2. QUESTION 2: RISK OF POSSIBLY SUICIDE-RELATED EVENTS, SELF-HARM AND HOSTILITY WITH PAROXETINE DATA FROM ALL AVAILABLE SOURCES

All data relating to the risk of self-harm, hostility and suicidal behaviour with paroxetine from all data sources including:

- *Clinical trials*
- *Spontaneous reporting*
- *Observational studies*
- *Healthy volunteer studies*
- *Consumer reports*

Response

2.1. Introduction

All data relating to the risk of possibly suicide-related events, self-harm and hostility with paroxetine are presented in this section. Data are presented from a number of sources and are presented in the following order: healthy volunteer studies, clinical trials, observational studies and post-marketing reports (including spontaneous and consumer reports). Furthermore, an extensive review of the literature has been performed and the findings are summarised here.

2.2. Healthy volunteer studies

2.2.1. Description of Phase I studies dataset

Tabular summaries of adverse events from all centrally-databased R&D Phase I volunteer studies involving paroxetine in immediate release (IR) and controlled release (CR) tablet form are presented in Appendix 2A. The data-set comprises a total of 1716 healthy volunteers participating in a total of 90 studies. Data are presented in three groups, according to the manner of eliciting the adverse events, the database used to store and collate the data, and the paroxetine formulation (separate groups for IR and CR tablet studies). A list of the studies is given in Appendix 2A, Table 1.

2.2.1.1. Group 1 (Original MAA for paroxetine in depression)

The first group comprises healthy volunteer studies conducted prior to the original Marketing Authorisation Application (MAA) for paroxetine in the treatment of depression and were filed as part of that application. In this group, a total of 570 volunteers were included in 64 studies which were conducted between 1980 and 1990. All studies in this group utilised the standard (IR) tablet formulation. Some studies included tests of psychomotor function to evaluate the effects of paroxetine both alone

and in combination with other centrally-acting drugs on reaction times, movement times and similar parameters, to determine if paroxetine caused or exacerbated sedation. No studies included psychological or psychiatric evaluation and a critical exclusion criterion for study entry was a history of mental illness.

Adverse event data in these studies were collected either by spontaneous reporting (either by supervising physician or volunteer) and/or by using standard symptom checklists at predetermined timepoints. The tables presented in Appendix 2A report all adverse events by the preferred terms; Table 2 describes the events from the single dose studies and Table 3 describes the events from the repeat dose studies.

2.2.1.2. Group 2 (Post Depression MAA studies)

This group comprises all volunteer studies conducted since submission of the original Depression MAA for paroxetine (i.e. from 1989 to the present day). A total of 409 volunteers in 16 studies are included in the dataset. These studies utilised either the standard paroxetine tablet or other bioequivalent dosage forms, namely the oral liquid and an oral capsule. All these studies were conducted either to demonstrate relative bioavailability/bioequivalence or to better characterise the pharmacokinetics of paroxetine. None of these studies incorporated any psychological or psychiatric evaluation, nor psychometric testing. As for Group 1, a critical exclusion criterion for study entry was a history of mental illness.

Adverse event data from these studies were collected in a different manner to those studies in Group 1, in that a response to a non leading standard question (e.g. "do you feel different since the last assessment?") was elicited from the volunteer, rather than using a symptom checklist. Any spontaneous adverse events reported by either the volunteers or supervising medical staff were also collected, as for Group 1 studies. The adverse events are listed in descending order of total frequency. Apart from the different manner in which the adverse events were collected, a different database was used to store and collate all phase I data in this group, hence the different presentation of the tables.

The tables presented in Appendix 2A for this group report all adverse events by the preferred terms, as for Group 1; Table 4 describes the events from the single dose studies and Table 5 describes the events from the repeat dose studies.

2.2.1.3. Group 3 (Paroxetine CR studies)

The third group of studies comprises those conducted in healthy volunteers using the controlled release (CR) formulation between 1994 and 2000. Since the pharmacokinetic profile of this tablet is significantly different from the standard immediate release tablet, the adverse event profile is similarly considered to be potentially distinct, thus they have been tabulated separately. This group comprises a total of 737 volunteers participating in 10 studies. These studies were pharmacokinetic in nature and none incorporated any psychological or psychiatric evaluation, nor psychometric testing. As for Groups 1 and 2, a critical exclusion criterion for study entry was a history of mental illness.

The manner in which the adverse events were collected and the database used to store and collate data across studies was identical to that used for the Group 2 studies.

Appendix 2A, Table 6 contains the adverse event data from this group which includes all studies with a dosing duration of up to 21 days. As for Group 2, all adverse events are grouped and listed by the preferred terms, in descending order of frequency.

2.2.2. Examination of Phase I dataset for adverse events relating to suicide, self-harm and hostility

All volunteers entering Phase I GSK studies would have been screened for past history of psychiatric illness and would have been excluded from study participation if any such history existed. Some of the volunteer studies included psychomotor testing to investigate pharmacodynamic consequences of potential drug-drug interactions. None of these studies included any psychological or psychiatric assessments before, during or after the study.

2.2.2.1. Possibly suicide-related adverse events

Any verbatim term relating to suicide such as suicide thoughts, suicide tendency, suicide attempt or suicide itself would be reported under the preferred term ‘suicide tendency’ on the GSK volunteer database (data in Groups 2 and 3). This preferred term is therefore focused on in the analyses of the data. However, for data in Group 1, an additional review of all verbatim terms has been conducted for completeness, as this is an early dataset which used a different adverse event coding system.

The summary data from Groups 1, 2 and 3 were searched for the terms "suicide", "suicidal thoughts", suicidal tendency" and "suicide attempt(s)", either as complete or partial wordstrings. No adverse events relating to the above terms were identified in the three group datasets.

In accordance with the searches being carried out on the Phase II/III clinical trial data, the healthy volunteer data were also searched for "possibly suicide-related" adverse events. Adverse events were to be included in the "possibly suicide-related" category if they met any of the following criteria:

a Preferred term is "Emotional lability", *and* the verbatim term contains 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 is "Intentional overdose" or "Overdose". (Specifically, "Accidental overdose" is excluded.)

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

In Group 1, there were 3 reports from a total of 395 volunteers of "Emotional lability" following single doses of paroxetine and 24 reports from a total of 110 volunteers following repeated dosing with paroxetine. There were also 7 reports of "Emotional lability" from a total of 65 volunteers following repeat dosing with placebo. In these studies, a standard symptom checklist was used, and the verbatim term for these events was "mood change" in all cases.

In Group 2, emotional lability was not reported following single doses but there were 2 reports from a total of 271 volunteers following repeated dosing with paroxetine and no reports on repeated dosing with placebo. The verbatim terms for these adverse events were "change in mood" and "muted mood".

In Group 3, there was one report of emotional lability described in verbatim terms as "tearful and unpredictable mood changes" which occurred after a single 25 mg dose of paroxetine CR. This volunteer was subsequently withdrawn from the study due to a combination of adverse experiences, but was followed up and the above episode resolved without incidence.

Overall, there were no events in this healthy volunteer population that met any of the criteria of preferred terms & wordstrings outlined in the criteria a, b, or c above utilised to capture any "possibly" suicide related events

2.2.2.2. Adverse events relating to self harm

The data sets were searched for adverse events relating to "Self-harm". Adverse events were to be included in the "self-harm" category if they met any of the following criteria:

a Preferred term is "Emotional lability", and the verbatim term contains 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 is "Intentional overdose" or "Overdose". (Specifically, "Accidental overdose" is excluded.)

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

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

Events coding to the preferred term "Emotional lability" have already been described in the previous section.

Overall, there were no events in this healthy volunteer population that met any of the criteria of preferred terms & wordstrings outlined above which were utilised to capture any events of self harm.

2.2.2.3. Adverse events relating to hostility

The datasets were searched for adverse events relating to "Hostility". Adverse events were to be included in the "hostility" category if they met any of the following criteria:

a Preferred term is "Hostility".

b The verbatim term contains any of the following text strings: "aggress", "anger", "hostil", "murder", or "violen". However, verbatim terms containing the text strings of "dream" or "nightmare" were excluded.

The only events found in the volunteer data related to the term "aggression". In Group 1, no such events were found. In Group 2, there were no reports of aggression following single doses, but there were 3 reports from a total of 271 volunteers of "aggressive reaction" following repeated dosing with paroxetine (no reports following repeated dosing with placebo). There were no reports of aggression in Group 3.

The three reports of aggressive reaction occurred in the same study but in three different individuals and on three different days. The verbatim terms assigned to these events (and their severity) were 2 cases of "aggression" (mild), and one of "aggressiveness" (moderate). These events resolved without further incident. Such events are occasionally seen across all phase I studies and are attributed to the necessity to confine volunteers to a clinical unit for several days in some studies.

2.2.3. Overall summary of healthy volunteer data

The GSK centrally-databased studies in healthy volunteers have been searched for adverse events relating to "suicide", "self-harm" and "hostility". Although, some events of "Emotional lability" were found, none of them satisfied the predetermined search criteria for "possibly" suicide-related events or "self-harm". Three adverse events relating to "hostility" (aggression) were found in the search, but these were mild or moderate in intensity and all resolved without incident.

In conclusion, there is no evidence from the healthy volunteer studies within this review to link paroxetine with possibly suicide related events or self harm, and no clear link with paroxetine and 'hostility'.

2.3. Clinical trials

2.3.1. Description of clinical trials dataset

Section 2.3 of this response reports on data from the 171 clinical studies that comprise the central R&D aggregated database (see Appendix 2B, Table 2.00). These 171 studies include data on more than 14,000 paroxetine-treated patients from controlled clinical

trials. Placebo run-in phases of these studies have not been included in any of the analyses.

There are some studies which are not on the central R&D aggregated database. These studies have been conducted or sponsored either by the SmithKline Beecham / GlaxoSmithKline central R&D function, or in the majority of cases by other SmithKline Beecham/GlaxoSmithKline functions/companies e.g. local affiliate companies, including local Phase IIIB and Phase IV clinical trials, but also include a full development programme conducted in Japan. Although these studies are not on the central R&D aggregated database, any serious adverse experiences from these studies will have been reported centrally and included in the paroxetine Periodic Safety Update Reports as appropriate; thus any serious adverse events from these additional studies which were deemed by the investigator to have a causal association with study medication will have been available to Regulatory Authorities worldwide.

2.3.2. Data from Item 3 (Suicide) of the Hamilton Depression Rating Scale

Item 3 of the Hamilton Depression Rating Scale (HAM-D) relates to suicide and is rated on a scale of 0 to 4: 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. Emergent suicidal ideation based on Item 3 of the HAM-D was examined in the adult placebo controlled trials, the adult active control trials and the paediatric placebo-controlled trials where the HAM-D was utilised, and the results are presented in the following table:

Table 2.1 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

Data Source: Appendix 2B, Tables 2.76, 2.77 and 2.78
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 the 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).

Change from baseline in Item 3 of the HAM-D was also examined in the adult placebo controlled, adult active control and paediatric placebo-controlled studies where the HAM-D was utilised, and the findings are summarised in the table below:

Table 2.2 Change from Baseline in HAM-D Item 3 by Treatment Group Randomised Phase LOCF

Population	Paroxetine			Placebo or Comparator			Treatment Difference*	95% CI	P-value
	N	Least Square Mean	SE	N	Least Square Mean	SE			
Adult Placebo-Controlled	3114	-0.53	0.01	1982	-0.36	0.01	-0.17	(-0.21, -0.13)	<0.01
Adult Active Control	4057	-0.78	0.01	2949	-0.72	0.01	-0.06	(-0.09, -0.03)	<0.01
Paediatric Placebo-Controlled	177	-0.27	0.04	180	-0.28	0.04	0.01	(-0.11, 0.13)	0.85

Data Source: Appendix 2B, Tables 2.79, 2.80 and 2.81

* Treatment Difference is "Paroxetine - Placebo" or "Paroxetine - Comparator". Negative differences correspond to Paroxetine treatment benefit in terms of change from baseline in Item 3 of the HAM-D.

In the adult placebo-controlled trials, a statistically significant treatment difference of -0.17 in favour of paroxetine versus placebo was seen in the change from baseline of Item 3 of the HAM-D (95% CI -0.21, -0.13; P<0.01). In the adult active control studies, a statistically significant treatment difference of -0.06 in favour of paroxetine versus active comparator was seen in the change from baseline of Item 3 of the HAM-D (95% CI -0.09, -0.03; P<0.01). There was no difference in the change from baseline in Item 3 of the HAM-D between the paroxetine treatment group and the placebo group in the paediatric placebo-controlled trials (Treatment Difference 0.01; 95% CI -0.21, -0.13; P=0.85).

2.3.3. Data from Item 10 (Suicide) of the Montgomery and Asberg Depression Rating Scale

Item 10 of the Montgomery and Asberg Depression Rating Scale (MADRS) relates to suicidal thoughts, including the "feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and preparations for suicide" and is rated on a scale

of 0 to 6. A score of 0 on Item 10 of the MADRS indicates that the patient "enjoys life or takes it as it comes"; a score of 2 indicates that the patient is "weary of life" and has "only fleeting suicidal thoughts"; a score of 4 indicates that the patient thinks they are "probably better off dead" and "suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention" and a score of 6 indicates that the patient has "explicit plans for suicide when there is an opportunity" or has made "active preparations for suicide". Emergent suicidal ideation based on Item 10 of the MADRS is difficult to define and so was not investigated. Change from baseline in Item 10 of the MADRS was examined in the adult placebo controlled, adult active control and paediatric placebo-controlled studies where the MADRS was utilised, and the findings are summarised in the table below:

Table 2.3 Change from Baseline in MADRS Item 10 by Treatment Group Randomised Phase LOCF

Population	Paroxetine			Placebo or Comparator			Treatment Difference*	95% CI	P-value
	N	Least Square Mean	SE	N	Least Square Mean	SE			
Adult Placebo-Controlled	3238	-0.43	0.01	2416	-0.23	0.02	-0.20	(-0.24, -0.16)	<0.01
Adult Active Control	1957	-0.86	0.02	1848	-0.81	0.02	-0.05	(-0.10, 0.01)	0.10
Paediatric Placebo-Controlled	179	-0.92	0.09	91	-1.03	0.12	0.12	(-0.17, 0.41)	0.43

Data Source: Appendix 2B, Tables 2.79, 2.80 and 2.81
* Treatment Difference is "Paroxetine - Placebo" or "Paroxetine - Comparator". Negative differences correspond to Paroxetine treatment benefit in terms of change from baseline in Item 10 of the MADRS.

In the adult placebo-controlled trials, a statistically significant treatment difference of -0.20 in favour of paroxetine versus placebo was seen in the change from baseline of Item 10 of the MADRS (95% CI -0.24, -0.16; P<0.01). There was no significant difference in the change from baseline in Item 10 of the MADRS between the paroxetine treatment group and the active comparator group in the adult active control trials or in the paediatric placebo-controlled trials.

2.3.4. Possibly suicide-related events

2.3.4.1. Definition of possibly suicide-related events

This section focuses on adverse events 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".

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

In the adult placebo-controlled trials there was a total of 4 completed suicides; 1 in the paroxetine treatment group (on-therapy) and 3 in the placebo group (all in the post-treatment period).

The search strategy described in Section 2.3.4.1 was run across the adult placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of possibly suicide-related events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the possibly suicide-related category relative to exposure is also shown.

Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.4 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Adult Placebo Controlled Trials On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%)	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57 , 1.18)	0.31
	PYE	1916	1313		
	n/PYE	0.03	0.04		0.28
Depression	n/N (%)	58/3421 (1.7%)	41/2117 (1.9%)	0.87 (0.58 , 1.31)	0.53
	PYE	671	428		
	n/PYE	0.09	0.10		0.62
GAD	n/N (%)	2/1182 (0.2%)	2/985 (0.2%)	0.83 (0.12 , 5.92)	1.00
	PYE	259	211		
	n/PYE	0.01	0.01		0.84
OCD	n/N (%)	1/542 (0.2%)	3/265 (1.1%)	0.16 (0.02 , 1.56)	0.11
	PYE	141	61		
	n/PYE	0.01	0.05		0.092
PMDD	n/N (%)	0/760 (0.0%)	0/379 (0.0%)		
	PYE	208	102		
	n/PYE	0.00	0.00		
PTSD	n/N (%)	3/786 (0.4%)	3/598 (0.5%)	0.76 (0.15 , 3.78)	1.00
	PYE	174	138		
	n/PYE	0.02	0.02		0.78
Panic	n/N (%)	0/920 (0.0%)	3/780 (0.4%)		0.096
	PYE	237	186		
	n/PYE	0.00	0.02		1.00
SAD	n/N (%)	2/870 (0.2%)	3/684 (0.4%)	0.52 (0.09 , 3.14)	0.66
	PYE	225	187		
	n/PYE	0.01	0.02		0.52

Data Source: Appendix 2B, Table 2.01

Table 2.5 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Adult Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	92/8481 (1.1%) 1916 0.05	63/5808 (1.1%) 1313 0.05	1.00 (0.72 , 1.38)	1.00 1.00
Depression	n/N (%) PYE n/PYE	74/3421 (2.2%) 671 0.11	44/2117 (2.1%) 428 0.10	1.04 (0.71 , 1.52)	0.92 0.71
GAD	n/N (%) PYE n/PYE	2/1182 (0.2%) 259 0.01	2/985 (0.2%) 211 0.01	0.83 (0.12 , 5.92)	1.00 0.84
OCD	n/N (%) PYE n/PYE	3/542 (0.6%) 141 0.02	4/265 (1.5%) 61 0.07	0.36 (0.08 , 1.63)	0.23 0.14
PMDD	n/N (%) PYE n/PYE	0/760 (0.0%) 208 0.00	0/379 (0.0%) 102 0.00		
PTSD	n/N (%) PYE n/PYE	7/786 (0.9%) 174 0.04	6/598 (1.0%) 138 0.04	0.89 (0.30, 2.65)	1.00 0.89
Panic	n/N (%) PYE n/PYE	3/920 (0.3%) 237 0.01	4/780 (0.5%) 186 0.02	0.63 (0.14, 2.84)	0.71 0.48
SAD	n/N (%) PYE n/PYE	3/870 (0.3%) 225 0.01	3/684 (0.4%) 187 0.02	0.79 (0.16 , 3.90)	1.00 0.82

Data Source: Appendix 2B, Table 2.02

Overall (i.e. across all indications) the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 0.9% in the placebo group. Although possibly-suicide related events occurred at a lower incidence in the paroxetine group than in the placebo group this difference was not statistically significant (paroxetine 66/8481 (0.8%), placebo 55/5808 (0.9%), OR 0.82, 95% CI 0.57, 1.18, P=0.31). The majority of possibly suicide-related events in both treatment groups occurred in the depression studies; 58 of the 66 (88%) events in the paroxetine group and 41 of the 55 (75%) events in the placebo group.

Many of the events from the depression studies (27 of the 58 depression study events in the paroxetine group, 29 of the 41 depression study events in the placebo group) occurred in Study 057. This study investigated the effect of paroxetine in the prevention of recurrent suicidal behaviour and episodes of intermittent brief depression, and the inclusion criteria specified that patients must have had a history of at least one episode of suicidal behaviour in addition to the index episode. In Study 057 alone, there was no

difference in the incidence of on-therapy possibly suicide-related events in the paroxetine treatment group compared to the placebo group (Data Source: Appendix 2B, Table 2.01a: paroxetine 27/131 (20.6%), placebo 29/136 (21.3%), OR 0.96, 95% CI 0.53, 1.73, P=1.00).

Overall in the "on-therapy plus 30 days post-therapy" population there was no difference in the incidence of possibly suicide-related events between treatment groups (paroxetine 92/8481 (1.1%), placebo 63/5808 (1.1%), OR 1.00, 95% CI 0.72, 1.38, P=1.00). There was a small increase in the incidence of possibly suicide-related events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population and this increase was seen in both the paroxetine treatment group (incidence increased from 0.8% to 1.1%) and in the placebo group (incidence increased from 0.9% to 1.1%). Therefore, in the 30 day post-therapy period alone, there was a greater percentage of possibly suicide-related events in the paroxetine treatment group (26/8481, 0.3%) than in the placebo group (8/5808, 0.1%). However, such a comparison is biased against the paroxetine treatment group since there was a lower percentage of possibly-suicide related events in the paroxetine treatment group than in the placebo group in the on-therapy phase, and therefore, a greater proportion of paroxetine-treated patients were at risk of reporting these events for the first time in the follow-up period. Furthermore, in a more controlled examination of adverse events that occur in the post-treatment phase of studies with a consistent taper and follow-up period, there is no difference in the incidence of possibly suicide-related events in the paroxetine treatment group compared to placebo group (see Question 6, Section 6.3.3.1).

The majority of the possibly suicide-related events that occurred on therapy were considered to be mild to moderate in intensity in both the paroxetine and placebo groups (Data Source: Appendix 2B, Table 2.03; paroxetine 60%, placebo 58%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.04).

In both the paroxetine treatment group and the placebo group, the majority of the possibly suicide-related events that occurred on therapy were considered by the investigators to be unrelated or probably unrelated to study medication (Data Source: Appendix 2B, Table 2.05; paroxetine 76%, placebo 66%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.06).

Further to the placebo-controlled studies described above, there is an additional central R&D adult placebo-controlled study that is not included on the aggregated database. This is Study 717 and this study investigated the effect of intermittent dosing with paroxetine CR on the treatment of PMDD. This study is not included on the aggregated database due to the nature of the intermittent dosing regime employed in the study making it difficult to merge with the other studies. In total, 373 patients were randomised into the double-blind treatment period of this study (119 paroxetine CR 25mg, 131 paroxetine CR 12.5mg and 123 placebo) and 2 patients reported possibly suicide-related events. Both patients were in the paroxetine CR 12.5mg treatment group; one event occurred on-therapy and the other event occurred post-therapy.

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

In the adult active control trials there was a total of 10 completed suicides; 5 in the paroxetine treatment group (1 on-therapy and 4 post-therapy) and 5 in the comparator group (2 on-therapy and 3 post-therapy).

The search strategy described in Section 2.3.4.1 was run across the adult active-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of possibly suicide-related events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the possibly suicide-related category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.6 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Control Medication Class Adult Active Control Trials On-Therapy (including Taper Phase)

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	55/6522 (0.8%) 1135 0.05	63/4969 (1.3%) 842 0.07	0.66 (0.46 , 0.95)	0.031 0.019
Tricyclic	n/N (%) PYE n/PYE	26/2953 (0.9%) 599 0.04	32/2754 (1.2%) 493 0.06	0.76 (0.45 , 1.27)	0.29 0.13
SSRI	n/N (%) PYE n/PYE	14/1200 (1.2%) 219 0.06	24/1218 (2.0%) 215 0.11	0.59 (0.30, 1.14)	0.14 0.099
Tetracyclic	n/N (%) PYE n/PYE	2/527 (0.4%) 68 0.03	4/518 (0.8%) 64 0.06	0.49 (0.09 , 2.68)	0.45 0.39
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	13/1766 (0.7%) 233 0.06	3/402 (0.7%) 51 0.06	0.99 (0.28 , 3.48)	1.00 0.93

Data Source: Appendix 2B, Table 2.19

Table 2.7 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Control Medication Class Adult Active Control Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	79/6522 (1.2%) 1135 0.07	76/4969 (1.5%) 842 0.09	0.79 (0.57 , 1.08)	0.17 0.11
Tricyclic	n/N (%) PYE n/PYE	37/2953 (1.3%) 599 0.06	41/2754 (1.5%) 493 0.08	0.84 (0.54 , 1.31)	0.49 0.19
SSRI	n/N (%) PYE n/PYE	20/1200 (1.7%) 219 0.09	26/1218 (2.1%) 215 0.12	0.78 (0.43, 1.40)	0.46 0.35
Tetracyclic	n/N (%) PYE n/PYE	2/527 (0.4%) 68 0.03	5/518 (1.0%) 64 0.08	0.39 (0.08 , 2.02)	0.28 0.25
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	20/1766 (1.1%) 233 0.09	4/402 (1.0%) 51 0.08	1.14 (0.39 , 3.35)	1.00 0.87

Data Source: Appendix 2B, Table 2.20

Overall (i.e. across all classes of active control medications), on-therapy possibly suicide-related events occurred at a lower incidence in the paroxetine group than in the active comparator group and this difference was statistically significant (paroxetine 55/6522 (0.8%), comparators 63/4969 (1.3%), OR 0.66, 95% CI 0.46, 0.95, P=0.031). Furthermore, there was a lower incidence of possibly suicide-related events in the paroxetine group compared to the other SSRIs (paroxetine 14/1200 (1.2%), SSRI comparators 24/1218 (2.0%), OR 0.59, 95% CI 0.30, 1.14, P=0.14).

There was a small increase in the incidence of possibly suicide-related events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population and this increase was seen in both the paroxetine treatment group (incidence increased from 0.8% to 1.2%) and in the active comparator group (incidence increased from 1.3% to 1.5%). Overall, in the "on-therapy plus 30 days post-therapy" population, possibly suicide-related events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant (paroxetine 79/6522 (1.2%), comparators 76/4969 (1.5%), OR 0.79, 95% CI 0.57, 1.08, P=0.17).

In the paroxetine group, 33% of the possibly suicide-related events that occurred on therapy were considered to be mild to moderate in intensity compared to 40% in the active comparator group, although intensity was unknown or unassessed in 11% of events

in the paroxetine group and 5% of events in the placebo group (Data Source: Appendix 2B, Table 2.21). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.22; paroxetine 33% mild to moderate and 11% unknown or unassessed, placebo 34% mild to moderate and 12% unknown or unassessed).

In both the paroxetine treatment group and the active comparator group, the majority of the possibly suicide-related events that occurred on therapy were considered by the investigators to be unrelated or probably unrelated to study medication Data Source: Appendix 2B, Table 2.23; paroxetine 53%, placebo 68%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.24; paroxetine 52%, placebo 63%).

2.3.4.4. Possibly suicide-related events from uncontrolled adult trials

This section includes data from uncontrolled paroxetine trials, paroxetine data from uncontrolled extension phases of controlled trials, paroxetine data from re-randomised phases of studies with multiple randomisations and paroxetine data from the uncontrolled first period of relapse-prevention studies.

In the adult uncontrolled paroxetine trials there was a total of 3 completed suicides (2 on-therapy, 1 post-therapy).

The search strategy described in Section 2.3.4.1 was run across all the adult paroxetine data in the central R&D aggregated database.

Overall, the incidence of on-therapy possibly suicide-related events was 0.8% (42/5448) (Data Source: Appendix 2B, Table 2.37). This was consistent with the on-therapy incidence of possibly suicide-related events reported in the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.4.2) and of the active-control clinical trials (see Section 2.3.4.3). As seen in the placebo-controlled clinical trials, the majority of these events occurred in the depression studies (33 of the 42 events, 79%).

In the "on-therapy plus 30 days post-therapy" population, the incidence of possibly suicide-related events was 1.1% (Data Source: Appendix 2B, Table 2.38). This was consistent with the incidence of possibly suicide-related events reported in the "on-therapy plus 30 days post-therapy" timeframe of the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.4.2) and of the active-control clinical trials (see Section 2.3.4.3).

Half of the possibly suicide-related events were considered to be severe in nature (Data Source: Appendix 2B, Tables 2.39 and 2.40) although between 57% and 60% were considered by the investigators to be unrelated or probably unrelated to study medication (Data Source: Appendix 2B, Tables 2.41 and 2.42).

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

There were no completed suicides in the paediatric placebo-controlled trials.

The search strategy described in Section 2.3.4.1 was run across the paediatric placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of possibly suicide-related events in two time periods: (1) "On therapy (including taper phase)", and, (2) "On therapy (including taper phase) plus 30 days". Person Year Exposure (PYE) was calculated for all patients, and the rate of patients in the "possibly suicide-related" category relative to exposure was calculated. Exposure was calculated only for the period on-therapy, i.e. the 30-day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.8 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	18/738 (2.4%) 176 0.10	7/647 (1.1%) 149 0.05	2.29 (0.95 , 5.51)	0.069 0.082
Depression	n/N (%) PYE n/PYE	14/378 (3.7%) 85 0.16	7/285 (2.5%) 61 0.11	1.53 (0.61 , 3.84)	0.50 0.43
OCD	n/N (%) PYE n/PYE	1/195 (0.5%) 41 0.02	0/205 (0.0%) 41 0.00		0.49
SAD	n/N (%) PYE n/PYE	3/165 (1.8%) 51 0.06	0/157 (0.0%) 46 0.00		0.25

Data Source: Appendix 2B, Table 2.55

Table 2.9 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	25/738 (3.4%) 176 0.14	8/647 (1.2%) 149 0.05	2.80 (1.25 , 6.25)	0.012 0.017
Depression	n/N (%) PYE n/PYE	20/378 (5.3%) 85 0.24	8/285 (2.8%) 61 0.13	1.93 (0.84 , 4.46)	0.12 0.16
OCD	n/N (%) PYE n/PYE	1/195 (0.5%) 41 0.02	0/205 (0.0%) 41 0.00		0.49
SAD	n/N (%) PYE n/PYE	4/165 (2.4%) 51 0.08	0/157 (0.0%) 46 0.00		0.12

Data Source: Appendix 2B, Table 2.56

Overall, the incidence of possibly suicide-related events observed on paroxetine therapy in the paediatric placebo-controlled studies was 2.4%, compared to 1.1% in the placebo group (OR 2.29, 95% CI 0.95, 5.51, P=0.069). The majority of on-therapy possibly suicide-related adverse events in the paroxetine-treated group were in patients with MDD (14 of 18 patients; 78%). All seven placebo patients who had on-therapy possibly suicide-related adverse events came from the MDD studies. A similar pattern is seen when the incidence of on-therapy possibly suicide-related events is examined for only the acute treatment phases of the placebo-controlled trials (Data Source: Appendix 2B, Table 2.57).

Overall, the incidence of possibly suicide-related events observed in the paediatric placebo-controlled studies including 30 days post-therapy was 3.4% in the paroxetine group and 1.2% in the placebo group and this difference was statistically significant (OR 2.80, 95% CI 1.25, 6.25 P=0.012). Again, the majority of these events were in patients with MDD: 20 of 25 patients (80%) in the paroxetine group and all 8 patients in the placebo group.

In the paroxetine group, 56% of the possibly suicide-related events that occurred on-therapy were considered to be mild to moderate in intensity compared to 43% in the placebo group (Data Source: Appendix 2B, Table 2.58). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.59; paroxetine 56%, placebo 50%).

The majority of the possibly suicide-related events that occurred on-therapy were considered by the investigators to be unrelated or probably unrelated to study medication Data Source: Appendix 2B, Table 2.60; paroxetine 83%, placebo 57%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-

therapy" population (Data Source: Appendix 2B, Table 2.61; paroxetine 84%, placebo 63%).

In addition to the placebo-controlled paediatric trials discussed above, the occurrence of possibly suicide-related events in Study 715 (open-label, repeat dose, dose-rising PK study in children and adolescents with OCD and/or depression), Study 716 (open-label extension study in children and adolescents who completed depression study 701, OCD Study 704 or PK Study 715) and the open-label phase of OCD Study 453 were investigated. In Study 715 (N=62 patients), 2 patients reported possibly suicide-related events in the "on-therapy plus 30 days" period. In Study 716 (N=265 patients), 9 patients reported possibly suicide-related events in the "on-therapy plus 30 days" period. In the open-label phase of Study 453 (N=339) 8 patients reported possibly suicide-related events in the "on-therapy plus 30 days" period. The incidence of possibly suicide-related events in the imipramine arm of the paediatric depression Study 329 was also investigated and was 4.2% (4/95), compared to 8.6% (8/93) in the paroxetine arm.

2.3.4.6. Time to first onset of possibly suicide-related events

The time to first onset of possibly suicide-related events was examined for the following three populations:

- Adult placebo-controlled trials
- Adult active-controlled trials
- Paediatric placebo-controlled trials

Adult placebo-controlled and active-controlled trials

The following table summarises the time to first onset of possibly-suicide related adverse events occurring on-therapy (including taper phase) in the adult placebo-controlled and active control trials.

Table 2.10 Time to First Onset of Possibly Suicide-Related Events by Treatment Group
Adult Placebo Controlled and Active Control Trials
On-Therapy (including Taper Phase)

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	66	55	55	63
Week 1	9 (13.6%)	10 (18.2%)	14 (25.5%)	13 (20.6%)
Week 2	4 (6.1%)	7 (12.7%)	4 (7.3%)	11 (17.5%)
Week 3	5 (7.6%)	4 (7.3%)	5 (9.1%)	9 (14.3%)
Week 4	15 (22.7%)	6 (10.9%)	12 (21.8%)	11 (17.5%)
Week 5	6 (9.1%)	3 (5.5%)	6 (10.9%)	2 (3.2%)
Week 6	3 (4.5%)	3 (5.5%)	3 (5.5%)	2 (3.2%)
Week 7	8 (12.1%)	2 (3.6%)	4 (7.3%)	5 (7.9%)
Week 8	3 (4.5%)	3 (5.5%)	1 (1.8%)	2 (3.2%)
Week 9	4 (6.1%)	3 (5.5%)	2 (3.6%)	2 (3.2%)
Week 10	3 (4.5%)	4 (7.3%)	0 (0.0%)	1 (1.6%)
Week 11	1 (1.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)
Week 12	0 (0.0%)	1 (1.8%)	2 (3.6%)	1 (1.6%)
Week 13-16	3 (4.5%)	3 (5.5%)	1 (1.8%)	1 (1.6%)
Week 17-20	2 (3.0%)	1 (1.8%)	0 (0.0%)	1 (1.6%)
Week 21-24	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
Week 25-52	0 (0.0%)	1 (1.8%)	0 (0.0%)	2 (3.2%)
Week 53+	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.82 and Table 2.84

On-therapy possibly suicide-related events were seen throughout the duration of the adult placebo-controlled and active control clinical trials. However, in the placebo-controlled trials, approximately half of the events in both treatment groups occurred in the first four weeks. In the active comparator studies, between 64% and 70% of the events occurred within the first four weeks.

The following table summarises the time to first onset of possibly-suicide related adverse events occurring during the 30 day period after cessation of the controlled period of treatment from the adult placebo-controlled and active control trials. It should be noted that this table does not include events reported in the 30 day follow-up period by patients who experienced a possibly suicide-related event in the on-therapy period.

Table 2.11 Time to First Onset of Possibly Suicide-Related Events by Treatment Group
Adult Placebo Controlled and Active Control Trials
30 Day Follow-Up Period

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	26	8	24	13
Week 1	20 (76.9%)	2 (25.0%)	15 (62.5%)	8 (61.5%)
Week 2	4 (15.4%)	2 (25.0%)	4 (16.7%)	1 (7.7%)
Week 3	1 (3.8%)	4 (50.0%)	2 (8.3%)	3 (23.1%)
Week 4	1 (3.8%)	0 (0.0%)	3 (12.5%)	0 (0.0%)
Week 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)

Data Source: Appendix 2B, Table 2.83 and Table 2.85

In both the paroxetine treatment groups, the placebo group and the active comparator group the possibly suicide-related events that occurred during the 30 day post-treatment period occurred throughout the whole period, although in the two paroxetine treatment groups and the active comparator group the majority of events occurred within the first week.

Paediatric Placebo-Controlled Trials

The following table summarises the time to first onset of possibly-suicide related adverse events occurring on-therapy (including taper phase) in the paediatric placebo-controlled trials.

Table 2.12 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%)

Data Source: Appendix 2B, Table 2.86

The on-therapy possibly suicide-related events are seen throughout the duration of the paediatric placebo-controlled clinical trials, and there was no difference between the paroxetine treatment group and placebo group with respect to the time to first occurrence of these events.

The following table summarises the time to first onset of possibly-suicide related adverse events occurring during the 30 day period after cessation of the controlled period of treatment from the paediatric placebo-controlled trials. It should be noted that this table does not include events reported in the 30 day follow-up period by patients who experienced a possibly suicide-related event in the on-therapy period.

Table 2.13 Time to First Onset of Possibly Suicide-Related Events by Treatment Group
Paediatric Placebo Controlled Trials
30 Day Follow-Up Period

Time Period	Paroxetine (N=738)	Placebo (N=647)
Total number of patients with event	7	1
Week 1	6 (85.7%)	1 (100.0%)
Week 2	1 (14.3%)	0 (0.0%)
Week 3	0 (0.0%)	0 (0.0%)
Week 4	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.87

Seven patients in the paroxetine treatment group reported a possibly suicide-related event in the 30 day period following cessation of treatment; 6 of these events occurred in the first week post-treatment. This compared to one patient in the placebo group who experienced a possibly suicide-related event in the first week of the 30 day post-treatment period.

2.3.5. Self-harm events

2.3.5.1. Definition of self-harm events

The definition of self harm adhered to in this section follows the definition of possibly suicide-related (see Section 2.3.4.1) 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.

2.3.5.2. Self-harm in adult placebo-controlled trials

The search strategy described in Section 2.3.5.1 was run across the adult placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of self harm events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the self harm category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.14 Incidence and Incidence Density for Self Harm by Treatment Group and Indication
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	51/8481 (0.6%) 1916 0.03	38/5808 (0.7%) 1313 0.03	0.92 (0.60 , 1.40)	0.75 0.69
Depression	n/N (%) PYE n/PYE	45/3421 (1.3%) 671 0.07	33/2117 (1.6%) 428 0.08	0.84 (0.54 , 1.32)	0.48 0.54
GAD	n/N (%) PYE n/PYE	2/1182 (0.2%) 259 0.01	0/985 (0.0%) 211 0.00		0.50
OCD	n/N (%) PYE n/PYE	1/542 (0.2%) 141 0.01	1/265 (0.4%) 61 0.02	0.49 (0.03 , 7.83)	0.55 0.55
PMDD	n/N (%) PYE n/PYE	0/760 (0.0%) 208 0.00	0/379 (0.0%) 102 0.00		
PTSD	n/N (%) PYE n/PYE	1/786 (0.1%) 174 0.01	1/598 (0.2%) 138 0.01	0.76 (0.05 , 12.18)	1.00 0.87
Panic	n/N (%) PYE n/PYE	0/920 (0.0%) 237 0.00	2/780 (0.3%) 186 0.01		0.21 1.00
SAD	n/N (%) PYE n/PYE	2/870 (0.2%) 225 0.01	1/684 (0.1%) 187 0.01	1.57 (0.14 , 17.39)	1.00 0.68

Data Source: Appendix 2B, Table 2.07

Table 2.15 Incidence and Incidence Density for Self Harm by Treatment Group and Indication
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	63/8481 (0.7%) 1916 0.03	41/5808 (0.7%) 1313 0.03	1.05 (0.71 , 1.56)	0.84 0.80
Depression	n/N (%) PYE n/PYE	55/3421 (1.6%) 671 0.08	35/2117 (1.7%) 428 0.08	0.97 (0.63 , 1.49)	0.91 0.99
GAD	n/N (%) PYE n/PYE	2/1182 (0.2%) 259 0.01	0/985 (0.0%) 211 0.00		0.50
OCD	n/N (%) PYE n/PYE	2/542 (0.4%) 141 0.01	1/265 (0.4%) 61 0.02	0.98 (0.09 , 10.83)	1.00 0.90
PMDD	n/N (%) PYE n/PYE	0/760 (0.0%) 208 0.00	0/379 (0.0%) 102 0.00		
PTSD	n/N (%) PYE n/PYE	1/786 (0.1%) 174 0.01	2/598 (0.3%) 138 0.01	0.38 (0.03, 4.20)	0.58 0.45
Panic	n/N (%) PYE n/PYE	1/920 (0.1%) 237 0.00	2/780 (0.3%) 186 0.01	0.42 (0.04, 4.68)	0.60 0.44
SAD	n/N (%) PYE n/PYE	2/870 (0.2%) 225 0.01	1/684 (0.1%) 187 0.01	1.57 (0.14 , 17.39)	1.00 0.68

Data Source: Appendix 2B, Table 2.08

Overall, the incidence of self harm on-therapy was 0.6% in the paroxetine treatment group and 0.7% in the placebo group. As for the possibly suicide-related events, self harm occurred at a lower incidence in the paroxetine group than in the placebo group although this difference was not statistically significant (paroxetine 51/8481 (0.6%), placebo 38/5808 (0.7%), OR 0.92, 95% CI 0.60, 1.40, P=0.75). In both treatment groups, the majority of self harm occurred in the depression studies; 45 of the 51 (88%) events in the paroxetine group and 33 of the 38 (87%) events in the placebo group.

Many of the self harm events from the depression studies (26 of the 45 depression study events in the paroxetine group, 28 of the 33 depression study events in the placebo group) occurred in Study 057 (Data Source: Appendix 2B, Table 2.07a). This study investigated the effect of paroxetine in the prevention of recurrent suicidal behaviour and episodes of intermittent brief depression, and the inclusion criteria specified that patients must have had a history of at least one episode of suicidal behaviour in addition to the index episode. In Study 057 alone, there was no difference in the incidence of on-therapy self

harm events in the paroxetine treatment group compared to the placebo group (Data Source: Appendix 2B, Table 2.07a: paroxetine 26/131 (19.8%), placebo 28/136 (20.6%), OR 0.96, 95% CI 0.53, 1.74, P=1.00).

There was a small increase in the incidence of self harm events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population in the paroxetine group (incidence increased from 0.6% to 0.7%) but overall across the indications in the "on-therapy plus 30 days post-therapy" population there was no difference between the incidence of self harm events between the paroxetine and placebo treatment groups (paroxetine 63/8481 (0.7%), placebo 41/5808 (0.7%), OR 1.05, 95% CI 0.71, 1.56, P=0.84).

The majority of the self harm events that occurred on therapy were considered to be mild to moderate in intensity (Data Source: Appendix 2B, Table 2.09; paroxetine 63%, placebo 53%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.10).

The majority of the self harm events that occurred on therapy were considered by the investigators to be unrelated or probably unrelated to study medication (Data Source: Appendix 2B, Table 2.11; paroxetine 80%, placebo 71%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.12).

There were no self harm events reported in Study 717 (the placebo-controlled intermittent dosing PMDD study which is not included in the central R&D aggregated database).

2.3.5.3. Self-harm in adult active-controlled trials

The search strategy described in Section 2.3.5.1 was run across the adult active-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of self harm events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the self harm category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.16 Incidence and Incidence Density for Self Harm by Treatment Group and Control Medication Class
Adult Active Control Trials
On-Therapy (including Taper Phase)

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	29/6522 (0.4%) 1135 0.03	32/4969 (0.6%) 842 0.04	0.69 (0.42 , 1.14)	0.16 0.12
Tricyclic	n/N (%) PYE n/PYE	17/2953 (0.6%) 599 0.03	22/2754 (0.8%) 493 0.04	0.72 (0.38 , 1.36)	0.34 0.16
SSRI	n/N (%) PYE n/PYE	6/1200 (0.5%) 219 0.03	6/1218 (0.5%) 215 0.03	1.02 (0.33, 3.16)	1.00 0.98
Tetracyclic	n/N (%) PYE n/PYE	2/527 (0.4%) 68 0.03	2/518 (0.4%) 64 0.03	0.98 (0.14 , 7.00)	1.00 0.96
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	4/1766 (0.2%) 233 0.02	2/402 (0.5%) 51 0.04	0.45 (0.08 , 2.49)	0.31 0.34

Data Source: Appendix 2B, Table 2.25

Table 2.17 Incidence and Incidence Density for Self Harm by Treatment Group and Control Medication Class
Adult Active Control Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	42/6522 (0.6%) 1135 0.04	42/4969 (0.8%) 842 0.05	0.76 (0.49 , 1.17)	0.22 0.17
Tricyclic	n/N (%) PYE n/PYE	26/2953 (0.9%) 599 0.04	29/2754 (1.1%) 493 0.06	0.83 (0.49 , 1.42)	0.59 0.26
SSRI	n/N (%) PYE n/PYE	8/1200 (0.7%) 219 0.04	7/1218 (0.6%) 215 0.03	1.16 (0.42, 3.21)	0.80 0.82
Tetracyclic	n/N (%) PYE n/PYE	2/527 (0.4%) 68 0.03	3/518 (0.6%) 64 0.05	0.65 (0.11 , 3.93)	0.68 0.61
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	6/1766 (0.3%) 233 0.03	3/402 (0.7%) 51 0.06	0.45 (0.11 , 1.82)	0.22 0.24

Data Source: Appendix 2B, Table 2.26

Overall, on-therapy self harm events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant (paroxetine 29/6522 (0.4%), comparators 32/4969 (0.6%), OR 0.69, 95% CI 0.42, 1.14, P=0.16).

There was a small increase in the incidence of self harm events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population and this increase was seen in both the paroxetine treatment group (incidence increased from 0.4% to 0.6%) and in the active comparator group (incidence increased from 0.6% to 0.8%). Overall, in the "on-therapy plus 30 days post-therapy" population, self harm events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant (paroxetine 42/6522 (0.6%), comparators 42/4969 (0.8%), OR 0.76, 95% CI 0.49, 1.17, P=0.22).

In the paroxetine treatment group, 55% of the on-therapy self harm events were considered to be severe in intensity compared to 69% of the events in the active comparator group (Data Source: Appendix 2B, Table 2.27). In the "on-therapy plus 30 days post-therapy" period, 57% of the events in the paroxetine treatment group were considered to be severe in intensity compared to 64% in the active comparator group (Data Source: Appendix 2B, Table 2.28).

Between 88% and 90% of the self-harm events that occurred "on therapy" and "on-therapy plus 30 days post-therapy" were considered by the investigators to be unrelated or probably unrelated to study medication or the relationship was unknown or unassessed (Data Source: Appendix 2B, Table 2.29 and Table 2.30).

2.3.5.4. Self-harm events from uncontrolled adult trials

This section includes data from uncontrolled paroxetine trials, paroxetine data from uncontrolled extension phases of controlled trials, paroxetine data from re-randomised phases of studies with multiple randomisations and paroxetine data from the uncontrolled first period of relapse-prevention studies.

The search strategy described in Section 2.3.5.1 was run across all the adult paroxetine data in the central R&D aggregated database.

The incidence of on-therapy self harm events across all indications was 0.5% (28/5448) (Data Source: Appendix 2B, Table 2.43). This was similar to the on-therapy incidence of self harm events reported in the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.5.2) and of the active-control clinical trials (see Section 2.3.5.3). As seen in the placebo-controlled clinical trials, the majority of these events occurred in the depression studies (22 of the 28 events, 79%).

In the "on-therapy plus 30 days post-therapy" population, the incidence of self harm events was slightly greater than in the "on-therapy" population (0.7% compared to 0.5%; Data Source: Appendix 2B, Table 2.44). This was similar to the incidence of self harm events reported in the "on-therapy plus 30 days post-therapy" timeframe of the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.5.2) and of the active-control clinical trials (see Section 2.3.5.3).

Half of the self harm events were considered to be severe in nature (Data Source: Appendix 2B, Tables 2.45 and 2.46) although a similar proportion were considered by the investigators to be unrelated or probably unrelated to study medication (Data Source: Appendix 2B, Tables 2.47 and 2.48).

2.3.5.5. Self-harm in paediatric placebo-controlled trials

The search strategy described in Section 2.3.5.1 was run across the paediatric placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of self harm events in two time periods: (1) "On therapy (including taper phase)", and, (2) "On therapy (including taper phase) plus 30 days". Person Year Exposure (PYE) was calculated for all patients, and the rate of patients in the self harm category relative to exposure was calculated. Exposure was calculated only for the period on-therapy, i.e. the 30-day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.18 Incidence and Incidence Density for Self Harm by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	15/738 (2.0%) 176 0.09	5/647 (0.8%) 149 0.03	2.66 (0.96 , 7.37)	0.069 0.072
Depression	n/N (%) PYE n/PYE	14/378 (3.7%) 85 0.16	5/285 (1.8%) 61 0.08	2.15 (0.77 , 6.05)	0.16 0.18
OCD	n/N (%) PYE n/PYE	0/195 (0.0%) 41 0.00	0/205 (0.0%) 41 0.00		
SAD	n/N (%) PYE n/PYE	1/165 (0.6%) 51 0.02	0/157 (0.0%) 46 0.00		1.00

Data Source: Appendix 2B, Table 2.62

Table 2.19 Incidence and Incidence Density for Self Harm Events by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	18/738 (2.4%) 176 0.10	5/647 (0.8%) 149 0.03	3.21 (1.19, 8.70)	0.019 0.028
Depression	n/N (%) PYE n/PYE	17/378 (4.5%) 85 0.20	5/285 (1.8%) 61 0.08	2.64 (0.96 , 7.24)	0.077 0.079
OCD	n/N (%) PYE n/PYE	0/195 (0.0%) 41 0.00	0/205 (0.0%) 41 0.00		
SAD	n/N (%) PYE n/PYE	1/165 (0.6%) 51 0.02	0/157 (0.0%) 46 0.00		1.00

Data Source: Appendix 2B, Table 2.63

Overall, the incidence of self harm observed on paroxetine therapy in the paediatric placebo-controlled studies was 2.0%, compared to 0.8% in the placebo group (OR 2.66, 95% CI 0.96, 7.37, P=0.069). The majority of on-therapy self harm events in the paroxetine-treated group were in patients with MDD (14 of 15 patients; 93%). All 5 placebo patients who had on-therapy self harm events came from the MDD studies. A similar pattern is seen when the incidence of on-therapy self harm events is examined for

only the acute treatment phases of the placebo-controlled trials (Data Source: Appendix 2B, Table 2.64).

Overall, the incidence of self harm events observed in the paediatric placebo-controlled studies including 30 days post-therapy was 2.4% in the paroxetine group and 0.8% in the placebo group and this difference was statistically significant (OR 3.21, 95% CI 1.19, 8.70 P=0.019). Again, the majority of these events were in patients with MDD: 17 of 18 patients (94%) in the paroxetine group and all 5 patients in the placebo group.

The majority of self harm events occurring "on therapy" and "on-therapy plus 30 days post-therapy" were mild to moderate in nature for both the paroxetine treatment group and the placebo group (Data Source: Appendix 2B, Table 2.65 and Table 2.66).

The majority of the self harm events that occurred on-therapy were considered by the investigators to be unrelated or probably unrelated to study medication (Data Source: Appendix 2B, Table 2.67; paroxetine 80%, placebo 60%). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.68; paroxetine 78%, placebo 60%).

In addition to the placebo-controlled paediatric trials discussed above, the occurrence of self harm events in Study 715 (open-label, repeat dose, dose-rising PK study in children and adolescents with OCD and/or depression), Study 716 (open-label extension study in children and adolescents who completed depression study 701, OCD Study 704 or PK Study 715) and the open-label phase of OCD Study 453 were investigated. In Study 715 (N=62 patients), 1 patient reported a self harm event in the "on-therapy plus 30 days" period. In Study 716 (N=265 patients), 5 patients reported self harm events in the "on-therapy plus 30 days" period. In the open-label phase of Study 453 (N=339) 2 patients reported self harm events in the "on-therapy plus 30 days" period. The incidence of self harm events in the imipramine arm of the paediatric depression Study 329 was also investigated and was 2.1% (2/95), compared to 7.5% (7/93) in the paroxetine arm.

2.3.5.6. Time to first onset of self-harm events

The time to first onset of self-harm events was examined for the following three populations:

- Adult placebo-controlled trials
- Adult active-controlled trials
- Paediatric placebo-controlled trials

Adult placebo-controlled and active-controlled trials

The following table summarises the time to first onset of self harm events occurring on-therapy (including taper phase) in the adult placebo-controlled and active control trials.

Table 2.20 Time to First Onset of Self Harm by Treatment Group Adult Placebo Controlled and Active Control Trials On-Therapy (including Taper Phase)

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	51	38	29	32
Week 1	5 (9.8%)	7 (18.4%)	6 (20.7%)	4 (12.5%)
Week 2	3 (5.9%)	4 (10.5%)	1 (3.4%)	2 (6.3%)
Week 3	4 (7.8%)	3 (7.9%)	2 (6.9%)	4 (12.5%)
Week 4	9 (17.6%)	2 (5.3%)	6 (20.7%)	9 (28.1%)
Week 5	6 (11.8%)	3 (7.9%)	3 (10.3%)	1 (3.1%)
Week 6	3 (5.9%)	2 (5.3%)	2 (6.9%)	1 (3.1%)
Week 7	6 (11.8%)	1 (2.6%)	2 (6.9%)	5 (15.6%)
Week 8	3 (5.9%)	2 (5.3%)	1 (3.4%)	0 (0.0%)
Week 9	4 (7.8%)	3 (7.9%)	2 (6.9%)	1 (3.1%)
Week 10	3 (5.9%)	2 (5.3%)	0 (0.0%)	1 (3.1%)
Week 11	1 (2.0%)	1 (2.6%)	1 (3.4%)	0 (0.0%)
Week 12	0 (0.0%)	1 (2.6%)	2 (6.9%)	1 (3.1%)
Week 13-16	2 (3.9%)	2 (5.3%)	1 (3.4%)	1 (3.1%)
Week 17-20	2 (3.9%)	1 (2.6%)	0 (0.0%)	1 (3.1%)
Week 21-24	0 (0.0%)	2 (5.3%)	0 (0.0%)	0 (0.0%)
Week 25-52	0 (0.0%)	1 (2.6%)	0 (0.0%)	1 (3.1%)
Week 53+	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.88 and Table 2.90

On-therapy self harm events were seen throughout the duration of the adult placebo-controlled and active control clinical trials, although more than 40% of all events occurred within the first four weeks in both of the paroxetine treatment groups, the placebo control group and the active comparator group.

The following table summarises the time to first onset of self harm events occurring during the 30 day period after cessation of the controlled period of treatment from the adult placebo-controlled and active control trials. It should be noted that this table does not include events reported in the 30 day follow-up period by patients who experienced a self harm event in the on-therapy period.

Table 2.21 Time to First Onset of Self Harm by Treatment Group Adult Placebo Controlled and Active Control Trials 30 Day Follow-Up Period

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	12	3	13	10
Week 1	9 (75.0%)	1 (33.3%)	10 (76.9%)	7 (70.0%)
Week 2	3 (25.0%)	0 (0.0%)	3 (23.1%)	1 (10.0%)
Week 3	0 (0.0%)	2 (66.7%)	0 (0.0%)	1 (10.0%)
Week 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)

Data Source: Appendix 2B, Table 2.89 and Table 2.91

In the paroxetine treatment groups and the active comparator group the majority of the self harm events occurring in the 30 day post-treatment period do so in the first week. In the placebo group there were 3 patients who experienced self harm events in the 30 day post-treatment period; 1 in the first week and 2 in the third week.

Paediatric Placebo-Controlled Trials

The following table summarises the time to first onset of self harm events occurring on-therapy (including taper phase) in the paediatric placebo-controlled trials.

Table 2.22 Time to First Onset of Self Harm 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	15	5
Week 1	0 (0.0%)	1 (20.0%)
Week 2	2 (13.3%)	0 (0.0%)
Week 3	0 (0.0%)	0 (0.0%)
Week 4	2 (13.3%)	0 (0.0%)
Week 5-6	5 (33.3%)	2 (40.0%)
Week 7-8	1 (6.7%)	0 (0.0%)
Week 9-12	4 (26.7%)	1 (20.0%)
Week 13+	1 (6.7%)	1 (20.0%)

Data Source: Appendix 2B, Table 2.92

The on-therapy self harm events are seen throughout the duration of the paediatric placebo-controlled clinical trials, and there was no difference between the paroxetine treatment group and placebo group with respect to the time to first occurrence of these events.

The following table summarises the time to first onset of self harm events occurring during the 30 day period after cessation of the controlled period of treatment from the paediatric placebo-controlled trials. It should be noted that this table does not include events reported in the 30 day follow-up period by patients who experienced a self harm event in the on-therapy period.

Table 2.23 Time to First Onset of Self Harm Events by Treatment Group Paediatric Placebo Controlled Trials 30 Day Follow-Up Period

Time Period	Paroxetine (N=738)	Placebo (N=647)
Total number of patients with event	3	0
Week 1	3 (100.00%)	0 (0.0%)
Week 2	0 (0.0%)	0 (0.0%)
Week 3	0 (0.0%)	0 (0.0%)
Week 4	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.93

All 3 patients in the paroxetine treatment group who experienced a self harm event in the 30 day period following cessation of treatment did so in the first week. No placebo patients reported a self harm event in the 30 day post-treatment period.

2.3.6. Hostility

2.3.6.1. Definition of hostility

The vast majority of adverse events of hostility coded to the preferred term of "hostility". However, a few events coded to other preferred terms and so the following search strategy was employed to establish the definition of hostility events:

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

a Preferred term was "Hostility".

b The verbatim term contained any of the following text strings: "aggress", "anger", "hostil", "murder", or "violen". However, verbatim terms containing the text strings of "dream" or "nightmare" were excluded.

c 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.

2.3.6.2. Hostility in adult placebo-controlled trials

The search strategy described in Section 2.3.6.1 was run across the adult placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of hostility events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the hostility category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.24 Incidence and Incidence Density for Hostility by Treatment Group and Indication
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	24/8481 (0.3%) 1916 0.01	16/5808 (0.3%) 1313 0.01	1.03 (0.55 , 1.94)	1.00 0.93
Depression	n/N (%) PYE n/PYE	11/3421 (0.3%) 671 0.02	7/2117 (0.3%) 428 0.02	0.97 (0.38 , 2.51)	1.00 1.00
GAD	n/N (%) PYE n/PYE	1/1182 (0.1%) 259 0.00	1/985 (0.1%) 211 0.00	0.83 (0.05 , 13.34)	1.00 0.88
OCD	n/N (%) PYE n/PYE	4/542 (0.7%) 141 0.03	4/265 (1.5%) 61 0.07	0.49 (0.12 , 1.96)	0.45 0.23
PMDD	n/N (%) PYE n/PYE	2/760 (0.3%) 208 0.01	0/379 (0.0%) 102 0.00		1.00
PTSD	n/N (%) PYE n/PYE	1/786 (0.1%) 174 0.01	1/598 (0.2%) 138 0.01	0.76 (0.05 , 12.18)	1.00 0.87
Panic	n/N (%) PYE n/PYE	2/920 (0.2%) 237 0.01	2/780 (0.3%) 186 0.01	0.85 (0.12, 6.03)	1.00 0.81
SAD	n/N (%) PYE n/PYE	3/870 (0.3%) 225 0.01	1/684 (0.1%) 187 0.01	2.36 (0.25 , 22.77)	0.64 0.43

Data Source: Appendix 2B, Table 2.13

Table 2.25 Incidence and Incidence Density for Hostility by Treatment Group and Indication
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	32/8481 (0.4%) 1916 0.02	16/5808 (0.3%) 1313 0.01	1.37 (0.75 , 2.50)	0.38 0.30
Depression	n/N (%) PYE n/PYE	12/3421 (0.4%) 671 0.02	7/2117 (0.3%) 428 0.02	1.06 (0.42 , 2.70)	1.00 0.85
GAD	n/N (%) PYE n/PYE	2/1182 (0.2%) 259 0.01	1/985 (0.1%) 211 0.00	1.67 (0.15 , 18.42)	1.00 0.69
OCD	n/N (%) PYE n/PYE	4/542 (0.7%) 141 0.03	4/265 (1.5%) 61 0.07	0.49 (0.12 , 1.96)	0.45 0.23
PMDD	n/N (%) PYE n/PYE	5/760 (0.7%) 208 0.02	0/379 (0.0%) 102 0.00		0.18
PTSD	n/N (%) PYE n/PYE	3/786 (0.4%) 174 0.02	1/598 (0.2%) 138 0.01	2.29 (0.24, 22.05)	0.64 0.45
Panic	n/N (%) PYE n/PYE	2/920 (0.2%) 237 0.01	2/780 (0.3%) 186 0.01	0.85 (0.12, 6.03)	1.00 0.81
SAD	n/N (%) PYE n/PYE	4/870 (0.5%) 225 0.02	1/684 (0.1%) 187 0.01	3.15 (0.35 , 28.29)	0.39 0.28

Data Source: Appendix 2B, Table 2.14

Overall, there was no difference in the incidence of on-therapy hostility events in the paroxetine treatment group compared to the placebo group (paroxetine 24/8481 (0.3%), placebo 16/5808 (0.3%), OR 1.03, 95% CI 0.55, 1.94, P=1.00). The hostility events that occurred in the adult placebo controlled trials were spread across the different indications.

There was a small increase in the incidence of hostility events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population in the paroxetine group (incidence increased from 0.3% to 0.4%) but overall across the indications in the "on-therapy plus 30 days post-therapy" population there was no difference between the incidence of hostility events between the paroxetine and placebo treatment groups (paroxetine 32/8481 (0.4%), placebo 16/5808 (0.3%), OR 1.37, 95% CI 0.75, 2.50, P=0.38).

The majority of hostility events occurring "on therapy" and "on-therapy plus 30 days post-therapy" were mild to moderate in nature for both the paroxetine treatment group and the placebo group (Data Source: Appendix 2B, Table 2.15 and Table 2.16; paroxetine 54% to 59%, placebo 69%).

At least 47% of hostility events in the paroxetine treatment group and at least 63% of those in the placebo group were considered by the investigators to be unrelated or probably unrelated to study medication or the relationship was unknown or unassessed (Data Source: Appendix 2B, Tables 2.17 and 2.18).

There were no hostility events reported in Study 717 (the placebo-controlled intermittent dosing PMDD study which is not included in the central R&D aggregated database).

2.3.6.3. Hostility in adult active-controlled trials

The search strategy described in Section 2.3.6.1 was run across the adult active-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of hostility events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the hostility category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.26 Incidence and Incidence Density for Hostility by Treatment Group and Control Medication Class
Adult Active Control Trials
On-Therapy (including Taper Phase)

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	18/6522 (0.3%) 1135 0.02	20/4969 (0.4%) 842 0.02	0.68 (0.36 , 1.30)	0.25 0.21
Tricyclic	n/N (%) PYE n/PYE	5/2953 (0.2%) 599 0.01	5/2754 (0.2%) 493 0.01	0.93 (0.27 , 3.22)	1.00 0.76
SSRI	n/N (%) PYE n/PYE	7/1200 (0.6%) 219 0.03	8/1218 (0.7%) 215 0.04	0.89 (0.32, 2.46)	1.00 0.77
Tetracyclic	n/N (%) PYE n/PYE	1/527 (0.2%) 68 0.01	4/518 (0.8%) 64 0.06	0.24 (0.03 , 2.19)	0.21 0.20
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	5/1766 (0.3%) 233 0.02	3/402 (0.7%) 51 0.06	0.38 (0.09 , 1.59)	0.17 0.17

Data Source: Appendix 2B, Table 2.31

Table 2.27 Incidence and Incidence Density for Hostility by Treatment Group and Control Medication Class
Adult Active Control Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	22/6522 (0.3%) 1135 0.02	22/4969 (0.4%) 842 0.03	0.76 (0.42 , 1.38)	0.37 0.32
Tricyclic	n/N (%) PYE n/PYE	7/2953 (0.2%) 599 0.01	6/2754 (0.2%) 493 0.01	1.09 (0.37 , 3.24)	1.00 0.94
SSRI	n/N (%) PYE n/PYE	8/1200 (0.7%) 219 0.04	8/1218 (0.7%) 215 0.04	1.02 (0.38, 2.71)	1.00 0.97
Tetracyclic	n/N (%) PYE n/PYE	1/527 (0.2%) 68 0.01	5/518 (1.0%) 64 0.08	0.20 (0.02 , 1.68)	0.12 0.13
Benzodiazepine	n/N (%) PYE n/PYE	0/76 (0.0%) 16 0.00	0/77 (0.0%) 18 0.00		
Other	n/N (%) PYE n/PYE	6/1766 (0.3%) 233 0.03	3/402 (0.7%) 51 0.06	0.45 (0.11 , 1.82)	0.22 0.24

Data Source: Appendix 2B, Table 2.32

Overall, on-therapy hostility events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant (paroxetine 18/6522 (0.3%), comparators 20/4969 (0.4%), OR 0.68, 95% CI 0.36, 1.30, P=0.25).

There was no percentage increase in the incidence of hostility events from the "on-therapy" population to the "on-therapy plus 30 days post-therapy" population in either the paroxetine treatment group or the active comparator group. Overall, in the "on-therapy plus 30 days post-therapy" population, hostility events occurred at a lower incidence in the paroxetine group than in the active comparator group although this difference was not statistically significant (paroxetine 22/6522 (0.3%), comparators 22/4969 (0.4%), OR 0.76, 95% CI 0.42, 1.38, P=0.37).

The majority of the hostility events that occurred on-therapy and "on-therapy plus 30 days post-therapy" were considered to be mild to moderate in intensity (Data Source: Appendix 2B, Table 2.33 and Table 2.34; paroxetine 56% to 59%, active comparator 73-75%).

In the paroxetine group, 44% of the on-therapy hostility events were considered by the investigators to be unrelated or probably unrelated to study medication compared to 25%

in the active comparator group (Data Source: Appendix 2B, Table 2.35). A similar pattern was seen in the "on-therapy plus 30 days post-therapy" population (Date Source: Appendix 2B, Table 2.36).

2.3.6.4. Hostility events from uncontrolled adult trials

This section includes data from uncontrolled paroxetine trials, paroxetine data from uncontrolled extension phases of controlled trials, paroxetine data from re-randomised phases of studies with multiple randomisations and paroxetine data from the uncontrolled first period of relapse-prevention studies.

The search strategy described in Section 2.3.6.1 was run across all the adult paroxetine data in the central R&D aggregated database.

The incidence of on-therapy hostility events across all indications was 0.2% (11/5448) (Data Source: Appendix 2B, Table 2.49). This was similar to the on-therapy incidence of hostility events reported in the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.6.2) and of the active-control clinical trials (see Section 2.3.6.3).

In the "on-therapy plus 30 days post-therapy" population, the incidence of hostility events was slightly greater than in the "on-therapy" population (0.3% compared to 0.2%; Data Source: Appendix 2B, Table 2.50). This was similar to the incidence of hostility events reported in the "on-therapy plus 30 days post-therapy" timeframe of the paroxetine group of the placebo-controlled clinical trials (see Section 2.3.6.2) and of the active-control clinical trials (see Section 2.3.6.3).

The majority of the hostility events that occurred on-therapy and "on-therapy plus 30 days post-therapy" were considered to be mild to moderate in intensity (Data Source: Appendix 2B, Table 2.51 and Table 2.52). The majority of the hostility events that occurred on-therapy and "on-therapy plus 30 days post-therapy" were considered by the investigators to be related, probably related or possibly related to study medication (Data Source: Appendix 2B, Table 2.53 and Table 2.54).

2.3.6.5. Hostility in paediatric placebo-controlled trials

The search strategy described in Section 2.3.6.1 was run across the paediatric placebo-controlled trials in the central R&D aggregated database and the results are presented in the following two tables which present the incidence of hostility events in two time periods: (1) "on therapy (including taper phase), and (2) "on therapy (including taper phase) plus 30 days post-therapy". Person Year Exposure (PYE) is shown and the rate of patients in the hostility category relative to exposure is also shown. Exposure was calculated only for the period on-therapy, i.e. the 30 day post-therapy window was not used in calculating exposure. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Table 2.28 Incidence and Incidence Density for Hostility by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	27/738 (3.7%) 176 0.15	4/647 (0.6%) 149 0.03	6.10 (2.12 , 17.54)	<0.001 <0.001
Depression	n/N (%) PYE n/PYE	7/378 (1.9%) 85 0.08	1/285 (0.4%) 61 0.02	5.36 (0.66 , 43.80)	0.15 0.13
OCD	n/N (%) PYE n/PYE	15/195 (7.7%) 41 0.37	1/205 (0.5%) 41 0.02	17.00 (2.22, 130.0)	<0.001 0.009
SAD	n/N (%) PYE n/PYE	5/165 (3.0%) 51 0.10	2/157 (1.3%) 46 0.04	2.42 (0.46, 12.67)	0.45 0.32

Data Source: Appendix 2B, Table 2.69

Table 2.29 Incidence and Incidence Density for Hostility Events by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%) PYE n/PYE	28/738 (3.8%) 176 0.16	4/647 (0.6%) 149 0.03	6.34 (2.21, 18.17)	<0.001 <0.001
Depression	n/N (%) PYE n/PYE	8/378 (2.1%) 85 0.09	1/285 (0.4%) 61 0.02	6.14 (0.76, 49.38)	0.086 0.099
OCD	n/N (%) PYE n/PYE	15/195 (7.7%) 41 0.37	1/205 (0.5%) 41 0.02	17.00 (2.22, 130.0)	<0.001 0.009
SAD	n/N (%) PYE n/PYE	5/165 (3.0%) 51 0.10	2/157 (1.3%) 46 0.04	2.42 (0.46, 12.67)	0.45 0.32

Data Source: Appendix 2B, Table 2.70

Overall, the incidence of hostility events observed on paroxetine therapy in the paediatric placebo-controlled studies was 3.7%, compared to 0.6% in the placebo group and this difference was statistically significant (OR 6.10, 95% CI 2.12, 17.54, P<0.001). The majority of on-therapy hostility events in the paroxetine-treated group were in patients with OCD (15 of 27 patients; 56%). A similar pattern is seen when the incidence of on-therapy hostility events is examined for only the acute treatment phases of the placebo-controlled trials (Data Source: Appendix 2B, Table 2.71).

Overall, the incidence of hostility events observed in the paediatric placebo-controlled studies including 30 days post-therapy was 3.8% in the paroxetine group and 0.6% in the placebo group and this difference was statistically significant (OR 6.34, 95% CI 2.21, 18.17 P<0.001).

Appendix 2B, Listing 2.01 provides the detail of all hostility events from the paediatric placebo-controlled population. These events consist mainly of aggression, oppositional behaviour and anger and the majority were mild to moderate in nature for both the paroxetine treatment group and the placebo group (Data Source: Appendix 2B, Table 2.72 and Table 2.73; paroxetine 64% to 70%, placebo 75%).

In the paroxetine treatment group, 37% of the on-therapy hostility events were considered by the investigators to be unrelated or probably unrelated to study medication compared to 75% in the placebo group (Data Source: Appendix 2B, Table 2.74). A similar pattern was seen in those events that occurred in the "on-therapy plus 30 days post-therapy" population (Data Source: Appendix 2B, Table 2.75).

In addition to the placebo-controlled paediatric trials discussed above, the occurrence of hostility events in Study 715 (open-label, repeat dose, dose-rising PK study in children and adolescents with OCD and/or depression), Study 716 (open-label extension study in children and adolescents who completed depression study 701, OCD Study 704 or PK Study 715) and the open-label phase of OCD Study 453 were investigated. In Study 715 (N=62 patients), 5 patients reported hostility events in the "on-therapy plus 30 days" period. In Study 716 (N=265 patients), 18 patients reported hostility events in the "on-therapy plus 30 days" period. In the open-label phase of Study 453 (N=339) 28 patients reported hostility events in the "on-therapy plus 30 days" period. The incidence of hostility events in the imipramine arm of the paediatric depression Study 329 was also investigated and was 3.2% (3/95), compared to 6.5% (6/93) in the paroxetine arm.

2.3.6.6. Time to first onset of hostility events

The time to first onset of hostility events was examined for the following three populations:

- Adult placebo-controlled trials
- Adult active-controlled trials
- Paediatric placebo-controlled trials

Adult placebo-controlled and active-controlled trials

The following table summarises the time to first onset of hostility events occurring on-therapy (including taper phase) in the adult placebo-controlled and active control trials.

Table 2.30 Time to First Onset of Hostility by Treatment Group Adult Placebo Controlled and Active Control Trials On-Therapy (including Taper Phase)

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	24	16	18	20
Week 1	3 (12.5%)	5 (31.3%)	3 (16.7%)	4 (20.0%)
Week 2	2 (8.3%)	0 (0.0%)	5 (27.8%)	2 (10.0%)
Week 3	0 (0.0%)	3 (18.8%)	3 (16.7%)	4 (20.0%)
Week 4	3 (12.5%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Week 5	1 (4.2%)	0 (0.0%)	0 (0.0%)	4 (20.0%)
Week 6	1 (4.2%)	1 (6.3%)	1 (5.6%)	3 (15.0%)
Week 7	3 (12.5%)	1 (6.3%)	1 (5.6%)	0 (0.0%)
Week 8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 9	3 (12.5%)	0 (0.0%)	1 (5.6%)	2 (10.0%)
Week 10	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 11	2 (8.3%)	0 (0.0%)	2 (11.1%)	0 (0.0%)
Week 12	2 (8.3%)	0 (0.0%)	1 (5.6%)	0 (0.0%)
Week 13-16	2 (8.3%)	2 (12.5%)	1 (5.6%)	0 (0.0%)
Week 17-20	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 21-24	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Week 25-52	0 (0.0%)	2 (12.5%)	0 (0.0%)	1 (5.0%)
Week 53+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.94 and Table 2.96

On-therapy hostility events were seen throughout the duration of the adult placebo-controlled and active control clinical trials in all of the treatment groups.

The following table summarises the time to first onset of hostility events occurring during the 30 day period after cessation of the controlled period of treatment from the adult placebo-controlled and active control trials. It should be noted that this table does not include events reported in the 30 day follow-up period by patients who experienced a hostility event in the on-therapy period.

Table 2.31 Time to First Onset of Hostility by Treatment Group Adult Placebo Controlled and Active Control Trials 30 Day Follow-Up Period

Time Period	Placebo Controlled Trials		Active Control Trials	
	Paroxetine (N=8481)	Placebo (N=5808)	Paroxetine (N=6522)	Comparator (N=4969)
Total number of patients with event	8	0	4	2
Week 1	5 (62.5%)	0 (0.0%)	3 (75.0%)	1 (50.0%)
Week 2	1 (12.5%)	0 (0.0%)	1 (25.0%)	1 (50.0%)
Week 3	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 4	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2B, Table 2.95 and Table 2.97

The number of hostility events occurring in the 30 day post-treatment period in the adult placebo-controlled and active control studies was low (including no events in the placebo group), but it appears that in the paroxetine treatment groups and the active comparator group most of the events occurred in the first week.

Paediatric Placebo-Controlled Trials

The following table summarises the time to first onset of hostility events occurring on-therapy (including taper phase) in the paediatric placebo-controlled trials.

Table 2.32 Time to First Onset of Hostility 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	27	4
Week 1	3 (11.1%)	0 (0.0%)
Week 2	1 (3.7%)	1 (25.0%)
Week 3	5 (18.5%)	1 (25.0%)
Week 4	3 (11.1%)	0 (0.0%)
Week 5-6	4 (14.8%)	1 (25.0%)
Week 7-8	2 (7.4%)	0 (0.0%)
Week 9-12	8 (29.6%)	0 (0.0%)
Week 13+	1 (3.7%)	1 (25.0%)

Data Source: Appendix 2B, Table 2.98

The on-therapy hostility events were seen throughout the duration of the paediatric placebo-controlled clinical trials, and there was no difference between the paroxetine treatment group and placebo group with respect to the time to first occurrence of these events.

There was just one hostility event that occurred in the 30 day period following cessation of treatment in the paediatric placebo controlled studies (paroxetine treatment group) and the event occurred in the first week (Data Source: Appendix 2B, Table 2.99).

2.4. Observational studies

This section reviews information regarding events of self-harm/suicidal behaviour and hostility reported in observational studies of paroxetine, specifically Prescription Event Monitoring (PEM) and GSK Post-Marketing Surveillance (PMS) studies. Events reported in the PEM study conducted independently of GSK are not included in any other analyses reported elsewhere in this document. In contrast, individual case reports from the PMS studies are included within the dataset of Post-Marketing Reports analysed in Section 2.5.

2.4.1. Reports of self harm/suicidal behaviour

2.4.1.1. Self-harm/suicidal behaviour reported during Prescription Event Monitoring (PEM)

Paroxetine PEM Data

In an observational cohort study conducted by the Drug Safety Research Unit, Southampton, UK, a population of 13,741 patients treated with paroxetine in general medical practice in the UK between March 1991 and March 1992 were investigated by the technique of Prescription Event Monitoring (PEM) [Inman , 1993].

In PEM, physicians are requested to report all significant events that are recorded in the patient's notes over a specified period following the first prescription of the drug under investigation. An 'event' is any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any other complaint which was considered of sufficient importance to enter in the patient's notes. In recognition that acute adverse drug reactions tend to occur early, most commonly during the first month after the initial prescription, the PEM "signalling" methodology incorporates a comparison of the rates of events during the first month of treatment with the mean rates for the same events during the subsequent follow-up period (typically the mean rates recorded during the second to sixth month of treatment, as was the case in the paroxetine study), to derive so-called rate ratios. Large rate ratios may simply be due to small numbers and this signalling process is therefore targeted to the analysis of events which occur during the first month with a frequency of a least one per 1,000 patients. Where the rate-ratios exceed three, experience has indicated that the events are either the result of a reaction to the drug, or a sign or symptom of the disorder being treated.

Within the PEM study of paroxetine, most of the 13,741 paroxetine recipients were studied for seven to nine months after first prescription, regardless of when treatment was stopped. With regard to demographics of the study population, where gender was specified (n=12,591), thirty-two percent of patients were male and 68% were female. The mean age of males was 48.6 years (range 14-93) and for females 48.8 years (range 13-

99). Two hundred and thirteen patients were aged between 10 and 19 years. Where indication was specified (n=12,150), 94% of patients had received paroxetine for depression and 33% of the total cohort of patients were still using paroxetine after a period of six months. Based on a sample of the first prescriptions for 4,394 patients, ninety-three percent of patients were prescribed an initial daily dose of 20 mg paroxetine. From the same sample of 4,394 patients, sixty-four percent of patients had no other drug prescribed on their first prescription of paroxetine. The drugs most frequently co-prescribed with paroxetine on the same prescription form included benzodiazepines (9% of patients), other hypnotics and anxiolytic agents (3%), analgesics (6%), other CNS-acting drugs (8%), cardiovascular drugs (8%) and gastrointestinal drugs (6%). Where an opinion about efficacy was given by the general practitioners, paroxetine treatment was reported to have been effective in 62% of patients.

Table 2.33, below, presents the numbers of events of self-injury, suicidal thought and suicide attempt/drug overdose reported at any time during or following treatment with paroxetine, analysed by month [Inman , 1993]. It is unknown whether multiple events were reported by the same subject.

Table 2.33 Numbers of events of self-injury, suicidal thought and suicide attempt/drug overdose reported at any time during or following treatment with paroxetine, analysed by month [Inman , 1993].

Month **Denominator**	1 to 6 13741	1 13734	2 13730	3 13724	4 13719	5 13717	6 13716	Total 13741
Self-injury	11	5	2	1	1	2	-	16
Suicidal thought	29	10	9	3	4	2	1	45
Suicide attempt, drug overdose	126	47	25	21	10	11	12	215

Within the signalling process, the event of suicide attempt/drug overdose provided a rate ratio of 3.0, however, this is not an unexpected finding given that the risk of suicidal behaviour inherent to depressive illness may persist in the first few weeks of antidepressant therapy, until significant remission occurs.

In a separate analysis of deaths recorded in patients included in the study cohort, a cause of death was established for 350 of the 416 patients who died. Two hundred and twenty-four deaths occurred during the six-month study period and 25 of these patients were reported to have committed suicide. Eight of these patients were known to have taken overdoses (none involving paroxetine) and 12 patients had committed suicide by violent means. In the other 5 cases the manner of death was not established. No deaths were attributed to paroxetine.

Comparative PEM data

Important data on the comparative incidence rates of suicide/parasuicide in patients treated with drugs within the SSRI class (fluoxetine, sertraline, paroxetine) and other antidepressants newly introduced to the UK market in the 1990's (moclobemide, venlafaxine and nefazodone) have been reported by the Drug Safety Research Unit within a published comparison of the Prescription Event Monitoring studies conducted on each of these drugs [Mackay , 1999]. The incidence rates of suicide/parasuicide in the first month of therapy, expressed as the rate of occurrence per 1,000 patient-months of treatment, were reported as follows: venlafaxine, 5.6; moclobemide 5.5; fluoxetine, 4.7; nefazodone, 3.9; paroxetine, 3.1 and sertraline, 2.7; These data are particularly significant, in that they provide no evidence to suggest that the incidence rate of these events in patients treated with paroxetine was any higher to the rate in patients treated with other members of the SSRI class. Moreover, the incidence rates of suicide/parasuicide were comparable between the cohorts treated with SSRIs and those treated with other antidepressant medications.

2.4.1.2. Self-harm/suicidal behaviour reported during Post-Marketing Surveillance Studies

In addition to PEM, nine large-scale Post-Marketing Surveillance studies have been conducted locally by GSK Germany (seven studies) and GSK Belgium (two studies) involving a total of over 19,000 adult patients (each study included between 974 and 4,024 patients). Individual case reports of self-harm/suicide-related behaviour documented in these studies are included within the dataset of Post-Marketing Adverse Event reports (Section 2.5.2) and the associated risk factor analyses (Question 3, Section 3.3.2), however, for completeness the overall numbers of such reports are documented here so as to provide an indication of their rate of reporting in the context of the known size of the study populations.

Studies conducted in Germany

The seven studies conducted by GSK Germany evaluated the safety and efficacy of paroxetine in the treatment of depressive disorders. These consisted of seven treatment observational cohort (TOC) studies as follows:

- one examining depression with special consideration of anxiety symptoms measured by the Boerner scale of fear (BOEAS),
- two examining depression with special consideration of the SISI-Type (Short Increment Sensitivity Index - characterised by active distraction such as escaping into exhaustive work schedules or exaggerated sport activities rather than a tendency to sadness and withdrawal from social life),
- two examining depression with associated symptomology of anxiety, and
- two examining depressive syndromes.

In total, 13,745 patients (mean age 49.1 - 55.7 years) received paroxetine over the course of the seven studies and were observed over a period of between 8 and 24 weeks. In all

seven studies safety was assessed by routine adverse event monitoring at each visit by the study investigators. Fourteen events were reported across the studies relating to suicide (two completed suicides, six suicide attempts, four reports of suicidal ideation, one report of increased suicidality and one report of an increased suicidal tendency).

Studies conducted in Belgium

The two observational studies completed by GSK Belgium similarly evaluated the safety and efficacy of paroxetine in the treatment of depression. The first of these studies evaluated the efficacy and safety of paroxetine in depressed patients treated by Belgian psychiatrists and general practitioners over a period of up to 46 weeks (patients were treated with paroxetine for 6 weeks with the possibility of extending therapy for a period of up to 46 weeks). A total of 4,024 patients (mean age of 48 ± 15 years) were observed over the course of the study. Adverse events were collected at each visit by the investigator asking the patient a non-leading question. There were sixty-four reports of serious AEs, which included one report of completed suicide and ten reports of suicide attempt.

The second study conducted by GSK Belgium evaluated the use of paroxetine in elderly depressed patients. A total of 1,364 patients (mean age 73) were treated with paroxetine over a period of six weeks. Adverse events were monitored at each visit by the study investigators. Two events were reported relating to suicide (one completed suicide and one suicidal tendency).

2.4.2. Reports of hostility

2.4.2.1. Hostility reported during Prescription Event Monitoring

Within the Prescription Event Monitoring study of paroxetine involving 13,741 patients, described in Section 2.4.1.1 [Inman , 1993], a total of 36 events of aggression were reported (of which 18 occurred during months one to six) and one of these events was specifically reported by the general practitioner to be a suspected adverse drug reaction to paroxetine. In addition, there were 19 events of assault (seven recorded in months one to six) and one event of murder, although it is not clear from the study report if these particular events were experienced by or carried out by the patient. Analysing the numbers of events of aggression, assault and murder by month of study (Table 2.34), no particular pattern of reporting emerges, and in particular there is no clustering of events within the first month of therapy.

Table 2.34 Numbers of events of aggression, assault and murder reported at any time during or following treatment with paroxetine, analysed by month [Inman , 1993]

Month / **Denominator**	1 to 6 / 13741	1 / 13734	2 / 13730	3 / 13724	4 / 13719	5 / 13717	6 / 13716	Total / 13741
Aggression	18	1	3	7	1	1	5	36
Assault	7	1	1	-	2	1	2	19
Murder	1	-	-	-	-	1	-	1

The published comparisons of the PEM studies of SSRIs have not specifically reported on data relating to aggression.

2.4.2.2. Hostility reported during Post-Marketing Surveillance Studies

Two reports of aggression were identified from the PMS studies conducted by GSK Germany and GSK Belgium involving a total over 19,000 patients (see Section 2.4.1.2). These comprised of one report of aggressivity and one aggressive reaction.

2.5. Post-Marketing Reports

2.5.1. Description of the overall dataset

Section 2.5 of the response contains data from the GSK clinical safety database. This database contains reports of adverse events from clinical trials (mainly serious reports), post-marketing surveillance (PMS) studies, spontaneous/unsolicited notifications, literature and regulatory sources. Reports relating to paroxetine which were received spontaneously by GSK have been included in this section of the response, irrespective of whether they were received from health professionals, published literature sources, regulatory authorities, consumers, family members, lawyers etc. In addition to these unsolicited notifications, solicited reports arising from Post-Marketing Surveillance (PMS) studies, which are not included in the Clinical Trials section of this document (see Section 2.3), are included in this Post-Marketing Reports section. In addition, an overview of the PMS studies are summarised in the Observational Studies section (see Section 2.4).

The GSK clinical safety database was searched to identify all post-marketing reports of adverse events, where paroxetine was a suspect drug, received by GSK by 31 May 2003. Adverse event reports relating to neonates exposed to paroxetine *in-utero* or infants exposed *via* breast-feeding have not been included in the scope of this review, but all other reports have been included. Forty-two thousand eight hundred and forty-four

(42,844) reports were included in the overall dataset, of which 41,472 reports (97%) concerned adults or patients of unspecified age and 1,372 reports (3%) concerned paediatric patients (<18 years). The vast majority of the cases were received spontaneously, but 647 cases (1.5% of the total) arose from PMS studies.

2.5.2. Identification of self harm/suicidal behaviour dataset

2.5.2.1. Definition of self harm/suicidal behaviour reports

The dataset of 42,844 paroxetine adverse event reports was searched to identify all reports documenting adverse events coded to the MedDRA preferred terms of;

> "Completed suicide", "Suicide attempt", "Suicidal ideation", "Non-accidental overdose", "Multiple drug overdose", "Self mutilation", "Intentional self-injury", "Self-injurious ideation" and "Depression suicidal".

Additionally, reports documenting AEs coded to the MedDRA preferred terms of:

> "Drug toxicity NOS", "Overdose NOS", "Poisoning NOS", "Therapeutic agent poisoning", "Gun shot wound", "Injury", "Injury asphyxiation", "Laceration", "Open wound", "Wound NOS" or "Morbid thoughts"

were individually assessed for potential inclusion.

Reports of overdoses in which the intention was not to cause self-harm or suicide but an attempt to increase efficacy or to abuse the drug were excluded from the dataset.

These searches for coded AE terms were supplemented by text string searches of the case narrative descriptions for phrases including:

> "suic", "mutilat", "hang", "self inflict" or "attempt".

The cases identified by these narrative searches were individually reviewed for potential inclusion.

2.5.2.2. Self harm/suicidal behaviour reports identified

Overall, 1,539 reports were retrieved for evaluation, covering the spectrum of events from completed suicides through to thoughts of self-harm. Of these, 69.5% (n = 1070) had either a healthcare professional or a regulatory authority as a report source, or were published in the medical literature. The remaining 30.5% (n = 469) were not medically validated and were received from consumers, lawyers or other sources.

The overall dataset consisted of 1,413 reports (92%) relating to adult patients or patients of unspecified age and 126 reports (8%) relating to paediatric patients. Of the cases relating to adults and patients of unspecified age, 306 (22%) reported a completed suicide, 726 (51%) reported an attempted suicide or an act of self-harm and 381 (27%) reported suicidal or self-harming ideation. Of the cases concerning paediatric patients, 15 (12%) reported a completed suicide, 88 (70%) reported an attempted suicide or an act of self-harm and 23 (18%) reported suicidal or self-harming ideation.

These two datasets (adult and paediatric events) form the basis for the analysis of potential risk factors as described in the response to Question 3 (Section 3.3).

One hundred and eighty-five reports occurred in both the self-harm/suicidal behaviour dataset and the hostility dataset and consequently these patients (160 adults or patients of unspecified age and 25 paediatric patients) are included in both analyses.

2.5.3. Identification of hostility dataset

2.5.3.1. Definition of hostility reports

The dataset of 42,844 paroxetine adverse event reports was searched to identify all reports documenting adverse events coded to the MedDRA preferred terms of:

> "Hostility", "Aggression", "Homicidal ideation", "Fight in school" or "Oppositional defiant disorder".

Additionally, reports documenting AEs coded to the MedDRA preferred terms of:

> "Murder", "Gun shot wound", "Violence-related symptom", "Injury", "Physical abuse", "Child abuse", "Physical assault", "Verbal abuse" or "Sexual abuse"

were individually assessed for potential inclusion (those reports in which the patient was alleged to have committed such acts, rather than being a victim, were included).

Reports describing events mapping to the MedDRA preferred term of "Anger" were also assessed to identify reports for inclusion in which anger was specifically reported as being directed at another individual.

These searches for coded AE terms were supplemented by text string searches of the case narrative descriptions for phrases including:

> "hostil", "aggress", "homicid", "violen" or "assault".

The cases identified by these narrative searches were individually reviewed for potential inclusion.

2.5.3.2. Hostility reports identified

Overall, 791 reports were retrieved for evaluation, covering the spectrum of events from acts of murder through to hostile thoughts. Of these, 55.0% (n = 435) had either a healthcare professional or a regulatory authority as a report source, or were published in the medical literature. The remaining 45.0% (n = 356) were not medically validated and were received from consumers, lawyers or other sources.

The overall dataset consisted of 685 reports (87%) relating to adult patients or patients of unspecified age and 106 reports (13%) relating to paediatric patients. Of the cases concerning adults and patients of unspecified age, 309 (45%) reported physical acts of aggression and violence (36 or 5% reported murder), 325 (47%) reported non-physical or unspecified aggression (including verbal), and 51 (8%) reported hostile or aggressive

ideation. Of the cases relating to paediatric patients, 57 (53%) reported physical acts of aggression and violence (12, 11% reported murder), 44 (42%) reported non-physical or unspecified aggression (including verbal), and five (5%) reported hostile or aggressive ideation.

These two datasets (adult and paediatric events) form the basis for the analysis of potential risk factors as described in the response to Question 3 (Section 3.3).

One hundred and eighty-five reports occurred in both the self-harm/suicidal behaviour dataset and the hostility dataset and consequently these patients (160 adults or patients of unspecified age and 25 paediatric patients) are included in both analyses.

2.6. Literature review

2.6.1. Introduction

An extensive review of the literature relating to the possibility of suicide-related events, self-harm and hostility with paroxetine has been performed and the findings are summarised here. In order to place this information in context with other antidepressant treatments an additional search was performed substituting paroxetine with serotonin selective reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and benzodiazepines and keeping all the other parameters the same.

2.6.2. Methodology

The initial literature search was performed using the Eagle system which consists of the following databases: Embase, MedLine, Derwent Drug File, Sci Search and Biosis.

The searches used the terms

- drug = "Paroxetine"
- keyword = 'homicide","suicide","hostility","violence","akathisia","aggression" or "self-harm"

As a result of the search, 657 references were generated and these were reviewed and assessed as to their relevance to the following categories:

> meta-analyses, Randomised Controlled Trials (RCTs), open label studies, observational studies, case histories and reviews containing pertinent citations.

In addition to the 657 references generated from the above search, pertinent articles cited within these references (particularly review articles) were also reviewed and assessed in the same manner.

2.6.3. Results

The majority of the references generated by the literature review have referred to the adult population, but, where cited, paediatric data is included and made reference to.

2.6.3.1. Suicide and suicidal ideation

Meta - analyses

The search yielded two meta-analyses specifically conducted on paroxetine studies [Lopez-Ibor, 1993] [Montgomery, 1995]. Their objective was to determine whether paroxetine was associated with any increase in suicidal thoughts or acts. Both analyses found that there were fewer treatment emergent suicidal thoughts on paroxetine compared with placebo and in the Montgomery analysis there was a significant advantage for paroxetine compared with active controls on the Montgomery and Asberg Depression Rating Scale (MADRS).

For other SSRIs, a retrospective analysis of pooled data from 17 double-blind clinical trials has been carried out on fluoxetine [Beasley, 1991] where the incidence of improvement in suicidality was significantly greater for fluoxetine versus placebo but no different from the incidence on TCAs. In addition a meta-analysis of placebo-controlled trials with fluvoxamine showed a significantly greater improvement in suicidal ideation compared to placebo [Letizia, 1996]. A further meta-analysis measuring across the class of selected SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) concluded that all the SSRIs had similar incidences of suicidal behaviour and thoughts [Edwards, 1999]. Finally, a recent review [Khan, 2000] of all antidepressant data on the FDA database consisting of 48,277 patients failed to show any differences in the suicide rates between placebo, SSRIs and other antidepressants.

Randomised Controlled Trials (RCTs)

One RCT compared paroxetine and the SSRI, fluoxetine in patients with major depression over a six-week period [Gagiano, 1993]. Using HAMD item 3 to measure suicidal ideation the authors reported that both treatment groups had similar decreases in scores. Additionally in a double-blind study [Moller, 1994], the difference in improvement of suicidal ideation between paroxetine and amitriptyline was similar.

Even when paroxetine was administered to patients without major depression but who were at risk of suicide [Verkes, 1998] it was significantly more effective than placebo in the prevention of recurrent suicidal behaviour in a population of 91 patients.

Results from trials conducted with other antidepressants have yielded similar results to those seen with paroxetine, with fluoxetine showing superiority to placebo and mianserin in reducing suicidal feelings [Muijen, 1988], superiority to placebo and comparable to TCAs in patients with mood disorders [Tollefson, 1993] and comparable results to clomipramine in treating suicidal patients [Sacchetti, 1991]. A small study with fluvoxamine (20 patients) found it to be more effective than imipramine in reducing suicidal ideas [Gonella, 1990], yet two studies showed no difference in outcome when compared to mianserin and desipramine [Nathan, 1990] [Perez, 1990]. In addition, one

study looked at fluoxetine versus placebo in a population with recurrent brief depression with a history of 2 or more suicide attempts but found that fluoxetine neither raised nor lowered the suicide attempt rate [Montgomery, 1994].

A study comparing the SSRI, sertraline and reboxetine in a group of healthy volunteers did however report two cases of suicidal ideation whilst on sertraline [Healy, 2000].

Observational Study

In a study of four SSRIs, fluoxetine (final cohort 12,692), fluvoxamine (final cohort 10,983), sertraline (final cohort 12,734) and paroxetine (final cohort 13,741) there was no statistical difference between the four drugs in the number of suicides [Mackay, 1997]. This was later confirmed by another study by the same group, this time looking at fluoxetine, sertraline, paroxetine and new antidepressants moclobemide, venlafaxine and nefazodone [Mackay , 1999]. The incidence rates of suicides/parasuicides were comparable between the cohorts treated with SSRIs and those treated with other antidepressant medications (see Section 2.4.1.1). An earlier study [Kapur, 1992] compared the risk of suicide on tricyclics versus non-tricyclic antidepressants (fluoxetine was included in this group) and also found no difference. This is in contrast to a study that looked at data from 222 suicides, where 41 had been prescribed an antidepressant within one month of the completed suicide [Donovan, 1999]. The authors concluded that the incidence of suicide was greater on SSRIs than on TCA medication but acknowledged a number of constraints of the study e.g. that SSRIs may have been preferentially prescribed to higher risk patients (a higher proportion had a history of deliberate self harm), not all suicides in the geographical region were included and the number of cases was small compared to national figures.

Reviews

Based on the literature available, one review has stated that given the decreased toxicity associated with SSRIs and the potential benefit that the serotonergic mechanism can provide, that they should be preferentially prescribed to patients at risk of suicide [Kasper, 1996] and a more recent review has concluded that the evidence examining whether particular classes of antidepressants invoke suicidal behaviour is neither convincing nor consistent [Baldwin, 2000]. The evidence for whether SSRIs have a superiority over TCAs in reducing the number of suicide attempts has also been reported as inconclusive [Muller-Oerlinghausen, 1999] [Matthews, 2000].

A recent review [Healy, 2003] has questioned the conclusions from meta-analyses conducted on SSRIs, the analysis of the randomised controlled trial data and in particular an analysis conducted by Khan et al (2000) of the FDA database of all SSRI clinical trial data. In contrast to Khan et al who stated that there were no differences in the suicide rates between placebo, SSRIs and other antidepressants, Healy's re-analysis has suggested a possible doubling of the risk of both suicides and suicide attempts on SSRIs compared with older antidepressants or non-treatment. However, Khan et al (2003) have also re-analysed the suicide data, in response to reports that SSRIs may increase suicidal risk. Their analysis centred on the antidepressant the patient was on at the time of suicide instead of an analysis based on combined suicide rates and suicide attempt rates for groups of trials for individual investigational drugs as they previously reported [Khan,

2000] [Khan, 2003]. Similar suicide rates were seen among those randomly assigned to an SSRI (0.59%), a comparator antidepressant (0.76%) or placebo (0.45%) again confirming that prescription of SSRIs does not seem to be associated with higher suicide rates.

Case Studies

1. A case of drug-induced akathisia with paroxetine and risperidone leading to suicide ideation was reported in an 83 year old depressed male. The authors concluded that there was an increased risk of akathisia in patients receiving antidepressants and neuroleptics [Hansen, 2001].
2. A 32 year man with OCD attempted suicide whilst on paroxetine and started having suicidal thoughts after 4 days on paroxetine. He no longer suffered suicidal thoughts following cessation of paroxetine. The authors concluded that the suicide attempt was partly induced by paroxetine [Goder, 2000].
3. Six cases of suicidal tendencies on fluoxetine were reported [Teicher, 1990]. Five of the patients were out-patients and one was an in-patient who developed intense suicidal thoughts, a mean of 26 days (range 12-50) after the start of fluoxetine treatment. These thoughts faded an average of 27 days after cessation of treatment.
4. A 32 year old woman with a history of major depression and panic attacks developed suicidal ideation after over 4 weeks on fluoxetine as her depression was starting to resolve. Once fluoxetine was discontinued the suicidal thoughts ceased. [Hamilton, 1992].
5. A 10 year old boy with major depression who frequently lost his temper was prescribed fluvoxamine. However after 4 weeks on treatment, his aggressive behaviour and suicidal ideation worsened. Fluvoxamine treatment was discontinued and the symptoms diminished but did not disappear completely. The patient was then started on paroxetine where the aggressive behaviour reappeared but there was no aggravation of suicidal ideation. The patient then stopped paroxetine and the aggressive behaviour subsided [Vorstman, 2001].
6. Six cases of suicidal ideation, aggressive behaviour or self harm (3 boys and 3 girls) aged 10 to 17 years old, diagnosed with Obsessive Compulsive Disorder were reported once they started treatment with fluoxetine. The cases reported either an increase in the intensity of the behaviours or de novo emergence and in 3 cases the patients reported suicidal ideation for 3 or more weeks after fluoxetine treatment had ceased [King, 1991].

2.6.3.2. Self harm

Cochrane Review 2003

A Cochrane review on the psychosocial and pharmacological treatments for deliberate self harm was performed in 1999 with the most recent update being on February 2003 [Hawton, 2003]. Under the category 'antidepressants versus placebo' three studies were included. The pooled odds ratio indicated no apparent benefit regarding repetition of deliberate self harm (DSH) for patients treated with mianserin, nomifensine or paroxetine

compared with placebo. However, the authors acknowledge that there were too few studies and the number of subjects was too small to have the statistical power to detect clinically meaningful differences. The paroxetine study [Verkes, 1998] did however demonstrate a benefit compared to placebo in those patients in the minor repeater group (less than five previous acts of deliberate self harm) with no difference in the major repeater (five or more acts) patients. It should be noted that the Verkes et al (1998) study was designed to look at suicide attempts and therefore was included in this review under acts of deliberate self harm.

Randomised Clinical Trials (RCTs)

The review did not highlight any specific RCTs to assess the effect of paroxetine on acts of deliberate self harm.

Observational Study

A prospective, observational cross-sectional study to assess if there was a possible link between the frequency of deliberate self-harm and antidepressant type use was performed [Donovan, 2000]. The authors concluded that the occurrence of deliberate self harm was higher with SSRIs than with TCAs, with fluoxetine being the highest in the SSRI group (relative risk (rr) of 6.6). Paroxetine had a relative risk of 4.0 which was comparable with some of the TCAs, clomipramine (rr 4.6) and imipramine (rr 3.9). The conclusion of the Donovan study has been questioned as to what impact on the results (i) the lack of diagnosis of the patient that would occur at emergency departments would make, and, (ii) whether a higher proportion of patients with borderline personality disorder, known for their frequent parasuicide gestures may have preferentially received SSRIs versus TCAs [Markowitz, 2001].

2.6.3.3. Hostility/Aggression

Meta-analyses

The review did not reveal any meta-analyses specifically looking at aggression and hostility associated with paroxetine compared with placebo. Two meta-analyses were performed on clinical trial data for fluoxetine however. The first analysis consisting of 3,992 patients and looked at events suggestive of aggression (hostility, personality disorder, antisocial reaction). The authors concluded that events were four times more likely to occur in placebo-treated patients than in fluoxetine-treated patients [Heiligenstein, 1993]. In the second analysis, 2,615 patients were on fluoxetine compared to 1,377 patients on placebo and the incidence of events termed the 'aggression cluster' were significantly lower in the fluoxetine-treated patients [Heiligenstein, 1997]. In addition, a meta-analysis of 3 SSRIs (fluoxetine, fluvoxamine and paroxetine) found no difference in event rates per 1000 patients of the term "aggression" between the SSRIs [Edwards, 1999].

Randomised Clinical Trials (RCTs)

A double-blind placebo-controlled study investigating the effects of paroxetine on healthy volunteers reported that they experienced a reduction in hostility, attributable to a

general decrease in negative affect and enhanced affiliative behaviour. They attributed these effects to serotonergic mechanisms but a limitation of the study is that they did not have a non-serotonergic antidepressant comparator arm [Knutson, 1998].

A study to assess the anti-aggressive effects of fluoxetine has been conducted in patients with personality disorders with current histories of impulsive aggressive behaviour (patients in whom this behaviour is prominent). Fluoxetine has been shown to produce a sustained reduction in scores on the Irritability and Aggression subscales of the Overt Aggression Scale-Modified for Outpatients compared to placebo [Caccaro, 1997].

Open label studies

The effects reported by Knutson and co-workers in a healthy volunteer study [Knutson, 1998] were taken one step further and a study specifically looking at the ability of paroxetine to modulate five basic dimensions of personality in depressed patients compared with desipramine and sertraline was conducted [Bagby, 1999]. There was no placebo control or random allocation in the trial design. They found that Anger-Hostility (measured by the NEO personality Inventory scale) was decreased for all antidepressants that did not correlate with a change in depression severity.

In contrast, a study in 19 adolescent inpatients reported a significant increase in verbal aggression, physical aggression towards objects and aggression towards self but not towards others being treated with fluoxetine, paroxetine or sertraline [Constantino, 1997].

Reviews

A review of SSRIs (mainly focussed on fluoxetine) and violence concluded that a small proportion of patients treated with SSRIs may become akathisic and others may show increases in anxiety in the initial phase of treatment but no increased susceptibility to aggression or suicidality can be connected with fluoxetine or any other SSRI. In fact SSRI treatment may reduce aggression, probably due to positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour directed towards oneself or others [Walsh, 2001].

Post-Marketing Surveillance

A post- marketing surveillance study by patient self-monitoring was conducted comparing the SSRIs, sertraline and fluoxetine with patients reporting a greater incidence of anger/aggression on fluoxetine compared to sertraline [Fisher, 1995].

Case studies

1. A 60 year old man with a history of depression was prescribed paroxetine for 2 days before shooting members of his family and then himself. He had a history of depression severe enough to keep him off work but did not follow recommendations to continue treatment during his bouts of depression [Fine, 2002].
2. A 40 year old man with depression after 4 days on paroxetine murdered his mother. He stated that after the first dose that he felt something change inside and after 2 days his physician advised him to halve his dose (20mg/d to 10mg/d). The author

also mentions a case where a man on fluoxetine killed his wife for no apparent reason [Uges, 1998].

3. A 47 year old man with a history of psychiatric disorders, especially aggressive and threatening behaviour, was prescribed fluoxetine for 1 month and stopped taking it 3 days before he murdered a number of people at his place of work [Fine, 2002].

2.6.4. Summary of literature data

The literature supports the clinical data in that:

- There are no reports of an increased incidence of suicidal ideation whilst on paroxetine in the meta-analyses and the controlled clinical trials versus placebo or comparators. This is consistent with reports of other SSRIs e.g. fluoxetine and sertraline which have investigated the impact of SSRIs and TCAs on suicidal ideation and have reported either statistical superiority of SSRIs to TCAs or no difference.
- Very little data exists on deliberate acts of self harm but the Cochrane review indicates that antidepressants do not induce acts of self harm but given the paucity of trial data they concluded that no recommendations could be made on the most effective treatment for patients who have recently engaged in acts of deliberate self harm. The only data indicating a difference between SSRIs and TCAs was via an observational study in which the lack of diagnosis of the patients and prescribing habits has been questioned.
- The evidence from meta-analyses and randomised clinical trials of SSRIs and in particular paroxetine does not suggest that there is any increased susceptibility to perform violent or aggressive acts compared with placebo. It has been suggested that SSRIs may in fact reduce aggression. Reviews of the available literature have suggested that a small proportion of patients treated with SSRIs may become akathisic and others may show increases in anxiety in the initial phase of treatment, an opinion which is consistent with the widely recognised view that symptoms of depression can worsen early after the initiation of therapy, but that the incidence is no greater on SSRIs compared to other antidepressants.
- From the review, case studies have been quoted and particular emphasis has been put on reporting the cases involving paroxetine. This list is by no means exhaustive and has not attempted to put them into any context with respect to the incidence of suicide, aggression, violence and acts of self harm in the population. It acknowledges that individual cases have occurred but the body of evidence reviewed in the literature does not suggest a direct causative relationship between the prescribing of paroxetine and other SSRI antidepressants and violent or suicidal behaviour.
- In addition, the reviews on similar datasets have been shown to report quite different results depending on the method of analysis [Healy, 2003; Khan, 2000]. Therefore, great care must also be taken when reviewing and interpreting the evidence.

2.7. Conclusions

Healthy Volunteer Data

- No events meeting the definition of "possibly suicide-related" or "self harm" were identified within the centrally-databased R&D Phase I studies.
- Three adverse events of "hostility" (aggression) were identified within the centrally-databased R&D Phase I studies. There was no evidence of any clear link between paroxetine and hostility from the healthy volunteer studies.

Adult Clinical Trial Data

- There was no evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment groups compared to the placebo / active comparator groups.
- The adult placebo-controlled clinical trial data showed a statistically significant treatment benefit with paroxetine compared to placebo in terms of change from baseline in two measures of suicidality (Item 3 of the HAM-D and Item 10 of the MADRS).
- In the adult placebo-controlled studies, there was no difference in the incidence of possibly suicide-related, self harm or hostility events between the paroxetine treatment group and the placebo group.
- In the adult active-controlled studies, there was a lower incidence of possibly suicide-related events in the paroxetine treatment group compared to the active comparator group overall.
- In general, at least half of the reported events occurred during the first four weeks of treatment with paroxetine and active comparators.

Paediatric Clinical Trial Data

- There was no conclusive evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment group compared to the placebo group.
- There was no significant difference between paroxetine and placebo in change from baseline of Item 3 of the HAM-D and Item 10 of the MADRS.
- There were no completed suicides in the paediatric placebo-controlled studies.
- The incidence of possibly suicide-related and self harm events was greater in paroxetine treated patients than in patients who received placebo, primarily in adolescents with major depressive disorder (see Question 3).
- There is insufficient active comparator data in the paediatric population to determine whether the effects are specific to paroxetine or are common to other antidepressants.
- In the paediatric population overall, paroxetine was associated with an increased risk of hostility compared to placebo. This was mainly seen in patients with OCD and in children under the age of 12 years (see Question 3).

Observational studies

- In Prescription Event Monitoring studies, the incidence rate of suicide/parasuicide in the first month of therapy reported for paroxetine (3.1 events per 1,000 patient months of treatment) was comparable to that observed with other SSRIs (fluoxetine, sertraline) and several additional modern antidepressants (moclobemide, nefazodone, venlafaxine).
- There was a low reporting of hostility-related events (26 events of aggression [n=18 events], assault [n=7] and murder [n=1]) during months one to six of therapy in a cohort of 13,741 patients treated with paroxetine and examined by Prescription Event Monitoring. Notably, there was no particular clustering of events in the first month of therapy that might be suggestive of a drug (or disease) related event.

Post-marketing reports

- The method of identification of reports describing self-harm/suicidal behaviour and reports describing hostility has been presented. The reports identified were divided into those concerning paediatric patients and those concerning adults or patients of unspecified age. The four resultant datasets form the basis for the analyses for potential risk factors as described in the response to Question 3 (see Question 3, Section 3.3).

Literature review

- There is no evidence in the literature of an increased incidence of suicidality on paroxetine compared to placebo in RCTs. In fact, quite the contrary with a decreased incidence being reported in those patients on paroxetine.
- The literature on the incidence of self harm on paroxetine is very sparse but there is presently no compelling evidence to suggest that patients on paroxetine experience any greater incidence of self harm compared to other antidepressants.
- Overall, the incidence of aggression and hostility does not appear to be increased in patients taking paroxetine. In general, there does not seem to be any causal link between aggression/hostility and any SSRIs.

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