.21)	1.00
40-49 years	12/1647 (0.7%)	13/1182 (1.1%)	0.66 (0.30, 1.45)	0.31
50-59 years	9/1038 (0.9%)	14/835 (1.7%)	0.51 (0.22, 1.19)	0.14
60-69 years	7/831 (0.8%)	5/626 (0.8%)	1.06 (0.33, 3.34)	1.00
≥70 years	4/457 (0.9%)	1/390 (0.3%)	3.43 (0.38, 30.83)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)		
No/Unknown	55/6510 (0.8%)	63/4958 (1.3%)	0.66 (0.46, 0.95)	0.03
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	10/969 (1.0%)	20/775 (2.6%)	0.39 (0.18, 0.85)	0.02
30-39 years	13/1542 (0.8%)	10/1144 (0.9%)	0.96 (0.42, 2.21)	1.00
40-49 years	12/1646 (0.7%)	13/1179 (1.1%)	0.66 (0.30, 1.45)	0.31
50-59 years	9/1031 (0.9%)	14/834 (1.7%)	0.52 (0.22, 1.20)	0.14
60-69 years	7/829 (0.8%)	5/625 (0.8%)	1.06 (0.33, 3.34)	1.00
≥70 years	4/457 (0.9%)	1/390 (0.3%)	3.43 (0.38, 30.83)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)		
Yes	0/12 (0.0%)	0/11 (0.0%)		
18-29 years	0/0 (0.0%)	0/4 (0.0%)		
30-39 years	0/2 (0.0%)	0/2 (0.0%)		
40-49 years	0/1 (0.0%)	0/3 (0.0%)		
50-59 years	0/7 (0.0%)	0/1 (0.0%)		
60-69 years	0/2 (0.0%)	0/1 (0.0%)		

The analysis below (Table 1.26) highlights the lack of possibly suicide-related events during treatment in young children (<12 years) regardless of previous exposure to paroxetine. As seen in Table 1.20 there were no possibly suicide-related events on therapy in paediatric patients exposed to paroxetine previously. This suggests such paediatric patients are no more likely to develop those events when treated with paroxetine than placebo regardless of age category, although the number of paediatric patients with previous exposure to paroxetine was low, particularly in the oldest age category (≥ 16 years).

In patients with no recorded use of paroxetine previously, there were more possibly suicide-related events in the paroxetine group than the placebo group in patients aged ≥ 16 years, and to a lesser extent in patients aged 12-15 years.

Table 1.26 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Paroxetine and Age Group Paediatric Placebo-Controlled Trials (On therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
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
No/Unknown	18/626 (2.9%)	7/535 (1.3%)	2.23 (0.93, 5.39)	0.07
<12 years	0/151 (0.0%)	0/145 (0.0%)		
12-15 years	10/288 (3.5%)	5/222 (2.3%)	1.56 (0.53, 4.63)	0.60
≥16 years	8/187 (4.3%)	2/168 (1.2%)	3.71 (0.79, 17.72)	0.11
Yes	0/112 (0.0%)	0/112 (0.0%)		
<12 years	0/54 (0.0%)	0/49 (0.0%)		
12-15 years	0/41 (0.0%)	0/47 (0.0%)		
≥16 years	0/17 (0.0%)	0/16 (0.0%)		

In adult placebo-controlled studies, there was a similar low incidence of possibly suicide-related events in the paroxetine and placebo groups in patients previously exposed to any SSRI (paroxetine 0.4% (6/1347); placebo 0.4% (5/1156), (Table 1.27). Possibly suicide-related events were reported in 2.1% (5/233) paroxetine patients aged 18-29 years with prior exposure to an SSRI compared with 1.7% (26/1494) in patients with no previous exposure or for whom previous exposure to SSRIs was unknown. This was the only age category that had more than one report of possibly suicide-related events in paroxetine-treated patients previously exposed to an SSRI, in which the incidence of events of interest was higher in patients with previous exposure than in patients without previous exposure.

Table 1.27 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Any SSRI and Age Group Adult Placebo-Controlled Trials (On therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	31/1727 (1.8%)	17/1204 (1.4%)	1.28 (0.70, 2.32)	0.46
30-39 years	18/2550 (0.7%)	18/1728 (1.0%)	0.68 (0.35, 1.30)	0.24
40-49 years	12/2270 (0.5%)	11/1515 (0.7%)	0.73 (0.32, 1.65)	0.52
50-59 years	3/1152 (0.3%)	9/807 (1.1%)	0.23 (0.06, 0.86)	0.03
60-69 years	0/530 (0.0%)	0/381 (0.0%)		
≥70 years	2/247 (0.8%)	0/172 (0.0%)		0.51
No/Unknown	60/7134 (0.8%)	50/4652 (1.1%)	0.78 (0.54, 1.14)	0.20
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	26/1494 (1.7%)	17/1010 (1.7%)	1.03 (0.56, 1.92)	1.00
30-39 years	18/2214 (0.8%)	16/1423 (1.1%)	0.72 (0.37, 1.42)	0.38
40-49 years	12/1895 (0.6%)	11/1190 (0.9%)	0.68 (0.30, 1.55)	0.39
50-59 years	3/906 (0.3%)	6/598 (1.0%)	0.33 (0.08, 1.32)	0.17
60-69 years	0/428 (0.0%)	0/289 (0.0%)		
≥70 years	1/192 (0.5%)	0/141 (0.0%)		
Yes	6/1347 (0.4%)	5/1156 (0.4%)	1.03 (0.31, 3.38)	1.00
18-29 years	5/233 (2.1%)	0/194 (0.0%)		0.07
30-39 years	0/336 (0.0%)	2/305 (0.7%)		0.23
40-49 years	0/375 (0.0%)	0/325 (0.0%)		
50-59 years	0/246 (0.0%)	3/209 (1.4%)		0.10
60-69 years	0/102 (0.0%)	0/92 (0.0%)		
≥70 years	1/55 (1.8%)	0/31 (0.0%)		1.00

In adult active control trials there were no possibly suicide-related events in patients previously exposed to any SSRI (Table 1.28).

Table 1.28 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Any SSRI and Age Group Adult Active Control Trials (On therapy)

Pre-randomisation paroxetine use?	Paroxetine n/N (%)	Comparator n/N (%)	Odds Ratio (95% CI)	P-value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.03
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	10/969 (1.0%)	20/779 (2.6%)	0.40 (0.18, 0.85)	0.02
30-39 years	13/1544 (0.8%)	10/1146 (0.9%)	0.96 (0.42, 2.21)	1.00
40-49 years	12/1647 (0.7%)	13/1182 (1.1%)	0.66 (0.30, 1.45)	0.31
50-59 years	9/1038 (0.9%)	14/835 (1.7%)	0.51 (0.22, 1.19)	0.14
60-69 years	7/831 (0.8%)	5/626 (0.8%)	1.06 (0.33, 3.34)	1.00
≥70 years	4/457 (0.9%)	1/390 (0.3%)	3.43 (0.38, 30.83)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)		
No/Unknown	55/6438 (0.9%)	63/4898 (1.3%)	0.66 (0.46, 0.95)	0.03
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	10/955 (1.0%)	20/768 (2.6%)	0.40 (0.18, 0.85)	0.02
30-39 years	13/1528 (0.9%)	10/1129 (0.9%)	0.96 (0.42, 2.20)	1.00
40-49 years	12/1622 (0.7%)	13/1157 (1.1%)	0.66 (0.30, 1.44)	0.31
50-59 years	9/1020 (0.9%)	14/825 (1.7%)	0.52 (0.22, 1.20)	0.14
60-69 years	7/823 (0.9%)	5/622 (0.8%)	1.06 (0.33, 3.35)	1.00
≥70 years	4/454 (0.9%)	1/386 (0.3%)	3.42 (0.38, 30.72)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)		
Yes	0/84 (0.0%)	0/71 (0.0%)		
18-29 years	0/14 (0.0%)	0/11 (0.0%)		
30-39 years	0/16 (0.0%)	0/17 (0.0%)		
40-49 years	0/25 (0.0%)	0/25 (0.0%)		
50-59 years	0/18 (0.0%)	0/10 (0.0%)		
60-69 years	0/8 (0.0%)	0/4 (0.0%)		
≥70 years	0/3 (0.0%)	0/4 (0.0%0		

As seen previously (Table 1.26) there were no possibly suicide-related events on therapy in young children (<12 years) regardless of previous exposure to SSRIs (Table 1.29). There was only one possibly suicide-related event in paediatric patients exposed to any SSRI previously. This suggests paediatric patients exposed to any SSRI previously are no more likely to develop those events when treated with paroxetine than placebo regardless of age category, although the number of paediatric patients with previous exposure to an SSRI was low, particularly in the oldest age category (≥ 16 years).

In patients not previously exposed to an SSRI or for whom previous exposure to SSRIs is unknown, there were more possibly suicide-related events in the paroxetine group than the placebo group in patients aged ≥ 16 years.

Table 1.29 Incidence of Possibly Suicide-Related Events by Treatment Group, Prior Exposure to Any SSRI and Age Group Paediatric Placebo-Controlled Trials (On therapy)

Pre-randomisation SSRI use?	Paroxetine n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	P-value
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
No/Unknown	17/587 (2.9%)	7/496 (1.4%)	2.08 (0.86, 5.07)	0.15
<12 years	0/139 (0.0%)	0/133 (0.0%)		
12-15 years	9/272 (3.3%)	5/198 (2.5%)	1.32 (0.44, 4.00)	0.79
≥16 years	8/176 (4.5%)	2/165 (1.2%)	3.88 (0.81, 18.55)	0.11
Yes	1/151 (0.7%)	0/151 (0.0%)		1.00
<12 years	0/66 (0.0%)	0/61 (0.0%)		
12-15 years	1/57 (1.8%)	0/71 (0.0%)		0.45
≥16 years	0/28 (0.0%)	0/19 (0.0%)		

1.4.2. Conclusion

In patients receiving paroxetine, the incidence of possibly suicide-related events was generally lower in patients that had been exposed previously to paroxetine or any SSRI, than in patients with no recorded prior use. However the incidence was also lower in patients previously exposed to paroxetine or any SSRI who received placebo, than in patients receiving placebo who had no record of prior exposure to an SSRI. The very small number of reports of possibly suicide-related events in patients with previous exposure to paroxetine or any SSRI meant that analysis by age category was not very informative. Examination by age did not suggest that the effect of prior exposure was confined to any particular age group.

1.5. Description of all clinical trials in the GSK central R&D aggregated database

A table has been prepared including information on all of the studies included in the GSK central R&D aggregated database (Appendix 1, Table of Studies). The information given for each study includes:

type of trial, duration, age of patients included, dosing, inclusion/exclusion criteria with respect to suicide (including specific information about how suicide risk was defined and measured), baseline level of suicidal risk, and information about previous exposure to paroxetine and/or other SSRIs.