Appendix 3: Supplementary information on suicidal and self-injurious behaviours in Study 329 [posted as supplied by author]

The suicidal cases in Study 329 were at the heart of the Department of Justice's case against GlaxoSmithKline (GSK)). There were differing views as to how many cases there were – FDA's view, GSK's view, and now RIAT's view.

See UNITED STATES *ex rel.* GREG THORPE, ET AL. [Consolidated] Plaintiffs, v. GLAXOSMITHKLINE PLC, and GLAXOSMITHKLINE LLC, Defendants
http://www.justice.gov/sites/default/files/opa/legacy/2012/07/02/us-complaint.pdf#page=11

1. Moreover, the FDA asked for additional information about patients in the studies who had experienced adverse events and who had withdrawn from the study prematurely, as well as why GSK used the term "emotional lability" to describe the five patients who attempted to commit suicide or exhibited other self-injurious behaviour. In May 2003, GSK for the first time provided the FDA with additional safety data from the studies.

2. Although GSK told the FDA there was no statistically significant difference in suicidality between placebo and Paxil in all the Paxil pediatric depression studies cumulatively, the difference between the potential suicide-related events among Paxil patients versus potential suicide-related events among placebo patients became statistically significant when the first 30 days after therapy were included in the analysis.

3. Likewise, upon closer examination the number of possible suicide-related events among the Study 329 Paxil patients increased beyond the five patients that GSK described in the JACAAP article as having "emotional lability". While collecting safety information for the FDA, GSK admitted that there were four more possible suicide-related events among Paxil patients in Study 329. In addition, the FDA later identified yet another possibly suicide-related event in the Study 329 Paxil patients, which also was not among the 11 serious adverse events listed in the JAACAP article. Thus, altogether 10 of the 93 Paxil patients in Study 329 experienced a possibly suicidal event, compared to one of the 87 patients on placebo. This is a fundamentally different picture of Paxil's pediatric safety profile than the one painted by the JAACAP article, which listed at most five possibly suicidal events among Paxil patients, brushed those off as unrelated to Paxil, and concluded that treating children with Paxil was safe.

Table A summarises the suicidal and self-injurious behaviours for each study drug in different phases, as reported by Keller et al. (2001) in their JAACAP article, as reported by GSK to the FDA in 2003, as determined by the FDA, and as determined by RIAT analysis.

Figure 1 presents similar information graphically.

Table B presents the reporting of the individual cases by GSK, FDA, and the RIAT team.

Table C provides details of the individual cases.

Table A: Suicidal and self-injurious behaviours in Study 329, by study drug and phase

	Paroxetine	Imipramine	Placebo
	Patients (events)	Patients (events)	Patients (events)
Keller et al.	5	3	1
GSK Acute	7	3	1
GSK Continuation & Taper	2 previous + 2 new	1	1
GSK Total	9	4	2
FDA	10	4	2
RIAT Acute & Taper	11 (14)	4 (6)	2
RIAT Continuation	1 previous + 1 new	1	2
RIAT Total	12 (15)	5 (7) 4 definite 1 possible	4 2 definite 2 possible

Figure 1

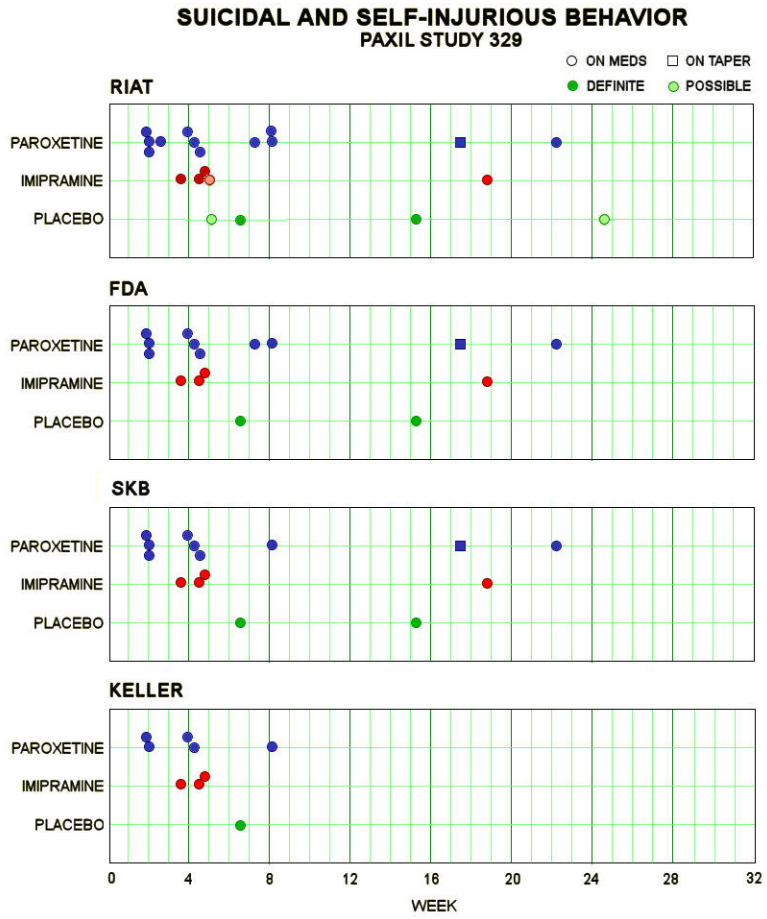

Table B: Suicidal and self-injurious behaviours in Study 329 as reported by GSK, FDA, and RIAT

Case	ID	Keller et al.	GSK	FDA	RIAT	Appendix (pages)		Clinical Study Report (pages)	
						D	G	Acute	Continuation.
1	329.002.00058		X	X	X	125	167		173
2	329.002.00245	X	X	X	X	28, 127	341	283	
3	329.003.00250	X	X	X	X	28, 131	511	288	177
4	329.003.00313	X	X	X	X	28, 132	553	289	
5	329.004.00015		X	X	X	28, 132	607		
6	329.006.00038	X	X	X	X	28, 143	1074	294	
7	329.006.00039				X	11, 144	1082		
8	329.001.00065	X	X	X	X	25, 29, 124	29	107, 272, 277	
9	329.005.00333		X	X	X	28, 142	1042	272, 292	
10	329.002.00106			X	X		257	281	
11	329.005.00011		X	X	X	28, 137	782, 783	500	
12	329.005.00089				X	28	442	272, 285	

As the Department of Justice Complaint above makes clear, there is now agreement on most of the suicidal cases in this study. GSK tagged as suicidal all the cases here except cases 00039, 00089 & 00106. We agree with all cases they tagged. FDA introduced case 00106 into the frame. We agree with FDA. The additional cases we identified are therefore cases 00039 and 00089.

Case 00039

This case had as verbatim term 'Superficial Scratches'. SKB[1] coded this as trauma. There were two cases of superficial lacerations coded as trauma – case 00039 (superficial scratches) and case 00197 (superficial laceration to the scalp). Both were coded blind and both were coded as suicidal. Case 00197 is a placebo case from the continuation phase – see Table 3 below.

The context partly influenced our choice of suicidality over trauma as the right coding option. There were 18 other trauma cases, 12 on placebo, 5 on paroxetine and 1 on imipramine (spreadsheet available on Study329.org). All involved fractures or sprains rather than lacerations and were coded as trauma. There are 3 SAE narratives in the Clinical Study Report that give a good "feel" for cases that both SKB and we coded as trauma.

In contrast, there were two cases of superficial scratches on paroxetine – cases 00039 and 00313. In case 00313, SKB coded superficial scratches as Emotional Lability. Case 00313 generated a Serious Adverse Event whereas 00039 did not. The narrative version of the verbatim term superficial scratches in cases 00313 was as follows:

> *He has cut himself in response to the voice on three occasions in the past six days. On the back of his hand he has carved a cross with small adorning cuts. On his forearms he has made 10-15 cuts each about six inches long. On his upper arm are three additional cuts.*

Clearly this cannot be trauma and SKB coded it as emotional lability.

The adverse event sheet for case 00039 shows that the superficial scratches happened over 10 days and involved multiple events and *was recorded as continuous. This is not consistent with trauma.

In case 00039, the HAM-D and Kiddie-SADS also recorded increased suicidal ideation/ gestures during this period and a later episode of suicidal ideation at week 6, and at week 6 aggravated depression was also listed as an adverse event in the CRF but did not make its way into the CSR.

The main use of the CRF in this case was to ensure that it contained nothing that would support a trauma coding. If there had been any indication of trauma other than its use as a verbatim term, we would not have recoded.

Based on the above, we recoded case 00039 as 'Suicidal event – Self-harm' and added 'suicidal ideation' (at week 6).

In contrast, placebo case 00197 shows zero ratings on suicide items. We have left this in the frame as a possible suicide attempt.

[1] The cases were coded by SKB in the CSR. Subsequently, in 2003, cases with suicidal and self-injurious behaviours were reported by GSK (formerly SKB) to the FDA.

Case 00089

This was a paroxetine patient coded as Euphoria by SKB. The narrative states that, starting at week four, her “behavioral symptoms worsened over the next two weeks through to completion of week eight of the study”. The patient reported increased feelings of elation and expansive mood. There was also a decreased need for sleep, increased energy, and an inflated self-esteem. Other symptoms included accelerated speech, flight of ideas, and motor hyperactivity. The school reported "impulsive and sexually provocative behaviour”.

There are a number of steers in the manuscript to a bipolar disorder and the eventual coding put on the case is Euphoria.

On 2 May, eight weeks after entering the study, “the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behaviour. The patient was deemed at risk to herself and was brought to the crisis service. She was hospitalized... and the decision was made she would not enter the continuation phase".

In this case, it would be appropriate to code grandiosity, impulsive behaviour, disinhibition, expansive mood, decreased need for sleep, increased energy, inflated self -esteem, accelerated speech, flight of ideas, motor hyperactivity, sexually provocative behaviour, agitation and suicidal behaviour.

All that is coded is euphoria and insomnia. Plus, Euphoria is listed in Appendix D page 130 as starting on 4 April, and that this was severe and this led to the drug being stopped. The Euphoria is classed as Serious because it led to hospitalization. The Suicidality has evaporated.

The Kiddie-SADS at week 6 is scored at 4 for suicidal acts for the current episode but none in the last two weeks – which is inconsistent with all prior scores for this item which score at 0.

This patient had 4 different CRFs, with as much as 40 pages in the difference between versions. A week before the event, one version of the CRF records the patient as being down-titrated from 4 paroxetine tablets to 3 per day, but another version of the CRF that is consistent with proposed changes in the query log removes this down-titration.

In this case, there is an additional note recording a series of significant discrepancies between the SAE narrative in the Clinical Study Report and the CRF(s).

Case 00106

On day 51, having apparently stopped her medication 3 days before, this patient threatened suicide in the course of what was reported to be an argument with her mother. She was hospitalized for two weeks. Her HAM-D scores prior to the event reveal nothing. She was discontinued from the study and there was no further assessment or follow up.

In appendix D, the original verbatim term was Psychiatric Hospitalization, but this was scratched out and replaced with oppositional defiant disorder, which was then coded in ADECs as hostility.

The query log raises the possibility that stopping the drug was part of an oppositional defiant disorder adverse event, which apparently went on for 2 days, according to the adverse event section.

For several reasons, this case looks most likely to be the one that the Department of Justice complaint cited above mentions is an extra suicidal event picked up by FDA.

It is suicidal event; whether or not it is the FDA extra event is a moot point.

Taper patients

Two other patients are of interest, 00058 and 00250, where the event happened during taper according to us, or continuation according to SKB. This is a new area where there can be legitimate differences of opinion.

Case 00058

GSK agree this case was a suicidal event, but they put it in the continuation phase. Anyone skimming the Serious Adverse Event narrative will likely agree with them, as the event appears to happen in the middle of the continuation phase.

But the date for the end of the continuation phase in this narrative is the notional end of the phase – not the actual end. Some reviewer may have innocently made a mistake here.

In fact this case had stopped drug three days before the overdose, then overdosed, and was discontinued completely from the study – three months before an independent assessor might have innocently thought they stopped taking the drug.

On this basis we have put the case into taper.

For GSK, in contrast, it seems once you enter continuation you are no longer acute, whereas we have opted for a deferred taper phase in people who go into continuation.

There is a real question about whether it is correct to treat all acute patients equally, in which case a purist will do what we did. Others might accept that all acute patients cannot be treated equally – some have tapers and some do not.

The field has not expressed a settled view on this issue. It may be an issue the field does not know exists.

There are other notable things about case 00058; most of pages where the adverse events section should be are missing – but fortunately the page with the intentional overdose is present.

Case 00250

This case has suicide attempts in acute phase and what SKB calls continuation phase. The company recognises both events, and codes both as Emotional Lability.

For the second event, the patient is poised between acute and continuation phases. They appear to run out of medication. The medication is tapered from paroxetine 40mg to 30mg, at which point the overdose happens and patient is discontinued.

There has been no continuation phase documentation filled. After the overdose, the first continuation phase pages are filled – a note that this patient is being discontinued because of an overdose.

SKB regard the patient as having entered continuation phase, although not a single continuation phase tablet is taken.

This is a patient on the cliff, we note in the paper, between acute and continuation phases into which one third of the sample in this study disappears.

Placing this patient in taper rather than continuation makes no difference to the number of suicidal patients, but it makes a slight difference to the number of events. This again is a matter of interpretation. We think the appropriate way forward is to note the ambiguity – which is not fully clear in the appendix.

Case 00015

SKB code self-mutilation in this case as Emotional Lability. We code it as Suicide Attempt.

SKB have another event in the continuation phase – suicidal ideation. We agree.

We note a further possible Suicidal Ideation in the acute phase. The HAM-D score a few days after the suicide attempt is a 3 – this may just refer to the gesture earlier that week or to accompanying Suicidal Ideation. The Kiddie-SADS covering the same period scores on the self-mutilation options and on the suicidal ideation option, while insisting that the self-mutilation was not suicidal.

Reviewing this CRF is unhelpful. Every problem feels minimized except for log notes about the patient's weight.

The patient later drops out of the study.

When patients drop out of a study for serious adverse events, companies are obliged to write a narrative that often sheds more light on what has been happening. There are 17 patients in Study 329 on whom SKB write such narratives – 11 paroxetine, 5 imipramine and 1 placebo patient in the acute phase and more in the continuation phase. Case 00015 is not among them.

There are other cases in the acute and continuation phases with serious events but who do not drop out. In such cases, a company is not obliged to write narratives but often does. Case 00015 has events that many would call serious but these are coded as mild – no narratives were written.

When a patient drops out of the study, the company must code the reason for withdrawal. In this case you might have expected adverse events or lack of efficacy. But SKB's stated reason is Other, and they cite a clash between school and this research study.

Possible events

We have noted a possible suicidal ideation event for case 00015 at Week 6 based on HAM-D and Kiddie-SADS scoring but would not be surprised if majority opinion did not support this. (It should be noted though that case 015 remains in the suicidal category because of the first undisputed suicidal event and the continuation phase event).

We also note an extra imipramine patient (00279) and two extra placebo patients (cases 00129 and 00197) that may be suicide cases. These are laid out in Table C.

Across the treatment arms of this study, there are a number of other events listed as abnormal thoughts or nightmares that may in fact have been suicidal or violent events. A full treatment of these issues would take these options into consideration using Structured MedDRA Questions (SMQs) to explore further.

Coding challenges

Coding involves a balance between coding flat with no presuppositions and applying expertise. In terms of coding flat, this means ideally a lay person. In terms of expertise, specialist knowledge and looking at the context can add important dimensions. Case 00039 brings these points out.

Taking a lay coder approach, coding superficial scratches as trauma makes sense. Taking an expert approach might lead to the same, as "we know" that many of these "gestures" in adolescents are not "truly" suicidal.

The expert "we know" and any "hunch" that this one is not truly suicidal needs to be resisted for a few reasons. First we have to resist because FDA insist on it – they insisted, for instance, that case 00015, which is self-mutilation but where the clinician insisted it was not suicidal, has to be included in the self-harm/suicidal group.

There is a reason behind this. A lot of completed suicides are not intended - as when someone playing with thoughts of suicide, kneeling down with a noose around their neck leans forward, not realizing that you can lose consciousness this way, and once you do, you strangle yourself.

Gestures can kill, and if SSRIs increase the rate of gestures, they may increase death rates.

Equally, in clinical practice, there are cases where there is real planning and lethal effort but the person survives and when asked afterwards can offer no reason for why they did what they did. Most liaison services regularly see cases like this. It is not clear whether these are extroverts, or what might once have been called alexithymics, but the point is you cannot just rely on stated intent.

Finally, coding all "trivial" things should increase the noise in the system, and other things being equal this should work to the advantage of the drug, as it will hide true signals. So a better company strategy in the case of blind coding if they want to hide problems is to over-code suicidality rather than under-code it.

It is highly likely that within these clinical trial databases there are a number of other suicide related events coded under headings such as thinking abnormally or nightmares.

Table C: Cases of suicidal & self-injurious behaviour in Study 329

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Paroxetine							
Case 1: 329.002.00058	Intentional overdose (Tylenol 80 pills)	Emotional lability	122 (during taper)	Appendix G: Withdrawal for Adverse Event (AE) intercurrent illness SAE narrative: *The patient was hospitalized on 19-Jan-95 after taking 80 Tylenol tablets…. The investigator considered the event to be moderately severe. The patient was withdrawn from the study due to the overdose.*	Suicide attempt/ self harm	-	Suicide attempt/ self harm
Case 2: 329.002.00245	Tylenol overdose (intentional)	Emotional lability	14	Appendix G: AE classed as severe. Withdrawn: AE intercurrent illness	Suicide attempt/ self harm		Suicide attempt/ self harm
Case 3: 329.003.00250	3.1. Overdose intentional	Emotional lability	37	Appendix G: SAE narrative: *The patient exceeded compliance from 19APR96 through 09May96. The overdose was rated by the investigator as serious, moderate in intensity and unrelated to the patient's use of the study drug.*	Suicide attempt/ self harm	-	Suicide attempt/ self harm
	3.2. Overdose intentional	Emotional lability	75 (during taper)	Appendix G: Severe AE. Withdrawn for Adverse Event intercurrent illness - SAE narrative: *The patient took a 20-tablet overdose of study medication. She was taken to the*	Suicide attempt/ self harm	p.267 Adverse Experience log: *Hospitalisation resulting from suicide attempt* and *Pt took overdose 'intentional'.*	Suicide attempt/ self harm

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
				emergency room by her sister….the patient was discharged from the general hospital and admitted to psychiatric unit as she remained suicidal. Appendix D - AE is logged as 'UNRELATED'.		- Series of query log entries whether to include suicidal ideation as another AE reason for hospitalisation. - 'Hospitalisation' removed as an AE; suicidal ideation not included. p.335 Query log states: *We asked the site to clarify if pt was hosp. for 'Suicidal ideation'. They answered that hosp. should show possibly related to study med.*	

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Case 4: 329.003.00313	4.1. Superficial cuts - risk to self	Emotional lability	12	Appendix G: classed as SAE, severe. Reason for withdrawal= AE intercurrent illness - *Patient was dropped due to hospitalization i.e. adverse experience.* Patient also auditory hallucinations on Day 12 (severe). SAE narrative: *Patient hospitalised for psychosis [no previous history of psychosis] with auditory hallucinations and superficial cuts. A voice commanded him to hurt himself.*	Suicide attempt/ self harm psychosis – missing from Appendix D	Week 2 visit a *serious attempt at suicide* reported on HAM-D scale p.182: *X experiencing auditory hallucinations. A voice commands him to hurt himself. He has cut himself in response to the voice on three occasions in the past six days. On the back of his hand he has carved a cross with small adorning cuts. On his forearm he has made 10-15 cuts, each about six inches long. On his upper arm are three additional cuts.* p.120 week 2 HAM-D item 3 suicide: *Attempts at suicide (any serious attempt rates 4)* - patient rated 4.	Suicide attempt/ self harm
	4.2. missing	-	12	SAE narrative: *The voice commanded the patient to jump off the roof. Although the patient went to the roof he did not jump. It was determined that the patient was a risk to himself.*	Suicidal ideation	-	Suicidal ideation
Case 5: 329.004.00015	5.1. Self-Mutilation	Emotional lability	31	Patient noted to have had an episode of self harming '*self mutilation'.*	Suicide attempt/ self harm	-	Suicide attempt/ self harm
	5.2. Missing	-	35	Increase in suicidal ideation on HAM-	Suicidal ideation		Suicidal

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
	Possible Event			D *suicide ideas or gesture* at week 5, as well as both suicidal ideation and self mutilation episodes on Kiddie-SADS.			ideation
	5.3 Suicidal Ideation	Emotional lability	73	Recorded as an adverse event but no SAE narrative. Patient dropped out 4 month later coded as Other.	Suicidal ideation		Suicidal ideation
Case 6: 329.006.00038	6. Attempted suicide (intentional)	Emotional lability	57	Appendix G: AE Severe, patient withdrawn: *Several personal crisis led patient to overdose on several medications including study medications on 12APR95 - move to withdraw.* SAE narrative: *Following a disagreement with her mother, the patient intentionally overdosed.*	Suicide attempt/ self harm	p.193 Week 8 paperwork not completed. Note on file: *Pt attempted suicide this day - in emergency room facilities.* - 'GI complaints' & 'Nausea' - coded as part of suicide attempt by SKB.	Suicide attempt/ self harm

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Case 7: 329.006.00039	7.1. Superficial scratches	Trauma	18	Appendix G: reason for withdrawal: Lack of Efficacy Day 92. AE coded as Trauma – Episode reported as CONTINUOUS over 12 days. No SAE narrative	Suicide attempt/self harm	Week 6 visit adverse events noted – fatigue, angry (not in Appendix D), more depressed, irritable mood. Kiddie-SADS scores: Week 4: 'Non-suicidal acts of self harm in last 2 weeks' = 4 (moderate)	Suicide attempt/ self harm
	7.2. missing	-	43	HAM-D weeks 5 & 6 – score '3' - 'suicidal ideas or gesture' The final visit described patient as having 'headaches- more severe than usual' – Recorded in Appendix D; *worse general/overall feeling depressed with a HAM-D score of 24*.	Suicidal ideation	Adverse event worsening depression – missing from Appendix D.	Suicidal ideation
Case 8: 329.001.0065	8.1. Needed 6 stitches to hand after breaking pictures (due to anger) resulted in hospitalisation to prevent aggression against self	Hostility	14	Other adverse event included on day 14: Worsening of depression, hospitalised (Severe, possibly related, stopped from study). SAE narrative: '*the patient became very angry....His anger subsided, but he expressed hopelessness and possible suicidal thoughts. The patient was hospitalized due to his severe anger outburst and a worsening of his depression... In the opinion of the investigator, the worsening of depression was possibly related to study medication.*'	Suicidal ideation	-	Suicidal ideation

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
	8.2 missing	-	14	Appendix G: reason for withdrawal: Adverse Event, including intercurrent *Needed psychiatric hospitalisation for increased aggression against self.*	Suicide Event – Self Harm	Study conclusion form reports hospitalisation for *increased aggression against self*. p.108 Adverse experience: *needed 6 stitches to hand. Aggression to self.* p.136 Query log reports: *Telephone report also indicates a symptom of increased self harm.* - Adverse events of 'self harm' 'hopelessness' 'inc anger' suicidal ideation' combined as HOSTILITY, but coded separately under MedDRA coding. Discussion in the CRF query log of the patient needing stitches to their hand following a *severe angry outburst* and *increased self `harm*.	Suicide attempt/ Self Harm
Case 9: 329.005.00333	Suicidal ideation	Emotional lability	37	Appendix G: Withdrawal 'Lack of Efficacy' (day 33). Severe SAE. Other adverse events included: abnormal dreams (day 19) for 11 days. SAE narrative: '*patient did not sleep well all night, cried and experienced suicidal intentions. She was subsequently hospitalized for severe suicidal ideation.*'	Suicidal ideation	p.198 & p.224: *Suicidal ideation. The pt had Prozac 5mg x1 pd given for MDD* - 'Depression worsening' added as additional AE. p.174 Adverse Experience log: *Suicidal Ideation.*	Suicidal ideation

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Case 10: 329.002.00106	Oppositional Defiant Disorder	Hostility	51	Appendix G records as a severe SAE. - SAE narrative: *patient was hospital-ised after an argument. She had become combative with her mother and had threatened suicide... several days before her hospitalisation she had not taken her study medication.*	Suicidal ideation/ gesture & Aggression	p.178: *no week 8 visit due to psychiatric hospitalization.* p.185 *Zoloft added for 'depression' following hospitalization for ODD.*	Suicidal ideation/ gesture & Aggression & Depression
Case 11: 329.005.00011	Overdose intentional	Emotional lability	156	SAE narrative: "the patient took an intentional overdose of Bayer aspirin… the patient had recently experienced several stressors (taunted by classmates about being depressed and failing grades. On the day of the event, the patient disobeyed her mother and became angry and went into a tantrum. The patient told her mother she just wanted to die and then proceeded to take an overdose.	Suicidal ideation and act		Suicidal ideation and act
Case 12: 329.003.00089	Elated and Expansive Mood	Euphoria	56	SAE narrative: "the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed at risk to herself and was brought to the crisis service. She was hospitalized... and the decision was made she would not enter the	Suicidal ideation/gesture		Suicidal ideation/ gesture

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
				continuation phase".			
Imipramine							
Case 1: 329.005.00295	Suicidal threat with scissors	Emotional lability	23	Appendix G: Adverse Event entered 'suicidal threat' = moderate and 'probably related'. Patient withdrawn on Day 53. Withdrawal: AE intercurrent illness - *investigators decision to discontinue study because pt threatened to kill parents.* This event coded as 'hostility' severe; probably related.	Suicide attempt/self harm	Kiddie-SADS Week 4: suicidal ideation increased to 3.	Suicide attempt/ self harm
Case 2: 329.012.00223	2.1. Suicidal ideation	Emotional lability	26	Appendix G: suicidal ideation coded as moderate lasting 10 days.	Suicidal Ideation	p.193 *SAE: Patient admitted to hospital for 3 days by precaution b/c she was more depressed with self mutilation and suicidal ideation.* Approx wk 4-5	Suicidal ideation
	2.2. Self-mutilation		31	Appendix G: self mutilation coded as moderate, continuous, and classed as a SAE. SAE narrative: '*the patient experienced depression and self mutilation for which she was hospitalized*'.	Suicide attempt/self harm	See above.	Suicide attempt/self harm
Case 3: 329.005.00113	3.1. Suicidal ideation	Emotional lability	32	Appendix G: Patient withdrawn on day 32. Reason: Adverse Event including intercurrent illness.	Suicidal ideation	See below.	Suicidal ideation
	3.2. missing	-	32	SAE narrative: '*Study medication was stopped on day 32 because of suicidal*	Suicidal gesture	Week 4 note on p.191: *Pt suicidal and went to ER.*	Suicidal gesture

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
				ideation with gesture considered to be of moderate severity.'		p.190 - *SAE for suicidal ideation and gesture started on 02Mar95.*	
Case 4: 329.010.00279	4.1. Strange thoughts	Thinking abnormal	33	No SAE narrative	? Suicidal ideation	No clarification given re: strange thoughts in query log *'pt and mother can't remember'*	? Suicidal ideation
Case 5: 329.012.00221	5.1 Overdose intentional	Emotional Lability	132	Patient up-dosed to Imipramine 250mg at week 4 and appears to have a manic reaction – leads to down-titration. Also has dizziness, constipation and dry mouth. Patient overdoses on lorazepam 8mg Coding changed to serious and at the upper limit of severity. SAE – overdoses on father's lorazepam after argument with girlfriend. Patient indicated overdose was impulsive, that he did not intend to die and was not activity suicidal. Patient recorded as withdrawing consent to study – refused down-titration – because he might be on placebo.	Suicide Attempt	Initially coded in CRF as mild with patient seen in hospital and discharged that day. After dropped out of study, coding changed to serious and at the upper limit of severity.	Suicide Attempt

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Placebo							
Case 1: 329.001.00123	Suicidal thoughts	Emotional lability	46	Appendix G: adverse event classed as severe, related, a SAE. Study drug was stopped and patient was withdrawn. Other adverse events noted = Worsening of depression day 46 Patient withdrawn DAY 49 'Lack of Efficacy'. SAE narrative: '*Approximately 6 weeks after commencing study 329, the patient experienced severe worsening of depression with severe suicidal thoughts'.*	Suicidal ideation	-	Suicidal ideation
Case 2: 329.009.00129	Missing	-	35	Patients HAM-D item 3 and Kiddie-SADS suicide ideation run at low grade suicidal ideation through the study 1-2 every week; Appendix G: Discontinues week 5: *Patient doing some what worse. Mother worried about increase in death wishes.*- coded as Lack of Efficacy	? Suicidal Ideation	Nothing else in CRF	? Suicidal ideation

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	RIAT MedDRA code based on CSR	Additional information from CRF	MedDRA code based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Case 3: 329.002.00241	Homicidal Ideation	Emotional Lability	106	SAE: Seven weeks into continuation phase, mother took to physician for "anger and irritability. The patient was evaluated and admitted due to severe suicidal and homicidal ideation (towards his parents).	Suicidal Ideation	Patient had abnormal ECG before entry and two suicidal gestures during the episode, one in the week before entry to trial. Close to protocol violation.	Suicidal ideation
Case 4: 329.009.00197	Superficial laceration to scalp	Trauma	172	On entry patient scored 2 on HAM-D item 3 and on Kiddie-SADS suicidal ideation but thereafter through acute and continuation phase scores 0. Six months into the study has a top of scalp laceration – no mention of stitching. Coded as mild. Augmentin (antibiotic) given.	? Suicide Attempt	Nothing else in CRF.	? Suicide Attempt

* The CRF included 'QUERIES AND ISSUE LOGS GENERATED FOR SB 29060-329'