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Results of investigation of "all adverse events and verbatim terms that might possibly refer to an event that could be part of suicidal thinking and/or suicide attempts" henceforth referred to as "possibly suicide-related" from review of Paediatric Studies

Amendment to evaluate "on-therapy" period in addition to "on-therapy plus 30 days post-therapy" period

Prepared by:

  
Biomedical Data Sciences  
GlaxoSmithKline

Date: 15th May 2003

**Placebo controlled trials, Broad definition (possibly suicide-related AEs)**

1. Patients in paediatric, placebo-controlled trials of paroxetine for any indication will be included in this report. (See Appendix A for list of studies included.) These are all from placebo-controlled trials, including paroxetine and placebo data from three-arm trials. Only the controlled sections of these trials will be utilized, i.e. uncontrolled extension phases and run-in periods will not be included.
2. Denominators for the subset of patients defined by point 1 will be confirmed.
3. Patients will be included in the "possibly suicide-related" category if they meet any of the following criteria:
  - Preferred term is "Emotional lability" *and* the verbatim term contains any of the following text strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat", "overdos", "self damag", "self harm", "self inflict", "self injur", "self-damag", "self-harm", "self-inflict", "self-injur", "shoot", "slash", or "suic".
  - Preferred term is "Overdose" or "Intentional overdose". (Specifically, "Accidental overdose" is excluded.)
  - Any other cases where the verbatim term contains the text string "overdos" or "suic", unless the term is indisputably not "possibly suicide-related", as judged by ██████████ Clinical Development and Medical Affairs.  
Any terms found through this search because the text string was a substring of another word unrelated to the search criteria, will be excluded on review by ██████████ Biomedical Data Sciences (for example, the word "acute" would be obtained when searching for "cut" but would be excluded on review).  
(See Appendix B for a listing of preferred and verbatim terms obtained from this search.)
4. Events, identified in 3 above, outside the "On-Therapy plus 30 Days Post Therapy" window, will be excluded from Table 1, and events outside the "On-Therapy" window will be excluded from Table 2. Only the on-therapy phase will be included for patients continuing into an extension phase. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Patients successfully completing suicide will be included in the "possibly suicide-related" category. These cases will be obtained from a computer search of the cause of death. Where the cause of death includes the text string "suic" or "overdos" then the patient will be included in the "possibly suicide-related" category, with the exception of any case where the cause of death *also* includes the text string "accident".
6. All events will be detailed in Appendix C.
7. PYE will be calculated for all patients, and the rate of patients in the "possibly suicide-related" category relative to exposure will be calculated. Exposure

will be calculated only for the period on-therapy, i.e. the 30-day post-therapy window will not be used in calculating exposure.

8. The hypothesis of no association between treatment and incidence of "possibly suicide-related" events will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
9. The number of patients in the "possibly suicide-related" category relative to PYE (incidence density) will be analysed using SAS<sup>®</sup> PROC GENMOD. No comparison will be made where the model fails to converge.
10. Appendix C will list all patients in the "possibly suicide-related" category in both treatment groups.
11. Terms identified above to be used in computer searches are *not* case-sensitive.

Table 1: Incidence, person year exposure, and incidence density for "possibly suicide-related" events, by treatment group and indication (On Therapy plus 30 days post-therapy)				
Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	20/378 (5.3%)	8/285 (2.8%)	0.12
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.24	0.13	0.16
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)	0.49
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.02	0.00	n/a
Social Anxiety	n/N (%)	4/165 (2.4%)	0/157 (0.0%)	0.12
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.08	0.00	n/a
Overall	n/N (%)	25/738 (3.4%)	8/647 (1.2%)	0.01
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.14	0.05	0.02

**Footnotes to Table 1**

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.
2. No early onset attempted suicides occurred for patients tapering from single blind / open label paroxetine prior to receiving randomized placebo.

Table 2: Incidence, person year exposure, and incidence density for "possibly suicide-related" events, by treatment group and indication (On Therapy)				
Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	14/378 (3.7%)	7/285 (2.5%)	0.50
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.16	0.11	0.43
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)	0.49
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.02	0.00	n/a
Social Anxiety	n/N (%)	3/165 (1.8%)	0/157 (0.0%)	0.25
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.06	0.00	n/a
Overall	n/N (%)	18/738 (2.4%)	7/647 (1.1%)	0.07
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.10	0.05	0.08

**Footnotes to Table 2**

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.
2. No early onset attempted suicides occurred for patients tapering from single blind / open label paroxetine prior to receiving randomized placebo.
3. The following eight patients experienced possibly suicide-related events during the 30 day window post therapy and therefore do not contribute to the event counts: (329.002.00058, 329.005.00333, 377.042.00315, 377.049.00479, 701.154.25768, 701.180.25639, 701.183.27620 (Depression) and 676.011.24283 (Social Anxiety).

## Appendix A Study Population

Protocol Title	Indication
STUDY 329	Depression
STUDY 377	Depression
STUDY 453	OCD
STUDY 676	Social Anxiety
STUDY 701	Depression
STUDY 704	OCD

Appendix B1 Adverse Event Terms Identified as "Possibly Suicide-Related"

Preferred Term	Verbatim Term	Possibly Suicide Related
ABNORMAL LABORATORY VALUE	OVERCOMPLIANCE/PAXIL OVERDOSE	NO
ABNORMAL LABORATORY VALUE	UNINTENTIONAL OVERDOSE OF STUDY MEDICATION	NO
DEPRESSION	DEPRESSIVE EPISODE WITH SUICIDAL IDEATION AND ACTING OUT BEHAVIOR	YES
DEPRESSION	SUICIDAL RISK, DEPRESSION WORSE	YES
EMOTIONAL LABILITY	ATTEMPTED SUICIDE	YES
EMOTIONAL LABILITY	AUDITORY HALLUCINATIONS SUPERFICIAL CUTS	YES
EMOTIONAL LABILITY	SIGNIFICANT RISK TO SELF	YES
EMOTIONAL LABILITY	BENZODIAZEPINES OVERDOSE	YES
EMOTIONAL LABILITY	DEPRESSIVE EPISODE WITH SUICIDAL IDEATION AND ACTING OUT BEHAVIOR	YES
EMOTIONAL LABILITY	HOSPITALIZATION DUE TO SUICIDAL THOUGHTS	YES
EMOTIONAL LABILITY	IDEAS OF SELF HARM(SUICIDAL IDEATIONS)	YES
EMOTIONAL LABILITY	INCREASED SUICIDAL IDEATION	YES
EMOTIONAL LABILITY	INTENTIONAL TYLENOL OVERDOSE TOOK 80 PILLS	YES
EMOTIONAL LABILITY	MAJOR DEPRESSION SELF MUTILATION	YES
EMOTIONAL LABILITY	MILD SELF-MUTILATION (ARM CUTS)	YES
EMOTIONAL LABILITY	OVERDOSE	YES
EMOTIONAL LABILITY	OVERDOSE (BROMAZEPAM VALIUM)	YES
EMOTIONAL LABILITY	OVERDOSE (INTENTIONAL)	YES
EMOTIONAL LABILITY	OVERDOSE (TENTATIVE OVERDOSE)=SUICIDE ATTEMPT	YES

Preferred Term	Verbatim Term	"Possibly Suicide Related"
EMOTIONAL LABILITY	OVERDOSE (WITH BAYER EXTRA STRENGTH)	YES
EMOTIONAL LABILITY	OVERDOSE OF LORAZEPAM (TOTAL 8MG) DROWSINESS AND ATAXIA	YES
EMOTIONAL LABILITY	OVERDOSE ON 27-28 TYLENOL PILLS	YES
EMOTIONAL LABILITY	PARASUICIDE	YES
EMOTIONAL LABILITY	PT TOOK OVERDOSE	YES
EMOTIONAL LABILITY	PT. HOSPITALIZED FOR HOMICIDAL SUICIDAL IDEATION	YES
EMOTIONAL LABILITY	SELF DAMAGING ACTS	YES
EMOTIONAL LABILITY	SELF INFLICTED SCRATCH ON RT. WRIST	YES
EMOTIONAL LABILITY	SELF-MUTILATION	YES
EMOTIONAL LABILITY	SLAPPING HERSELF IN THE FACE (AUTOMUTILATION)	YES
EMOTIONAL LABILITY	SUICIDAL IDEATION	YES
EMOTIONAL LABILITY	SUICIDAL IDEATIONS	YES
EMOTIONAL LABILITY	SUICIDAL INTENT	YES
EMOTIONAL LABILITY	SUICIDAL RISK, DEPRESSION WORSE	YES
EMOTIONAL LABILITY	SUICIDAL THINKING	YES
EMOTIONAL LABILITY	SUICIDAL THOUGHTS	YES
EMOTIONAL LABILITY	SUICIDAL THREAT WITH SCISSORS	YES
EMOTIONAL LABILITY	SUICIDALITY	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPT	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPT (BY OVERDOSE)	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPTS	YES
EMOTIONAL LABILITY	THREAT OF SUICIDE	YES

Preferred Term	Verbatim Term	"Possibly Suicide Related"
EMOTIONAL LABILITY	VAGUE SUICIDAL IDEATION	YES
EMOTIONAL LABILITY	WORSENER SUICIDAL THOUGHTS	YES
HOSTILITY	DEPRESSIVE EPISODE WITH SUICIDAL IDEATION AND ACTING OUT BEHAVIOR	YES
HOSTILITY	PT. HOSPITALIZED FOR HOMICIDAL SUICIDAL IDEATION	YES
HYPERTENSION	HYPERTENSION SECONDARY TO INTENTIONAL OVERDOSE OF STUDY MEDS	NO

**Appendix B2 Cause of Death Terms Identified**

Verbatim Term
None

### Appendix C Patients with "Possibly Suicide-Related" Events

Protocol Title	Patient	Verbatim term
STUDY 329	329.001.00123	SUICIDAL THOUGHTS
STUDY 329	329.002.00058	INTENTIONAL TYLENOL OVERDOSE TOOK 80 PILLS
STUDY 329	329.002.00241	PT. HOSPITALIZED FOR HOMICIDAL SUICIDAL IDEATION
STUDY 329	329.002.00245	OVERDOSE ON 27-28 TYLENOL PILLS
STUDY 329	329.003.00250	OVERDOSE
STUDY 329	329.003.00313	AUDITORY HALLUCINATIONS SUPERFICIAL CUTS SIGNIFICANT RISK TO SELF
STUDY 329	329.004.00015	SELF-MUTILATION
STUDY 329	329.005.00011	OVERDOSE (WITH BAYER EXTRA STRENGTH)
STUDY 329	329.005.00333	SUICIDAL IDEATION
STUDY 329	329.006.00038	ATTEMPTED SUICIDE
STUDY 377	377.005.00231	SUICIDE ATTEMPT (BY OVERDOSE)
STUDY 377	377.009.00225	SUICIDE ATTEMPT
STUDY 377	377.010.00068	BENZODIAZEPINES OVERDOSE
STUDY 377	377.011.00061	OVERDOSE
STUDY 377	377.023.00172	ATTEMPTED SUICIDE
STUDY 377	377.024.00158	SLAPPING HERSELF IN THE FACE (AUTOMUTILATION)
STUDY 377	377.029.00024	SELF DAMAGING ACTS
STUDY 377	377.030.00181	SUICIDAL RISK, DEPRESSION WORSE
STUDY 377	377.041.00294	OVERDOSE (TENTATIVE OVERDOSE)=SUICIDE ATTEMPT
STUDY 377	377.042.00310	PARASUICIDE
STUDY 377	377.042.00315	OVERDOSE

Protocol Title	Patient	Verbatim term
STUDY 377	377.049.00479	SUICIDAL INTENT
STUDY 377	377.053.00508	SUICIDE ATTEMPT
STUDY 676	676.011.24283	VAGUE SUICIDAL IDEATION
STUDY 676	676.014.24376	SUICIDAL THOUGHTS
STUDY 676	676.100.24705	SELF INFLICTED SCRATCH ON RT. WRIST
STUDY 676	676.101.24629	THREAT OF SUICIDE
STUDY 701	701.154.25768	SUICIDALITY
STUDY 701	701.163.25718	OVERDOSE (INTENTIONAL)
STUDY 701	701.180.25639	OVERDOSE
STUDY 701	701.183.27617	MILD SELF-MUTILATION (ARM CUTS)
STUDY 701	701.183.27620	SUICIDAL IDEATION
STUDY 704	704.033.25513	HOSPITALIZATION DUE TO SUICIDAL THOUGHTS

**Results of investigation of suicide attempts identified by narrow definition  
algorithm, from review of Paediatric Studies**

**Amendment to evaluate "on-therapy" period in addition to "on-therapy plus  
30 days post-therapy" period**

**Prepared by:**

**[REDACTED]  
Biomedical Data Sciences  
GlaxoSmithKline**

**Date: 15th May 2003**

**Placebo controlled trials, Narrow definition (suicide attempts)**

1. Patients in paediatric, placebo-controlled trials of paroxetine for any indication will be included in this report. (See Appendix A for list of studies included.) These are all from placebo-controlled trials, including paroxetine and placebo data from three-arm trials. Only the controlled sections of these trials will be utilized, i.e. uncontrolled extension phases and run-in periods will not be included.
2. Denominators for the subset of patients defined by point 1 will be confirmed.
3. Patients will be included in the "suicide-attempts" category if they meet any of the following criteria:
  - Preferred term is "Emotional lability", *and* the verbatim term contains any of the following text strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat", "overdos", "self damag", "self harm", "self inflict", "self injur", "self-damag", "self-harm", "self-inflict", "self-injur", "shoot", "slash", or "suic", *and* the verbatim term does *not* contain any of the following text strings: "idea", "intent", "plan", "tendency", "think", "thought", "threat", or "wish". Additionally, any cases where the verbatim terms contain only the text "suicidal", "suicidality", or "suicide" will *not* be included as "suicide attempts".
  - Preferred term is "Intentional overdose" or "Overdose". (Specifically, "Accidental overdose" is excluded.)
  - Any other cases where the verbatim term contains the text string "overdos" or "suic" unless the term is indisputably not a "suicide-attempt", as judged by ██████████ ██████████ Clinical Development and Medical Affairs.  
Any terms found through this search because the text string was a substring of another word unrelated to suicides will be excluded on review (for example, the word "acute" would be obtained when searching for "cut").  
(See Appendix B for a listing of preferred and verbatim terms obtained from this search.)
4. Events, identified in 3 above, outside the "On-Therapy plus 30 Days Post Therapy" window, will be excluded from Table 1, and events outside the "On-Therapy" window will be excluded from Table 2. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Patients successfully completing suicide will *not* be included in the "suicide-attempts" category.
6. All events will be detailed in Appendix C.
7. PYE will be calculated for all patients, and the rate of patients in the "suicide-attempts" category relative to exposure will be calculated. Exposure will be calculated only for the period on-therapy, i.e. the 30-day post-therapy window will not be used in calculating exposure.

8. The hypothesis of no association between treatment and incidence of "suicide-attempts" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
9. The number of patients in the "suicide-attempts" category relative to PYE (incidence density) will be analysed using SAS<sup>®</sup> PROC GENMOD. No comparison will be made where the model fails to converge.
10. Appendix C will list all patients in the "suicide-attempts" category in both treatment groups.
11. Terms identified above to be used in computer searches are *not* case-sensitive.

Table 1: Incidence, person year exposure, and incidence density for suicide attempts, by treatment group (On Therapy plus 30 days post-therapy)				
Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	17/378 (4.5%)	5/285 (1.8%)	0.08
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.20	0.08	0.08
OCD	n/N (%)	0/195 (0.0%)	0/205 (0.0%)	n/a
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.00	0.00	n/a
Social Anxiety	n/N (%)	1/165 (0.6%)	0/157 (0.0%)	1.00
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.02	0.00	n/a
Overall	n/N (%)	18/738 (2.4%)	5/647 (0.8%)	0.02
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.10	0.03	0.03

**Footnotes to Table 1**

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.

Table 2: Incidence, person year exposure, and incidence density for suicide attempts, by treatment group (On Therapy)				
Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	14/378 (3.7%)	5/285 (1.8%)	0.16
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.16	0.08	0.18
OCD	n/N (%)	0/195 (0.0%)	0/205 (0.0%)	n/a
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.00	0.00	n/a
Social Anxiety	n/N (%)	1/165 (0.6%)	0/157 (0.0%)	1.00
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.02	0.00	n/a
Overall	n/N (%)	15/738 (2.0%)	5/647 (0.8%)	0.07
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.09	0.03	0.07

**Footnotes to Table 2**

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.
2. The following three patients experienced a suicide attempt during the 30 day window post therapy and therefore do not contribute to event counts: 329.002.00058, 377.042.00315, 701.180.25639 (Depression).

## Appendix A Study Population

Protocol Title	Indication
STUDY 329	Depression
STUDY 377	Depression
STUDY 453	OCD
STUDY 676	Social Anxiety
STUDY 701	Depression
STUDY 704	OCD

Appendix B Adverse Event Terms Identified as Suicide Attempts

Preferred Term	Verbatim Term	Suicide Attempt
ABNORMAL LABORATORY VALUE	OVERCOMPLIANCE/PAXIL OVERDOSE	NO
ABNORMAL LABORATORY VALUE	UNINTENTIONAL OVERDOSE OF STUDY MEDICATION	NO
DEPRESSION	DEPRESSIVE EPISODE WITH SUICIDAL IDEATION AND ACTING OUT BEHAVIOR	NO
DEPRESSION	SUICIDAL RISK, DEPRESSION WORSE	NO
EMOTIONAL LABILITY	ATTEMPTED SUICIDE	YES
EMOTIONAL LABILITY	AUDITORY HALLUCINATIONS SUPERFICIAL CUTS	YES
EMOTIONAL LABILITY	SIGNIFICANT RISK TO SELF	
EMOTIONAL LABILITY	BENZODIAZEPINES OVERDOSE	YES
EMOTIONAL LABILITY	INTENTIONAL TYLENOL OVERDOSE TOOK 80 PILLS	YES
EMOTIONAL LABILITY	MAJOR DEPRESSION SELF MUTILATION	YES
EMOTIONAL LABILITY	MILD SELF-MUTILATION (ARM CUTS)	YES
EMOTIONAL LABILITY	OVERDOSE	YES
EMOTIONAL LABILITY	OVERDOSE (BROMAZEPAM VALIUM)	YES
EMOTIONAL LABILITY	OVERDOSE (INTENTIONAL)	YES
EMOTIONAL LABILITY	OVERDOSE (TENTATIVE OVERDOSE)=SUICIDE ATTEMPT	YES
EMOTIONAL LABILITY	OVERDOSE (WITH BAYER EXTRA STRENGTH)	YES
EMOTIONAL LABILITY	OVERDOSE OF LORAZEPAM (TOTAL 8MG) DROWSINESS AND ATAXIA	YES
EMOTIONAL LABILITY	OVERDOSE ON 27-28 TYLENOL PILLS	YES
EMOTIONAL LABILITY	PARASUICIDE	YES

Preferred Term	Verbatim Term	Suicide Attempt
EMOTIONAL LABILITY	PT TOOK OVERDOSE	YES
EMOTIONAL LABILITY	SELF DAMAGING ACTS	YES
EMOTIONAL LABILITY	SELF INFLICTED SCRATCH ON RT. WRIST	YES
EMOTIONAL LABILITY	SELF-MUTILATION	YES
EMOTIONAL LABILITY	SLAPPING HERSELF IN THE FACE (AUTOMUTILATION)	YES
EMOTIONAL LABILITY	SUICIDAL RISK, DEPRESSION WORSE	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPT	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPT (BY OVERDOSE)	YES
EMOTIONAL LABILITY	SUICIDE ATTEMPTS	YES
EMOTIONAL LABILITY	DEPRESSIVE EPISODE WITH SUICIDAL IDEATION AND ACTING OUT BEHAVIOR	NO
HOSTILITY	PT. HOSPITALIZED FOR HOMICIDAL SUICIDAL IDEATION	NO
HOSTILITY	HYPER TENSION SECONDARY TO INTENTIONAL OVERDOSE OF STUDY MEDS	NO

### Appendix C Patients with Suicide Attempts

Protocol Title	Patient	Verbatim term
STUDY 329	329.002.00058	INTENTIONAL TYLENOL OVERDOSE TOOK 80 PILLS
STUDY 329	329.002.00245	OVERDOSE ON 27-28 TYLENOL PILLS
STUDY 329	329.003.00250	OVERDOSE
STUDY 329	329.003.00313	AUDITORY HALLUCINATIONS SUPERFICIAL CUTS SIGNIFICANT RISK TO SELF
STUDY 329	329.004.00015	SELF-MUTILATION
STUDY 329	329.005.00011	OVERDOSE (WITH BAYER EXTRA STRENGTH)
STUDY 329	329.006.00038	ATTEMPTED SUICIDE
STUDY 377	377.005.00231	SUICIDE ATTEMPT (BY OVERDOSE)
STUDY 377	377.009.00225	SUICIDE ATTEMPT
STUDY 377	377.010.00068	BENZODIAZEPINES OVERDOSE
STUDY 377	377.011.00061	OVERDOSE
STUDY 377	377.023.00172	ATTEMPTED SUICIDE
STUDY 377	377.024.00158	SLAPPING HERSELF IN THE FACE (AUTOMUTILATION)
STUDY 377	377.029.00024	SELF DAMAGING ACTS
STUDY 377	377.030.00181	SUICIDAL RISK, DEPRESSION WORSE
STUDY 377	377.041.00294	OVERDOSE (TENTATIVE OVERDOSE)=SUICIDE ATTEMPT
STUDY 377	377.042.00310	PARASUICIDE
STUDY 377	377.042.00315	OVERDOSE
STUDY 377	377.053.00508	SUICIDE ATTEMPT
STUDY 676	676.100.24705	SELF INFLICTED SCRATCH ON RT. WRIST
STUDY 701	701.163.25718	OVERDOSE (INTENTIONAL)
STUDY 701	701.180.25639	OVERDOSE

Protocol Title    Patient    Verbatim term  
STUDY 701    701.183.27617    MILD SELF-MUTILATION (ARM CUTS)

**Paroxetine**

**Clinical Evaluation of "Possibly Suicide-Related" Adverse Events in  
Paroxetine Hydrochloride Pediatric Clinical Trials**



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## I. Background

In response to an FDA inquiry about the constituent symptoms included in the preferred term "emotional lability" a post-hoc analysis of adverse events, possibly related to suicidality, was conducted. Thirty three subjects in the pediatric placebo controlled trials of paroxetine for any indication were identified in a post-hoc statistical analysis of "possibly suicide-related" Adverse Events (AEs). As with any statistical analysis confined to a narrow categorical limit, especially when it is not prospectively defined, the analysis of "possibly suicide-related" Adverse Events (AEs) did not take into account relevant and potentially contributing clinical factors. This report focuses on a clinical review of these 33 cases.

Only the controlled sections of these pediatric placebo controlled trials were utilized in the statistical analysis, i.e. uncontrolled extension phases and run-in periods were not included. Subjects were included in the "possibly suicide-related" category if they met the "broad analysis" definition criteria under the preferred term "emotional lability" and verbatim terms containing a number of text strings related to suicidal ideation, suicide attempts, and self inflicted harm. Subjects who met criteria under the preferred term of "overdose" and "intentional overdose" were also included. Essentially, all subjects with a post-randomization suicide attempt and subjects with new or worsening suicidal ideation occurring after randomization, including those in the taper and post discontinuation phases, were included in the clinical analysis. It should be noted that the post discontinuation phase was uncontrolled, and the data from this phase are difficult to interpret since new medications may have been started; patients were aware that the study was ending; follow-up was variable and less systematic; no accounting is made for the possible return of symptoms, and discontinuation symptoms may have resulted in inadvertent unblinding.

The thirty three cases with "possibly suicide-related" AEs were identified out of 1385 subjects in pediatric clinical trials 329, 377, 701, 676, 704 and 453. Studies 329, 377 and 701 were pediatric depression studies and twenty eight of the thirty three suicidal subjects assigned to either paroxetine or placebo were identified in these trials. Sufficient efficacy was not demonstrated in these pediatric depression trials to warrant submission to regulatory authorities requesting a claim of efficacy. Four patients with suicidality were identified in the Social Anxiety Disorder trial 676, and one suicidal patient was identified in study 704 in Obsessive Compulsive Disorder (OCD). Efficacy was demonstrated in these

pediatric Social Anxiety Disorder and Obsessive Compulsive Disorder trials. Study 453 in pediatric OCD had no reported suicide-related AEs in the double-blind phase. Therefore, all 33 cases were identified in studies 329, 377, 701, 676, and 704. No deaths were reported in any of these pediatric studies (Tables 1 and 2).

Serious adverse event narratives and case report forms were used as reference materials for the clinical review which included an overview of verbatim descriptions of the suicidal events and an analysis of several key clinical factors including the treatment phase during which these events occurred, investigator reported relatedness to study drug, demographics, comorbidity, study drug dosage before and during the events, duration of treatment, concomitant medications, depression scale suicidality scores before, during, and after the event when available, comorbid psychiatric and medical history and the presence of proximate psychosocial stressors.

## II. Study Phase

The incidence of events of suicidality were analyzed in two ways. These included an analysis of all events occurring post randomization (Table 1) and a second analysis of events occurring only on study drug, including taper phase events (Table 2). Most events of suicidality occurred during the treatment phase for both the paroxetine and placebo groups.

Paroxetine events - 17/25 occurred during the treatment phase, 1/25 occurred during the taper phase, and 7/25 events occurred during the 30 day post last dose period.

Placebo events - 6/8 occurred during the treatment phase and 1/8 occurred one day after the initiation of the taper phase and 1/8 occurred during the 30 day post last dose period.

As noted there were seven paroxetine and one 30 day post last dose events. All eight 30 day post last dose events occurred within 4 days of stopping either paroxetine or placebo.

## III. Relatedness

Most reports of post-randomisation suicidality were judged by the clinical investigator to be unrelated to either paroxetine or placebo. Only "unrelated" and

"probably unrelated" events required an explanation on the SAE form if the event was considered serious. Non-serious AEs did not require any explanation. In these trials the explanation as to why these events were unrelated and probably unrelated were under reported as only 7/16 investigators completed this information.

Paroxetine Events - Related 1 , Possibly Related 3, Probably Unrelated 5 , Unrelated 16

Placebo Events - Related 1, Possibly Related 2 , Probably Unrelated 1 , Unrelated 4

The one related event for the subject on placebo was reported by the investigator as related to "lack of efficacy".

The one paroxetine patient with a "related" SAE of suicidality, which occurred during the taper phase, was a 16 year old white female who reported that she ingested 100 tablets of paroxetine following a fight with her mother one day after being withdrawn from the study due to lack of efficacy and approximately 6 weeks after the initiation of study medication. She was on 50 mg paroxetine/day the day before the event. The patient was brought to the emergency room approximately 7 to 8 hours after the time she reportedly ingested the overdose of medication and approximately 32 hours after her last per protocol scheduled dose of paroxetine. A urine drug screen conducted by the emergency room physician was found to be negative for approximately 700 compounds including paroxetine and other antidepressants. The drug screen was only positive for caffeine, opening up the possibility that the patient did not actually ingest 100 tablets of paroxetine and that she was not taking her study medication as required per protocol.

With respect to ratings on the CDRS this patient had shown slight improvement in her depressed mood on the day prior to the event (CDRS; Item 11= 4 compared to baseline CDRS; Item 11= 6). The patient did not endorse significant depressed mood on the KADS at baseline (score = 0 "hardly ever") nor on the day prior to the event (score = 0). Ratings of irritability on both the CDRS and the KADS were improved on the day prior to the event, when the patient indicated she "hardly ever" felt irritable, compared to baseline when she felt irritable "most of the time".

There was no evidence of suicidal ideation on either the CDRS or the KADS the day prior to the event.

The patient did not display any signs of worsening mood or irritability at the early withdrawal visit, nor were there signs of suicidal ideation. In fact, the patient's condition was considered by the investigator to be "minimally improved". The patient was not taking any concomitant medications. The only adverse event that she experienced during the trial was insomnia which lasted for approximately 8 days and did not overlap with the event. Given this patient's negative urine drug screen for the presence of paroxetine, possible lack of compliance with study medication improved CDRS and KADS rating scale scores just prior to the event, and the presence of a proximate psychosocial stressor, relatedness of the SAE of suicidality to paroxetine in this case cannot be accounted for in the record.

#### **IV. Dose Range**

Fixed dose studies to determine dose response and dose related adverse events were not included in the pediatric program. All suicidal events occurred while subjects were enrolled in flexible dose studies, and all events occurred while subjects were on paroxetine across a range of doses from 20 mg to 50 mg daily with most events taking place while subjects were on between 20 mg to 40 mg daily. One event occurred at 50 mg daily. Four subjects on paroxetine had an escalation of 10 mg in their daily dose within one week prior to the event. Four patients assigned to paroxetine were on no medication at the time of the event (stopped prior to event). None of the 8 placebo patients had a dose escalation within one week prior to the suicidal event. No determination of a dose dependent effect on the emergence or worsening of suicidality can be ascertained from these data.

#### **V. Duration of Treatment**

Subjects with new or worsening post-randomisation suicidality were on paroxetine for an average of 54 days prior to their suicidal event and on placebo for an average of 61 days prior to the event with a range of 11-156 days for paroxetine and 5-108 days for placebo. The median number of days exposure prior to the event was 42 days for the paroxetine group and 63.5 days for those on placebo. No clear relationship between time on study drug and the development of suicidality is apparent.

## VI. Concomitant Medications and Substances

Subjects were on a variety of concomitant medications for multiple different medical indications. Only one patient on paroxetine was on a concomitant medication, "Benzocaine for weight loss," with a possible contributing psychoactive component; one other patient overdosed on tranxene which may also have been taken concomitantly at other times; one admitted to smoking marijuana several days prior to the event, and one was found to have cannaboids on a drug screen. Subjects on placebo were on no concomitant medication with a significant contributing psychoactive component.

## VII. Demographics

In the all patients (children and adolescents combined) all studies population (329, 377, 701, 704, 676) there were more females randomized to paroxetine compared to placebo (57.6% [370/642] female paroxetine patients versus 50.1% [275/549] female placebo patients). For adolescents (ages 12-18 years) in the all studies population, there was also a higher proportion of females randomized to paroxetine compared to placebo (61.0% [296/485] female adolescent paroxetine patients compared to 53.4% [213/399] female adolescent placebo patients). Gender characteristics for the child age subgroup (ages 7-11 years) are not presented here since all but one of the suicidal subjects were adolescents. Unlike the higher proportion of females randomized to paroxetine in the all studies population (total and adolescent subgroups), there were similar proportions of females between groups in MDD studies 329, 701 and 377 in the adolescent age subgroup (63.0% [206/327] female paroxetine patients compared to 62.6% [149/238] female placebo patients).

In the "broad analysis" of suicidality there were a total of 645/1191 (54.1%) female and 546/1191 (45.8%) male pediatric subjects ages 7-18 years of age in studies 329, 377, 701, 676 and 704. Adolescent females ages 12-18 years accounted for 509/884 (57.6%) of total subjects and adolescent males ages 12-18 years accounted for 375/884 (42.4%) of total subjects.

Of the 33 subjects with post-randomisation new or worsening suicidality there was a preponderance of females. Twenty-six out of 33 (79%) of suicidal subjects were female and 7/33 (21%) were male. There were 20/25 (80%) female subjects in the paroxetine group with suicidality and 5/25 (20%) male subjects. There were 6/8 (75%) female and 2/8 (25%) male subjects included in the placebo group with suicidality.

Most paroxetine and placebo patients with suicidality characterized themselves as white (18/25 on paroxetine 5/8 on placebo).

Study 704 in OCD and 701 in Major Depressive Disorder included children ages 7-11 and adolescents ages 12-18. Study 701 had one child age 11 with suicidality. No children under the age of 11 years were reported as suicidal. The age range for adolescents who reported suicidality was 12 to 18 years. The average age for the paroxetine group reporting suicidality in all pediatric studies was 15.4 years and 14.3 years for the placebo group.

### VIII. Cormorbidity

Seven out of 25 paroxetine subjects had at least one ongoing comorbid DSM-IV psychiatric diagnosis at the time of entry into the study and 3/25 paroxetine subjects had a history of past psychiatric diagnosis at the time of entry into the study. Five out of 8 subjects on placebo had either a past or concurrent comorbid psychiatric disorder. No pattern of comorbid concurrent or past psychiatric history emerged as contributing to suicidality. However, the presence of comorbid concurrent and past psychiatric disorders such as Substance Abuse, ADHD, Borderline Personality (traits), Conduct Disorder and Anxiety Disorders cannot be ruled out as possibly contributing to a worsening in the patient's condition or at least rendering the patient less prone to treatment response. One patient developed what was reported as new onset auditory hallucinations. Evidence of a thorough evaluation of previous psychotic symptomatology was not apparent in the records available for review, and incipient bipolar or psychotic disorder cannot be ruled out for this subject.

### IX. Nature and History of Suicidality

Post Randomization Suicide Attempts vs Suicidal Ideation:  
Twenty-five out of 33 (76%) of the total reports of "possibly suicide-related" adverse events were in the paroxetine group and 8/33 (24%) were in the placebo group. Seventeen out of 25 (68%) of patients reported as suicidal on paroxetine had suicide attempts vs. 6/8 (75%) patients on placebo. The remaining 8/25 (32%) subjects on paroxetine had suicidal ideation only vs. 2/8 (25%) on placebo with suicidal ideation only. No clear relationship between drug and suicidal attempt vs. ideation is apparent. Subject PID: 377.024.00158 is described as experiencing an episode of "automutilation" in the form of face slapping. There is no mention of suicidal ideation or suicidal intent, and although this subject is counted as a

suicide attempt in the paroxetine group it is the clinical reviewer's opinion that this subject should not be included as suicidal.

**Method of Suicidality:**

The most common method of suicide attempt for both the paroxetine and placebo groups was overdose. Several subjects in both groups made "suicide gestures" in particular wrist scratching and superficial cutting are noted by the investigators. No clear relationship between drug and method of suicidal attempt is apparent..

**History of Past Suicide Attempts and/or Past Suicidal Ideation:**

Sixteen out of 25 subjects randomized to paroxetine and 6/8 subjects randomized to placebo who were identified with worsening or new suicidality after randomization had a history of one or more suicide attempts and/or suicidal ideation prior to their entry into the study as reported on the suicidal ideation/suicidal acts questions of their KSADS-L (used in MDD studies 329 and 377) or by the investigator's report of the subjects' past psychiatric history. Of these 16 subjects on paroxetine, 10 subjects had past suicidal ideation alone, 3 subjects had both past suicidal ideation and one or more suicide attempts and 3 subject had a past suicide attempt. Of the 6 subjects on placebo, 3 subjects had past suicidal ideation alone, one subject had both past suicidal ideation and one or more past suicide attempts, 2 subjects had a past suicide attempt. No clear relationship between drug and history of suicidal attempt and/or ideation is apparent.

**Presence of Suicidality at Randomization:**

Eight out of 25 (32%) of the subjects in the paroxetine group and 4/8 (50%) of the placebo group had suicidality already present at randomization prior to taking study medication as measured by a HAM-D Item 3 score  $\geq 3$  in study 329, MADRS Item 10  $\geq 3$  in study 377, or CDRS item 13  $\geq 3$  in studies 701 and 676. Study 704 in OCD had no depression scale or suicide item measurement. Five out of 25 (20%) of these subjects on paroxetine and 2/8 (25%) of these subjects on placebo scored 4 on the MADRS Item 10 indicating the presence of serious suicidality at the time of randomization and before starting study medication. No clear relationship between drug and suicidality at randomization is apparent.

**Presence of Suicidality at Randomization and Subsequent Suicide Attempts vs. Suicidal Ideation:**

Six out of 17 (35%) of patients on paroxetine identified as attempting suicide subsequent to randomization had suicidal ideation already present at the time of randomization as did 3/6 (50%) of the placebo group who had a post

randomization suicide attempt. Two out of 8 (25%) of patients on paroxetine who were identified with suicidal ideation subsequent to randomization had suicidal ideation already present at the time of randomization as did 1/2 (50%) of the placebo group with post randomization suicidal ideation.

Presence of Suicidality at Randomization and Overlapping History of Suicide Attempts, Suicidality, and Psychosocial Stressors: Six out of 25 subjects on paroxetine and 3/8 subjects on placebo had overlapping suicidality reported at randomization, a past history of suicide attempts and/or suicidality, and/or psychosocial stressors.

## X. Proximate Psychosocial Events

Psychosocial factors were prominent prior to the suicidal event in 10/25 of the paroxetine cases with post-randomization suicidality and 1/8 subjects on placebo.

## XI. Summary

Thirty three cases of "possibly suicide-related" adverse events were identified in the treatment, taper, and post discontinuation phases of pediatric clinical trials 329, 377, 701, 676 and 704, with most events occurring in depression trials 329, 377 and 701. Sufficient efficacy was not demonstrated in these pediatric depression trials to warrant submission to regulatory authorities requesting a claim of efficacy. The disorder specific statistical analyses of the incidence of "possibly suicide-related" adverse events for subjects in the treatment, taper, and post discontinuation phases showed no statistically significant differences between the paroxetine and placebo groups (Table 1). An overall statistical analysis of "possibly suicide-related" adverse events that included subjects in the treatment, taper, and post discontinuation phases for all indications combined showed that the paroxetine group had a numerically and statistically greater number "possibly suicide-related" AE compared to the placebo group (Table 1). However, when "possibly suicide-related" AEs for subjects who discontinued paroxetine were excluded from this analysis, i.e. when only treatment and taper events were included, there was no statistically significant difference in "possibly suicide-related" AEs between the paroxetine and placebo groups in both the individual disorders analysis as well as the overall combined disorders analysis (Table 2).

The analyses for "on-drug" subjects is seen to be the more relevant and scientifically defensible analysis as this is limited to a more controlled drug-

placebo comparison, i.e. during the randomized, placebo-controlled portions of the study. The analysis which includes subjects in the 30-day "off-drug" period (Table 1) is confounded by a number of different factors. New medications may have been started; patients were aware that the study was ending; follow-up was variable and less systematic; no accounting is made for the possible return of symptoms, and discontinuation symptoms may have resulted in unintended unblinding. It should also be noted that the "on therapy plus 30-days" analyses, include, in the numerator, all events occurring during the double-blind phase as well as any events in the 30 days after stopping treatment. The denominator however, (exposure and PYE) includes only those days during the double-blind phase, and not the 30 day period after stopping treatment.

A further clinical review of these 33 cases confirms that paroxetine was not associated with any completed suicide. Also, the method of suicide attempt did not appear to be any more impulsive or serious for the suicidal subjects in the paroxetine group compared to the placebo group. Among the events identified in subjects on paroxetine with a post-randomisation "possibly suicide-related" serious adverse event, 21/25 (84%) events were judged by the clinical investigators to be unrelated or probably unrelated to paroxetine.

No determination of a dose dependent effect on the emergence or worsening of suicidality related to paroxetine can be ascertained from the data. No clear relationship between the number of days on paroxetine or placebo and the development of suicidality was apparent..

Concomitant medications and substances with a psychoactive component may have played a role in complicating the clinical course of at least 4 subjects with suicidality assigned to the paroxetine group and none in the placebo group. However, concomitant medications and cannabis abuse or its presence as part of a drug screen were not reported by any investigator as directly leading to suicidality in any subject.

Several subjects on paroxetine and placebo had one or more past or concurrent comorbid psychiatric disorder. Proportionally more subjects on placebo had such disorders. The presence of comorbid concurrent and/or past psychiatric disorders such as Substance Abuse, ADHD, Borderline Personality (traits), Conduct Disorder and Anxiety Disorders seen in subjects with suicidality in these trials cannot be ruled out as possibly contributing to treatment resistance or a worsening clinical course for both paroxetine and placebo treated subjects with suicidality

The all patients all pediatric studies and "broad analysis" calculation of gender distribution showed a greater total number of female adolescents randomized to either paroxetine or placebo compared to males. In both analyses there was a greater number of female adolescents randomized to paroxetine compared to placebo and there was between 3 to 4 times as many females than males among the 33 post-randomisation suicidality cases. The imbalance of females with suicidality compared to males suggests that females were at greater risk for post randomisation emergence of suicide attempts or new or worsening suicidal ideation in these studies. This is consistent with what has been reported in the adolescent literature. When unequal gender distribution between paroxetine and placebo groups is not a factor, which was the case in depression studies 329, 377 and 701, a statistical analysis of post-randomisation suicidality in these studies shows no statistical difference in "possibly suicide-related" adverse events between the paroxetine and placebo groups.

A history of suicide attempts and/or suicidal ideation as well as the presence of suicidality at randomization measured by the suicide item of the HAM-D, MADRS, or CDRS was likely to have complicated the clinical course of a significant number of subjects who reported suicidality after randomization in both the paroxetine and placebo groups. Subject PID: 377.024.00158 with the face slapping related AE should not be counted as having a "possibly suicide-related" event. Also, post-randomisation psychosocial factors were pointed to by investigators as contributing to post-randomisation suicidality in both groups.

## **XII. Discussion**

A statistical analysis confined to categorical limits such as "possibly suicide-related" AEs or new and worsening post randomisation suicidality may obscure important contributing clinical findings and should prompt us to impose limits on how we interpret such data. Further caution should be taken when interpreting the clinical meaning of the relative incidence of suicidal ideation and suicide attempts between the paroxetine and placebo groups in these pediatric studies when we consider that there were no completed suicides while subjects were on paroxetine and that 21/25 (84%) of the reported suicidal events occurring while subjects were on paroxetine were judged by the clinical investigators to be unrelated and probably unrelated to paroxetine.

In addition, seriously suicidal subjects are generally excluded from clinical drug trials, e.g. subjects with MADRS scores of 4. This was not the case in our pediatric trials. Instead, as is sometimes allowed, it was left up to the investigator's clinical judgement to determine suicide risk and then include or exclude suicidal subjects accordingly. Since past suicidal ideation and suicide attempts in adolescents are among the strongest predictors of future suicidal behaviours, this same positive correlation seen in our pediatric trials cannot be discounted and may have contributed to the reported incidence of suicidality seen in these studies, especially considering that some of these suicidal subjects were included with potentially confounding comorbid psychiatric disorders and psychosocial stressors.

Also, the total number of adolescents randomised to the paroxetine group contained a greater proportion of female adolescents compared to the placebo group. Female adolescents are reported to be at 2 to 4 times higher risk for suicidal ideation and attempts compared to their male counterparts who complete suicide more frequently. This higher proportion of females in the total paroxetine group may have contributed to the higher incidence of suicidality seen with paroxetine.

During the course of a psychiatric clinical drug trial in a pediatric population there are many factors that can account for adverse event reports of aggression, emotional lability, impulsivity, agitation, suicidal ideation and suicide attempts. Emotional regulation, in general, is a developmentally acquired process that requires a child and adolescent to experience a variety of situations from which they learn coping skills. This process is complex, not well understood, and is impacted by biological/neurological and environmental factors. By virtue of their age and inexperience children and adolescents have less developed coping skills than adults which may place them at greater risk for emotional dysregulation, especially when they are experiencing the stress of a mental disorder. In part, this may account for why completed suicide is the third leading cause of death among young people and why adverse events related to emotional dysregulation are likely to be reported in pediatric trials and in clinical settings (NIMH 1999, King RA et al 1991, Keller MB et al 2001, Emslie GJ 2002)

In summary, confounding clinical, demographic, psychosocial and developmental factors were present in subjects enrolled in our pediatric clinical trials. From a clinical perspective these should be viewed as contributing to the incidence and cause of adverse events such as aggression, emotional lability, impulsivity,

agitation, suicidal ideation and suicide attempts and not attributed solely to paroxetine or placebo.

### XIII. TABLES

Table 1: Incidence, person year exposure, and incidence density for "possibly suicide-related" events, by treatment group and indication (On Therapy plus 30 days post-therapy)				
Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	20/378 (5.3%)	8/285 (2.8%)	0.12
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.24	0.13	0.16
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)	0.49
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.02	0.00	n/a
Social Anxiety	n/N (%)	4/165 (2.4%)	0/157 (0.0%)	0.12
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.08	0.00	n/a
Overall	n/N (%)	25/738 (3.4%)	8/647 (1.2%)	0.01
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.14	0.05	0.02

**Footnotes to Table 1**

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.
2. No early onset attempted suicides occurred for patients tapering from single blind / open label paroxetine prior to receiving randomized placebo.

Indication		Paroxetine	Placebo	P-value
Depression	n/N (%)	14/378 (3.7%)	7/285 (2.5%)	0.50
	PYE	85	61	
	n/PYE (rate relative to exposure)	0.16	0.11	
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)	0.49
	PYE	41	41	
	n/PYE (rate relative to exposure)	0.02	0.00	
Social Anxiety	n/N (%)	3/165 (1.8%)	0/157 (0.0%)	0.25
	PYE	51	47	
	n/PYE (rate relative to exposure)	0.06	0.00	
Overall	n/N (%)	18/738 (2.4%)	7/647 (1.1%)	0.07
	PYE	176	149	
	n/PYE (rate relative to exposure)	0.10	0.05	

Footnotes to Table 2

1. Exposure for one placebo patient (676.015.24401) could not be calculated due to missing start and stop dates of medication.
2. No early onset attempted suicides occurred for patients tapering from single blind / open label paroxetine prior to receiving randomized placebo.

The following eight patients experienced possibly suicide-related events during the 30 day window post therapy and therefore do not contribute to the event counts: (329.002.00058, 329.005.00333, 377.042.00315, 377.049.00479, 701.154.25768, 701.180.25639, 701.183.27620 (Depression) and 676.011.24283 (Social Anxiety).

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