15. QUESTION 15

Submit information regarding the severity and nature of the suicide-related events in the children studies including the number of events that led to discontinuation of medication.

Response

15.1. Introduction

It is assumed that the adverse events of interest are those described in the original response as being adverse events which could possibly be related to suicide, a term that would include 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".

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

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

The search strategy described above 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". Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

Table 15.1 Incidence of 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 (%)	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95 , 5.51)	0.069
Depression	n/N (%)	14/378 (3.7%)	7/285 (2.5%)	1.53 (0.61 , 3.84)	0.50
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)		0.49
SAD	n/N (%)	3/165 (1.8%)	0/157 (0.0%)		0.25

Table 15.2 Incidence of 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 (%)	25/738 (3.4%)	8/647 (1.2%)	2.80 (1.25 , 6.25)	0.012
Depression	n/N (%)	20/378 (5.3%)	8/285 (2.8%)	1.93 (0.84 , 4.46)	0.12
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)		0.49
SAD	n/N (%)	4/165 (2.4%)	0/157 (0.0%)		0.12

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.

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.

15.2. Nature and Severity of possibly suicide-related events

Descriptions of possibly suicide-related events occurring at any time during the on therapy plus 30 days post-therapy time period in paediatric placebo-controlled trials (i.e. all events mentioned in the previous section) are given in Appendix 1, Listing 1.01. The event descriptions include subject identifier, age and sex, the preferred term and investigator's verbatim text description of the event, when the event started relative to the start and stop of randomised study medication, the duration of the event and it's course (intermittent or constant, and if intermittent the number of episodes) the severity of the event (mild, moderate or severe), action taken with respect to the investigational drug (none, dose reduced, dose increased or drug stopped), the investigator's opinion as to whether the event was related to the investigational drug (related, possibly related, probably unrelated or unrelated), whether corrective therapy was given, and whether the event was reported as a serious adverse experience (SAE).

A summary of the possibly suicide-related events reported in paediatric placebo-controlled studies outlined in Appendix 1, Listing 1.01 is provided in Table 15.3.

Table 15.3 Verbatim Terms and Severity of the Possibly Suicide-Related Events by Treatment Group and Indication
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Subject No	Verbatim Term	Severity	Indication	Treatment Group
329.002.00058	INTENTIONAL TYLENOL OVERDOSE TOOK 80 PILLS	Moderate	MDD	Paroxetine
329.002.00245	OVERDOSE ON 27- 28 TYLENOL PILLS	Severe	MDD	Paroxetine
329.003.00250	OVERDOSE	Moderate	MDD	Paroxetine
329.003.00313	AUDITORY HALLUCINATIONS SUPERFICIAL CUTS SIGNIFICANT RISK TO SELF	Severe	MDD	Paroxetine
329.004.00015	SELF- MUTILATION	Mild	MDD	Paroxetine
329.005.00011	OVERDOSE (WITH BAYER EXTRA STRENGTH)	Severe	MDD	Paroxetine
329.005.00333	SUICIDAL IDEATION	Severe	MDD	Paroxetine
329.006.00038	ATTEMPTED SUICIDE	Severe	MDD	Paroxetine
377.009.00225	SUICIDE ATTEMPT	Mild	MDD	Paroxetine
377.011.00061	OVERDOSE	Severe	MDD	Paroxetine
377.023.00172	ATTEMPTED SUICIDE	Moderate	MDD	Paroxetine
377.024.00158	SLAPPING HERSELF IN THE FACE (AUTOMUTILATION)	Moderate	MDD	Paroxetine
377.030.00181	SUICIDAL RISK, DEPRESSION WORSE	Moderate	MDD	Paroxetine
377.042.00310	PARASUICIDE	Mild	MDD	Paroxetine
377.042.00315	OVERDOSE	Moderate	MDD	Paroxetine
377.049.00479	SUICIDAL INTENT	Severe	MDD	Paroxetine
377.053.00508	SUICIDE ATTEMPT	Mild	MDD	Paroxetine
676.011.24283	VAGUE SUICIDAL IDEATION	Mild	SAD/SP	Paroxetine
676.014.24376	SUICIDAL THOUGHTS	Moderate	SAD/SP	Paroxetine
676.100.24705	SELF INFLICTED SCRATCH ON RT. WRIST	Mild	SAD/SP	Paroxetine
676.101.24629	THREAT OF SUICIDE	Mild	SAD/SP	Paroxetine
701.163.25718	OVERDOSE (INTENTIONAL)	Severe	MDD	Paroxetine
701.180.25639	OVERDOSE	Severe	MDD	Paroxetine
701.183.27620	SUICIDAL IDEATION	Mild	MDD	Paroxetine
704.033.25513	HOSPITALIZATION DUE TO SUICIDAL THOUGHTS	Severe	OCD	Paroxetine
329.001.00123	SUICIDAL THOUGHTS	Severe	MDD	Placebo
329.002.00241	PT. HOSPITALIZED FOR HOMICIDAL SUICIDAL IDEATION	Severe	MDD	Placebo
377.005.00231	SUICIDE ATTEMPT (BY OVERDOSE)	Severe	MDD	Placebo
377.010.00068	BENZODIAZEPINES OVERDOSE	Mild	MDD	Placebo
377.029.00024	SELF DAMAGING ACTS	Moderate	MDD	Placebo
377.041.00294	OVERDOSE (TENTATIVE OVERDOSE)= SUICIDE ATTEMPT	Moderate	MDD	Placebo
701.154.25768	SUICIDALITY	Moderate	MDD	Placebo
701.183.27617	MILD SELF- MUTILATION (ARM CUTS)	Mild	MDD	Placebo

Of the 25 reports in paroxetine-treated patients, 13 can be categorised as suicide attempts, 8 as suicidal ideation and 4 as self-mutilation. Of the eight reports in placebo patients, 3 were suicide attempts, 3 were suicidal ideation, and 2 were self-mutilation. As mentioned previously, there were no deaths in the paroxetine paediatric programme and hence no suicide attempt was successful.

The severity of the possibly suicide-related events that occurred in the on-therapy plus 30 days post-therapy time period in the paediatric placebo-controlled studies is shown in Table 15.4. Overall, possibly suicide-related events described as "severe" were reported by 1.4% (10/738) of patients receiving paroxetine and by 0.5% (3/647) of patients receiving placebo. In the paroxetine group, 60% (15/25) of the possibly suicide-related events that occurred in the on-therapy plus 30 days post-therapy time period were considered to be mild or moderate in intensity compared to 62.5% (5/8) in the placebo group. In patients from the depression studies, 55% (11/20) of such events in the paroxetine group were mild or moderate in intensity compared to 62.5% (5/8) in the placebo group.

As noted previously, all possibly suicide-related events that occurred in patients treated with placebo were in patients in depression studies. Of the few events that occurred in patients treated with paroxetine in indications other than depression, all four events in patients with Social Anxiety Disorder were of mild or moderate intensity. The single event from Obsessive Compulsive Disorder studies was reported as severe.

Table 15.4 Severity of 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**			
		Overall	Mild	Moderate	Severe
Overall	% (n/N)	3.4% (25/738)	1.1% (8/738)	0.9% (7/738)	1.4% (10/738)
Depression	% (n/N)	5.3% (20/378)	1.3% (5/378)	1.6% (6/378)	2.4% (9/378)
OCD	% (n/N)	0.5% (1/195)	0% (0/195)	0% (0/195)	0.5% (1/195)
SAD	% (n/N)	2.4% (4/165)	1.8% (3/165)	0.6% (1/165)	0% (0/165)
Indication		**Placebo**			
		Overall	Mild	Moderate	Severe
Overall	% (n/N)	1.2% (8/647)	0.3% (2/647)	0.5% (3/647)	0.5% (3/647)
Depression	% (n/N)	2.8% (8/285)	0.7% (2/285)	1.1% (3/285)	1.1% (3/285)
OCD	% (n/N)	0% (0/205)	0% (0/205)	0% (0/205)	0% (0/205)
SAD	% (n/N)	0% (0/157)	0% (0/157)	0% (0/157)	0% (0/157)

The number of patients discontinuing study medication due to possibly suicide-related events that occurred in the on-therapy plus 30 days post-therapy time period in the paediatric placebo controlled studies is shown in Table 15.5. In patients with possibly suicide-related events, similar proportions discontinued study medication because of the event in the paroxetine (48%, 12/25) and placebo (62%, 5/8) treatment groups, (Table 15.5). Overall, 1.6% (12/738) of patients receiving paroxetine and 0.8% (5/647) of patients receiving placebo discontinued study medication due to the event. Of the 12 events leading to discontinuation from paroxetine, 7 were described as severe, 3 as moderate and 2 as mild. Hence paroxetine was not stopped in 3 cases that were described as severe, 4 as moderate and 6 as mild. Of the 5 events that led to stopping placebo, 3 were described as severe, one as moderate and one as mild. The placebo patients with possibly suicide-related events whose treatment was not stopped had events reported as moderate (2) or mild (1).

Table 15.5 Patients Discontinuing Study Medication due to Possibly Suicide-Related Events by Treatment Group, Event Severity and Indication Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		**Paroxetine**			
		Overall	Mild	Moderate	Severe
Overall	% (n/N)	1.6% (12/738)	0.3% (2/738)	0.4% (3/738)	0.9% (7/738)
Depression	% (n/N)	2.6% (10/378)	0.3% (2/378)	0.5% (2/378)	1.6% (6/378)
OCD	% (n/N)	0.5% (1/195)	0% (0/195)	0% (0/195)	0.5% (1/195)
SAD	% (n/N)	0.6% (1/165)	0% (0/165)	0.6% (1/165)	0% (0/165)
Indication		**Placebo**			
		Overall	Mild	Moderate	Severe
Overall	% (n/N)	0.8% (5/647)	0.2% (1/647)	0.2% (1/647)	0.5% (3/647)
Depression	% (n/N)	1.8% (5/285)	0.4% (1/285)	0.4% (1/285)	1.1% (3/285)
OCD	% (n/N)	0% (0/205)	0% (0/205)	0% (0/205)	0% (0/205)
SAD	% (n/N)	0% (0/157)	0% (0/157)	0% (0/157)	0% (0/157)

15.3. Conclusion

The incidence of possibly suicide-related events observed in paediatric placebo-controlled studies was greater in patients treated with paroxetine than with placebo. However, there were no completed suicides in either treatment group, and the nature and severity of those events, and the proportion of patients discontinuing study medication because of those events, were similar in both groups. The possibly suicide-related events in both treatment groups were predominantly from patients with depression.