A randomized, controlled trial of the efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: Restoring Study 329

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Competing interests – as attached

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Abstract

Background: A randomised controlled trial (GSK's Study 329) was conducted from 1994 to 1998, and published by Keller et al. in 2001. It was recovered under the Restoring Invisible and Abandoned Trials (RIAT) initiative.

Objectives: The primary objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

Method: 275 adolescents (12 to 18 years old) with major depression were randomised to 8 weeks double-blind treatment with paroxetine (20–40 mg), imipramine (200–300 mg), or placebo. The pre-specified primary efficacy variables were: change from baseline to the end of the acute treatment phase in total Hamilton Depression Scale (HAM-D) score; and the proportion of responders (HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Pre-specified secondary outcomes were (1) changes from baseline to endpoint in the following parameters: depression items in K-SAD-L; Clinical Global Impressions; Autonomous Functioning Checklist; Self-Perception Profile; Sickness Impact Scale, (2) predictors of response, (3) number of patients who relapse during the maintenance phase.

Results: The responses to paroxetine and imipramine were not statistically or clinically significantly different from placebo for any measure. Clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events, were observed in the paroxetine group.

Conclusions: Paroxetine was neither well tolerated nor effective for major depression in adolescents. Imipramine, given in high doses, was also poorly tolerated and was not shown to be effective.

Trial registration: Registration number and name of trial register: SmithKline Beecham study 29060/329.

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Supplementary material / data can be found at [URL]

A randomised, controlled trial of the efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: Restoring Study 329

Background

In 2013, in the face of the selective reporting of outcomes of randomised controlled trials (RCTs), an international group of researchers called on funders and investigators of abandoned (unpublished) or misreported trials to publish undisclosed outcomes or correct misleading publications.[1] This initiative was dubbed 'restoring invisible and abandoned trials' (RIAT). The researchers identified many trials requiring restoration, and emailed the funders, asking them to signal their intention to publish the unpublished trials or publish corrected versions of misreported trials. Should funders and investigators fail to undertake to correct a trial that has been identified as unpublished or misreported, independent groups have been encouraged to publish an accurate representation of the clinical trial based on the relevant regulatory information.

The current article represents a RIAT publication of Study 329, which was funded by SmithKline Beecham (SKB; subsequently GlaxoSmithKline, GSK) and led by Dr Martin Keller. This double-blinded RCT to evaluate the efficacy and safety of paroxetine, imipramine and placebo for adolescents diagnosed with major depression was reported in the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP)* in 2001 (hereafter 'Keller et al.'). [2] The RIAT researchers named Study 329 as an example of a misreported trial in need of restoration. Keller et al., which was largely ghostwritten,[3] claimed efficacy and safety for paroxetine at odds with the data,[4] This is problematic because the article has been influential in the literature supporting the use of antidepressants in adolescents.[5]

On 14 June 2013, the RIAT researchers notified GSK that Keller et al. appeared not to represent adequately the underlying data from Study 329. GSK did not signal any intent to publish a corrected version of the article. In later correspondence, GSK stated that it does 'not agree that the article is false, fraudulent or misleading', and asserted that Keller et al. 'accurately reflects the honestly-held views of the clinical investigator authors'.[6]

Consequently, we have reanalysed Study 329 according to the RIAT statement.. To this end, we have used the Clinical Study Report (CSR; GSK's 'Final Clinical Report') available on the GSK website,[7] other publically available documents,[8] and the data access system SAS Solutions OnDemand,[9] on which GSK has posted some Study 329 documents (available only to users approved by GSK). Following negotiation,[10] GSK posted de-identified individual case report forms (CRFs) on that site. A table of sources of data consulted in preparing each part of this paper is available as Appendix 1.

Study 329 was a multicenter eight-week double-blind RCT (acute phase), followed by a six-month continuation phase. Its primary objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression. Secondary objectives were to identify predictors of treatment outcomes across clinical subtypes; to provide information on the safety profile of paroxetine and imipramine when these agents were given for 'an extended period of time'; and to estimate the rate of

relapse among imipramine, paroxetine and placebo responders who were maintained on treatment. Study enrolment took place between April 1994 and March 1997.

The first RIAT trial publication was a surgery trial that had only been partly published before.[11]. As far as we are aware, this is the first time that a previously published RCT has been reported in a published paper by a different team of authors.

Methods

Except where indicated, in accordance with RIAT recommendations, our methods are those set out in the 1994 Study 329 protocol,[12] as outlined in our RIAT Audit Record (RIATAR) (Appendix 1). In cases where the methodology published by Keller et al. diverged from the protocol, we followed the protocol. Where the protocol was not specific, we chose by consensus standard methods that best presented the data. The original 1993 protocol had minor amendments in 1994 and 1996. Furthermore, the CSR reported some procedures that varied from those specified in the protocol. Where relevant, we have referred to these variations.

Participants

275 adolescents between the ages of 12 and 18 years, meeting *DSM-IV* criteria[13] for a current episode of major depression of at least 8 weeks duration, were recruited for the study (the protocol specified *DSM-III* criteria, which are very similar). Table 1 lists the eligibility criteria.

Table 1. Study eligibility criteria.

Inclusion Criteria	**Exclusion Criteria**
Adolescents between ages of 12 and 18, meeting *DSM-III-R* criteria for major depression for at least 8 weeks; Child Global Assessment Scale severity score < 60; Hamilton Depression Scale (17-item) score ≥ 12; Medically healthy; IQ ≥ 80 (based on Peabody Picture Vocabulary Test).	Current or past *DSM-III-R* diagnosis of: bipolar disorder, schizoaffective disorder, anorexia nervosa, bulimia, alcohol or drug abuse/dependence, obsessive-compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder; Current (within 12 months) *DSM-III-R* diagnosis of post-traumatic stress disorder; Adequate antidepressant trial within 6-months; Suicidal ideation with a definite plan, suicide attempt during current depressive episode, or history of suicide attempt by medication overdose; Medical illness which contraindicates the use of heterocyclic antidepressants; Current use of psychotropic medications (including anxiolytics, antipsychotics, mood stabilizers), or illicit drugs; Organic brain disease, epilepsy or mental retardation; Patients who are pregnant or lactating;

	Sexually active females not using reliable contraception; Use of an investigational drug within 30 days or within five half-lives of the investigation drug.

Patients identified by telephone screening as potential participants were subsequently evaluated at the study site. Patients and parents were interviewed separately using the Schedule for Affective Disorders and Schizophrenia for Adolescents - Lifetime Version (K-SADS-L). Following this initial assessment, and signing of the informed consent form by both patient and parent, a 7 to 10 day screening period was used to obtain past clinical records and to document that the depressive symptoms were stable.

The protocol called for 300 subjects, but this was reduced to 275. Recruitment was slower than expected and, reportedly because of limited medication supplies (mainly placebo) due to expiry, a midcourse evaluation of 189 patients was carried out, without breaking the blind, revealing less variability in HAM-D scores (SD 8) than anticipated. Therefore the recruitment target was reduced on the grounds that it would have no negative impact on the estimated 80% power required to detect a four-point difference between placebo and active drug groups. In addition, the number of sites was increased from 6 centres to 12 (10 in the United States and 2 in Canada).

The recruitment period ran from April 1994 until 15 March 1997, and the acute phase was completed on 7 May 1997. In a small number of patients, 30-day follow-up data in cases that went into the continuation phase were collected into 1998.

Interventions

Study medication was provided to patients in weekly blister packs. Patients were instructed to take the medication twice daily. There were 6 dosing levels. Over the first four weeks, all patients were titrated to level 4, corresponding to paroxetine 20 mg or imipramine 200 mg, regardless of response. Non-responders could be titrated up to level 5 or 6 over the following four weeks. This corresponds to a maximum dose of paroxetine 60 mg and a maximum dose of imipramine of 300 mg. These imipramine doses are high for adolescents. In the six comparator studies submitted by SKB as part of their 1991 Approval NDA for paroxetine in adults, the mean imipramine dose overall was 140mg, with a mean endpoint dose of 170mg.[14]

Medication compliance was evaluated based on the number of capsules dispensed, taken, and returned. Non-compliance was defined as taking less than 80% or greater than 120% of the number of capsules expected to be returned at two consecutive visits, and resulted in withdrawal. Any patient missing two consecutive visits was also withdrawn from the study.

Patients were provided with 45-minute weekly sessions of supportive psychotherapy,[15] primarily for the purpose of assessing the treatment effects.

Outcomes

Patients were evaluated weekly during the 8 week duration of the acute treatment phase.

1. Principal Endpoints for Efficacy

Primary Efficacy Variables

The pre-specified primary efficacy variables were: change in total Hamilton Depression Scale (HAM-D)[16] score from the beginning of the treatment phase to the endpoint of the acute phase; and the proportion of *responders* at the end of the eight week acute treatment phase. *Responders* were defined as patients who had a 50% or greater reduction in the HAM-D or a HAM-D score equal to or less than 8.

Secondary Efficacy Variables

The pre-specified secondary efficacy variables were:

a) Changes from baseline to endpoint in the following parameters:

- Depression items in K-SAD-L
- Global Impression Scale?
- Autonomous Functioning Checklist[17] (listed in the protocol as Autonomic Function Checklist)
- Self-Perception Profile
- Sickness Impact Scale.

b) Predictors of response (endogenous subtypes, age, prior episodes, duration and severity of present episode, comorbidity with separate anxiety, attention deficit, and conduct disorder).

c) The number of patients who relapse during the maintenance phase (referred to in the CSR and in this paper as 'continuation phase').

However, both before and after breaking the blind, changes were made by the sponsors to the secondary outcomes as previously detailed.[4] We could not find any document that provided any scientific rationale for these post-hoc changes, [18] and the outcomes are therefore not reported in this paper.

2. Principal Endpoints for harms

An adverse experience/event (AE) was defined in the trial protocol (p. 18) as:

> 'any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with drug or placebo and whether or not considered drug related. (p. 18)
>
> This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments.'

AEs were to be elicited by the investigator asking a non-leading question such as: 'Do you feel different in any way since starting the new treatment/the last assessment?'. Details of treatment emergent AEs, their severity, including any change in study drug administration, investigator attribution to study drug, any corrective therapy given, and outcome status were

documented. Attribution or relationship to study drug was judged by the investigator to be 'unrelated', 'probably unrelated', 'possibly related', ‘probably related’ or 'related'.

Vitals signs and ECGs were obtained at weekly visits. Patients with potentially concerning cardiovascular measures either had their medication dose reduced or were withdrawn from the study. In addition, if the combined serum levels (obtained at weeks 4 and 8) of imipramine and desipramine exceeded 500 mcg/ml, the patient was to be withdrawn from the study.

Clinical laboratory tests, including clinical chemistry, hematology and urinalysis were carried out at the screening visit and at the end of week 8. Clinically significant laboratory abnormalities were to be included as adverse events.

Source of harms data

The harms data in this paper cover the acute phase, a taper period and an up to 30-day follow-up phase for those who discontinued because of adverse events, to ensure comparability with Keller et al. None of the tables contains data from the continuation phase.

AE data come from the CSR lodged on GSK’s website,[19] primarily Appendix D. Appendix B provides details of concomitant medications. The body of the CSR contains summary narratives for patients who had AEs that were designated as serious or led to withdrawal. Of the eleven paroxetine patients with AEs designated as serious, nine discontinued because of AEs. A large number of other patients discontinued because of AEs that were not regarded as serious, or for lack of efficacy or protocol violations (see Figure 1). None of these latter discontinuations led to patient narratives.

The tables laid out in Appendix D of the CSR give key clinical terms used along with Adverse Drug Events Coding System (ADECS) codes, ratings of severity and ratings of relatedness.

It became clear when we examined the key clinical terms that there were a number of events that had been left uncoded into ADECS, and had not been tabulated. For instance, a number of patient narratives of serious AEs that led to discontinuation from the trial contained AEs that had not been coded or assembled within the tables of AEs.

Therefore we approached GSK for access to CRFs. GSK made available all 275 CRFs for patients entered into Study 329. However, the CRFs were only available through a remote desktop facility (SAS Solutions OnDemand Secure Portal)[9], which made it difficult and extremely time-consuming to inspect the records properly.[20] Accordingly we could not examine all CRFs. Instead we purposefully selected for audit 93 CRFs (34%) to check if all AE data had been faithfully transcribed into the CSR. This audit comprised all 85 participants identified in CSR Appendix H who were withdrawn from the study, along with 8 further participants who were known from prior inspection of the CSRs to have become suicidal. 31 of the CRFs that were checked were from the paroxetine group, 40 from the imipramine group and 22 from placebo.

All CRFs were reviewed by JLN, who is trained in the use of the Medical Dictionary for Regulatory Activities (MedDRA®, MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical

Requirements for Registration of Pharmaceuticals for Human Use (ICH)" www.meddra.org). The second auditor (MN) is a clinician, untrained in this system. There was full agreement between these auditors about reasons for discontinuation and side effect coding (no quantitative indicator of inter-rater agreement was used).

These 93 CRFs were scrutinised for all AEs occurring during the acute, taper and follow-up phases, and a tally of total AEs was used to compare against the AE totals reported in CSR Appendix D.

This audit process gave rise to additional AEs. It also led to recoding of a number of the reasons for discontinuation. The new AEs and the reasons for changing discontinuation category are recorded in Tables i and viii in Appendix 2 accompanying this paper.

Roughly 1000 pages were missing from the CRFs audited.

Coding of Adverse Events

The original protocol for Study 329 makes no mention of how AEs from this trial would be coded. The CSR specifies that the AEs noted by clinical investigators in this trial were coded using the Adverse Drug Experience Coding System (ADECS) that was being used by SKB at the time. ADECS was derived from a coding system developed by the United States Food and Drug Administration (FDA), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), but is not itself a recognized system.

We coded AEs using MedDRA, which has replaced COSTART for the FDA and is by far the most commonly used coding system today. For coding purposes, we have taken the original terms used by the clinical investigators as transcribed from the original CRFs into the CSR, and applied MedDRA codes to these descriptions.

In general, MedDRA coding stays closer to the original clinician description of the event than ADECS does. For instance, MedDRA codes 'sore throat' as 'sore throat', but GSK, using ADECS, coded it as 'pharyngitis' (inflammation of the throat). Sore throats may arise because of pharyngitis, but when someone is taking SSRIs they may indicate a dystonic reaction in the oro-pharyngeal area.[21]

Classifying a problem as a 'respiratory system disorder' (inflammation) rather than as a 'dystonia' (a central nervous system disorder) can make a significant difference to the apparent AE profile of a drug.

In staying closer to the original description of events, MedDRA codes suicidal events as 'suicidal ideation' or 'suicidal events' rather than the ADECS option of 'emotional lability'; similarly, aggression is more clearly flagged as 'aggressive events' rather than 'hostility'.

The initial recoding was done blind, but it was not possible to be blind in relation to the extra events located in the serious AE and discontinuation narratives, because allocation status was written into the narrative of the events.

Box 1: Coding Challenges

Most recoding issues were clear-cut. Patient 00039 was our most ambiguous case.

Within two weeks of starting the acute phase, this patient was reported as 'more tired' and 'more sick'. There was also an additional handwritten note, 'softness of speech', beside item 8 of the HAM-D, which was rated as 'Obvious retardation at interview'. These were not coded as AEs in CSR Appendix D.

During week 2, the patient was recorded under AEs as being 'more depressed' and having 'superficial scratches'. These were coded by GSK as 'depression' and 'trauma'. We recoded them as 'aggravated depression' and, initially, 'self harm/suicide attempt'.

However, self-harm and suicide attempt are different phenomena. It may or may not be possible to resolve whether self-harm or suicide attempt is the correct coding.

The patient discontinued treatment during the continuation phase. Had she been deemed to have discontinued because of an AE, there would have been a patient narrative that might have made it clearer which of these options was more likely; however, because she was deemed to have discontinued for lack of efficacy, there is no patient narrative.

At the week 6 visit, a number of AEs were noted – 'fatigue', 'more angry' (missing from Appendix D), 'more depressed', 'irritable mood', 'grimacing face' and 'blinking eyes' (the last two were coded together as myoclonus by GSK but were recoded separately by us).

On the basis of being more angry, depressed and irritable, along with an increase in HAM-D suicide item score from 1 or 2 at screening, baseline and the initial weeks of the study to 3 (suicide idea or gesture) in weeks 5 & 6, we opted for 'suicide attempt'.

At the final visit, notes were made in a section headed 'adverse experiences', describing the patient as having 'headaches – more severe than usual' and 'Worse general/overall feeling depressed; HAMD score of 24'.

'Worsening Depression' was not recorded as an AE in Appendix D. The patient was noted as 'OUT OF STUDY' and designated as discontinuation for 'lack of efficacy'. We recoded this as 'Adverse Event (depression worsening)'.

Analysis of harms data

In analysing the harms data we have explored the discrepancies in the number of events between CRFs and the CSR; we present all AEs rather than only those happening at a particular rate (as Keller et al. did); we group events into broader system-organ-class (SOC) groups – psychiatric, cardiovascular, gastrointestinal, respiratory and other; we break down events by severity, selecting AEs coded as severe, and utilising the listing in CSR Appendix G of patients

who discontinued for any reason; we include an analysis of the effects of prior treatment, presenting the run-in phase profiles of medication taken by patients entering each of the three arms of the study, and comparing the list of AEs experienced by patients on concomitant medication (from Appendix B) versus those not on other medication; and we extract the events occurring during the taper and follow-up phase.

We have not undertaken statistical tests of harms data, as discussed below.

3. Patient withdrawal

A study patient could withdraw or be withdrawn prematurely for any of the following six reasons: 'Adverse experiences including intercurrent illness'; 'Insufficient therapeutic effect'; 'Deviation from protocol including non-compliance'; 'Loss to follow-up'; 'Termination by SB [SKB/GSK]'; 'Other (specify)'.

The CSR states that the primary reason for withdrawal was determined by the investigator. We have reviewed the codes given for discontinuation from the study, which are found in CSR Appendix G, and in a proportion of cases changed these.

Sample Size

The acute phase of the trial was initially based on a power analysis that indicated that a sample size of 100 patients per treatment group was required in order to have a statistical power of 80% for a two-tailed alpha level of 0.05 and an effect size of 0.40. This effect size entailed a difference of 4 in the HAM-D Total change from baseline scores at endpoint, specified in the protocol to be large enough to be clinically meaningful, considering a standard deviation (SD) of 10. No allowance was made in the power calculation for attrition (anticipated dropout rate) or non-compliance during the study.

Randomisation

A computer-generated randomization list of 360 numbers for the acute phase was generated and held by SKB. According to the CSR, treatments were balanced in blocks of 6 consecutive patients; however, there is an inconsistency in that in CSR Appendix A Randomisation Code details block sizes of both 6 and 8. Each investigator was allocated a block of consecutively numbered treatment packs, and patients were assigned treatment numbers in strict sequential order. Patients were randomised in a 1:1:1 ratio to treatment to paroxetine, imipramine, or placebo.

Blinding

Paroxetine was supplied as film-coated, capsule-shaped yellow (10 mg) and pink (20 mg) tablets. Imipramine (50 mg) was bought commercially and supplied as green film-coated round 50mg tablets. ‘Paroxetine placebos’ matched the paroxetine 20 mg tablets, and ‘imipramine placebos’

matched the imipramine tablets. All tablets were over-encapsulated in bluish-green capsules to preserve blinding.

The blind was to be broken only in the event of a serious AE that the investigator felt could not be adequately treated without knowing the identity of the study medication.

Statistical Methods

The primary population of interest was the intent-to-treat (ITT) population that included all patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. The demographic characteristics, description of the baseline depressive episode, additional psychiatric diagnoses, and personal history variables of the patients were summarized descriptively by treatment group.

The acute phase eight-week endpoint was of primary interest. Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last observation carried forward (LOCF, i.e. the last on-therapy assessment during the acute phase) and observed cases (OC) datasets.

We followed the methodology of the a priori 1994 study protocol. It did not provide explicit statistical hypotheses (null hypotheses and alternative hypotheses); nor were there justifications for the proposed statistical approaches or statistical assumptions underlying them.

The primary efficacy variable, proportion of responders (response), and the secondary efficacy variable, proportion of patients relapsing were treated as categorical variables. The primary efficacy variable, change in total HAM-D score over the acute phase, and the remaining secondary efficacy variables were treated as continuous variables.

In accordance with the protocol, the continuous variables were analyzed using parametric analysis of variance (ANOVA) with effects in the model including treatment, investigator, and treatment by investigator interaction. Pairwise comparisons were not done if the omnibus (overall) ANOVA was not statistically significant (two-sided $p<0.05$), as specified by the protocol (we acknowledge differing opinions about this issue in the statistical literature). The categorical variable was analyzed using logistic regression, with the same effects included. In either case, if the treatment by investigator interaction resulted in a two-sided p value >0.10, the interaction term was dropped from the model. All statistical tests were done using the Linear Model (LM) and General Linear Models (GLM) procedures of the R statistical package (version 2.15.2)[22] as provided by GSK.

For the relapse rate analyses, we included all responders (HAM-D ≤ 8 or ≥50% reduction in symptoms) meeting the original criteria for entry to the continuation phase of the study. Patients were considered to have relapsed if they no longer met the responder criteria (HAM-D ≤8 or ≥50% reduction in symptoms) or if they were withdrawn for 'Intentional Overdose'.

Results

Efficacy

The demographics of the groups are shown in Table 2, along with depression parameters, comorbidities, and baseline scores for the efficacy variables.

Table 2. Baseline characteristics

	Paroxetine n = 93	Imipramine n = 95	Placebo n = 87
Age (yr) [SD]	14.8 [1.6]	14.9 [1.6]	15.1 [1.6]
Sex M/F	35/58	39/56	30/57
Race %			
Caucasian	82.8%	87.4%	80.5%
African American	5.4%	3.2%	6.5%
Asian American	1.1%	2.1%	2.3%
Other	10.8%	7.4%	10.3%
Depression			
Episode duration (mo) [SD]	14 [18]	13 [17]	13 [17]
Age first episode (yr) [SD]	13.1 [2.8]	13.7 [2.7]	13.5 [2.3]
Prior episodes 0	0%	2%	0%
1	81%	79%	77%
2	12%	14%	14%
>3	7%	6%	8%
Comorbidity			
Any comorbid disorder §%	50%	45%	41%
Current Anxiety disorder §%	26%	28%	19%
ODD, CD, or ADHD §%	25%	26%	20%
Baseline Scores LSM [SEM]			
HAM-D	18.93 [0.44]	18.12 [0.43]	18.98 [0.44]
K-SADS-L	28.31 [9.52]	27.53 [0.51]	28.31 [0.52]
Autonomous Function	93.35 [3.10]	96.96 [3.10]	94.16 [3.17]
Self Perception Profile	63.97 [2.22]	63.54 [2.19]	63.35 [2.28]
Sickness Impact Profile	32.35 [1.23]	30.82 [1.23]	32.88 [1.27]

§ from the Screening K-SADS-L Structured Interview

Figure 1 summarises the allocations and discontinuations among the three treatment groups during the acute study period.

Insert Figure 1 here.

The flow chart covers the ITT population for the acute phase and the efficacy analysis. The paroxetine group was titrated to a dose of 20mg/day by week 4, with 55% moving to a higher dose (mean 28.0 mg/day, SD 8.4 mg) by week 8. The imipramine group was titrated to 200 mg/day by week 4, with 40% going higher (mean 205.8 mg/day, SD 63.9 mg) by week 8.

Efficacy

Figure 2 illustrates the longitudinal values for the two primary efficacy variables: mean change from baseline in the HAM-D score (with a difference of 4 points being pre-specified as clinically significant); and the percent responding, defined as a decrease in HAM-D score by 50% or more from baseline or a final HAM-D score of 8 or below. (Scores on the HAM-D can vary from zero to a maximum of 52). The difference between paroxetine and placebo fell short of the pre-specified level of clinical significance (4 points) and neither primary outcome achieved statistical significance at any measured interval during the acute phase.

Insert Figure 2 here.

The analysis included both OC and LOCF datasets. The results at week 8 are shown in Table 3.

Table 3. OC and LOCF datasets for primary and secondary outcomes

Primary Efficacy Variables [8 Weeks]

		Paroxetine		Imipramine		Placebo		*p*
	Data	LSMean [SEM]	n	LSMean [SEM]	n	LSMean [SEM]	n	ANOVA
HAM-D Change	OC	-12.09 [0.86]	67	-10.64 [0.95]	56	-10.47 [0.86]	66	0.259
	LOCF	-10.33 [0.80]	90	-9.12 [0.80]	94	-8.98 [0.82]	87	0.415
		criteria met	[+/-]	criteria met	[+/-]	criteria met	[+/-]	X^2
HAM-D Response ≥ 50% drop or ≤8	OC	79.4%	54/13	80.6%	40/16	65.2%	43/23	0.133
	LOCF	65.6%	59/31	58.5%	55/39	55.2%	48/39	0.389

Secondary Efficacy Variables [8 Weeks]

		Paroxetine		Imipramine		Placebo		*p*
		LSMean [SEM]	n	LSMean [SEM]	n	LSMean [SEM]	n	ANOVA
K-SADS-L Change	OC	-12.09 [0.91]	67	-10.85 [0.98]	56	-10.76 [0.91]	65	0.463
	LOCF	-11.45 [0.82]	83	-9.52 [0.81]	88	-9.26 [0.82]	85	0.105
CGI Mean Score	OC	1.88 [0.15]	68	2.16 [0.17]	56	2.37 [0.16]	66	0.062
	LOCF	2.36 [0.15]	90	2.70 [0.15]	94	2.74 [0.16]	87	0.143
Autonomous Function Check List Change	OC	14.60 [2.79]	58	11.75 [3.00]	52	9.09 [2.77]	60	0.382
	LOCF	14.56 [2.80]	60	11.27 [2.93]	57	8.95 [2.75]	62	0.368
Self Perception Profile Change	OC	13.03 [2.31]	60	13.21 [2.47]	55	12.64 [2.30]	60	0.894
	LOCF	13.35 [2.34]	61	13.03 [2.41]	60	11.34 [2.28]	63	0.784
Sickness Impact Profile Change	OC	-9.85 [1.61]	62	-13.10 [1.74]	55	-10.73 [1.61]	62	0.191
	LOCF	-10.04 [1.60]	63	-12.99 [1.67]	60	-9.92 [1.56]	65	0.180

There was no statistical significance (considered at $p<0.05$) or clinical significance demonstrated for any of the primary or secondary efficacy variables in either the OC or LOCF datasets, so further (pairwise) analysis was considered unjustified.

Although the protocol listed predictors of response among the secondary efficacy variables, the absence of statistically or clinically significant differences among the three arms rendered this analysis void.

The protocol also listed the relapse rate in the continuation phase for responders as a secondary outcome variable. Our calculation differed from the CSR calculation because we included those whose HAM-D scores rose above the 'response' range and those who intentionally overdosed. In the continuation phase, the dropout rates were too high in all groups for any precise interpretation: paroxetine 33/51 [65%]; imipramine 25/39 [64%]; and placebo 21/34 [62%]. The recorded relapses were paroxetine 25/51 [49%]; imipramine 16/39 [41%]; and placebo 12/34 [35%]. Although the relapse rate was lower in the placebo group, the results were not statistically significant, p=0.440 [Chi-square 2x3].

Harms

Audit of Clinical Records Forms

The non-random audit of 34% of CRFs produced the data shown in Tables 4 and 5 below.

Table 4. AEs found in CRFs vs. AEs listed in Appendix D

	Paroxetine (n=31)	**Imipramine (n=40)**	**Placebo (n=22)**
AEs found in CRFs	159	257	77
AEs found in Appendix D	136	240	67
% underestimate in relying only on Appendix D	14%	7%	13%

Table 5. Additional AEs found during audit of 93 CRFs (acute phase plus taper)

SOC Type	**Paroxetine (n=31)**	**Imipramine (n=40)**	**Placebo (n=22)**
Cardiovascular	0	5	0
Gastrointestinal	4	4	2
Psychiatric	12	1	4

Respiratory	0	1	1
Other	7	6	3
Total	**23**	**17**	**10**

Recoding and Representation of Adverse Event Data

Table 6 presents AEs found in this study according to System-Organ-Class (SOC). We contrast those presented in the Keller paper (**Keller et al**), those recoded from the CSR Appendix D (**CSR recoded**), and those resulting from our CRF audit of 93 cases. Two estimates are provided for this latter category. **CRF audit** adds the actual cases identified from those 93 cases to the CSR recoded figure and **CRF estimated** shows the estimated total number of side effects likely to have been found in the study had we been able to audit all records, based on the following calculations: for the paroxetine group, the number of each additional AE found in the audit was multiplied by 3 (total number of patients /number of patients in audit - 93/31) and this figure was added to the actual number of each AE found in the CSR recode; for the imipramine group the multiplication factor was 2.4 (95/40); and for the placebo group it was 4 (87/22). Since the CRFs used in our audit were not selected at random, our estimates of increases relative to what was derived from the CSR may be inflated for some or all AEs. Alternative treatments of the data could give different results. A full listing of AEs can be found in Appendix 2 to this paper.

Table 6. Adverse events in CSR and CRF audit

	Paroxetine N=93				**Imipramine N=95**				**Placebo N=87**			
Type of Adverse Event	**Keller et al**	**Reanalysis – CSR check only**	**Reanalysis of CSR plus additional audit AEs**	**Estimate of total AEs based on CRF audit**	**Keller et al**	**Reanalysis – CSR check only**	**Reanalysis of CSR plus additional audit AEs**	**Estimate of total AEs based on CRF audit**	**Keller et al**	**Reanalysis – CSR check only**	**Reanalysis of CSR plus additional audit AEs**	**Estimate of total AEs based on CRF audit**
Cardiovascular SOC*	5	45	45	45	42	131	136	143	6	32	32	32
Gastro-Intestinal SOC	84	112	116	124	106	147	151	157	66	79	81	87
Psychiatric SOC*	115	101	113	137	135	63	64	65	65	24	28	40
Respiratory SOC	33	42	42	42	27	22	23	24	37	39	40	43
All other SOCs	28	179	186	200	30	189	195	204	38	156	159	168
TOTAL	**265**	**479**	**502**	**548**	**340**	**552**	**569**	**593**	**212**	**330**	**340**	**370**

One reason why the Keller et al. figures are lower than ours is because Keller et al. only presented data for AEs reported for 5% of patients or more. The CSR and CRF figures also differ substantially from the Keller figures because symptoms such as dizziness and headaches have been moved from the Nervous System cluster to 'cardiovascular' for dizziness and 'other' for headaches.

In Keller et al, the paroxetine rate of psychiatric AEs (Table 6) was 1.8 times the placebo rate, while in the CSR figures it is 4 times, making the differences between placebo and paroxetine more salient in the primary datasets than in Keller et al. For all AEs combined, Keller et al. reported a paroxetine burden of AEs 1.25 times that of the placebo burden, compared with 1.5 times in the CSR figures. Behavioural adverse events are further broken down in Table 7.

Table 7. Behavioural adverse events (acute phase plus taper)

Psychiatric disorders	Paroxetine (n=93)			Imipramine (n=95)			Placebo (n=87)		
	CSR recoded	CRF audit	CRF estimated	CSR recoded	CRF audit	CRF estimated	CSR recoded	CRF audit	CRF estimated
Abnormal dreams	3	3	3	5	5	5	2	2	2
Depression worsening	5	7	11	3	3	3	2	3	6
Aggression (including anger)	7	8	10	3	3	3	0	0	0
Agitation	0	1	3	1	1	1	0	0	0
Akathisia	18	18	18	12	12	12	8	8	8
Anxiety	2	2	2	0	0	0	1	2	5
Depersonalisation	0	0	0	1	1	1	1	1	1
Disinhibition	4	4	4	1	1	1	2	2	2
Hallucination	1	1	1	1	1	1	0	0	0
Paranoia	1	1	1	0	0	0	0	0	0
Psychosis	1	2	4	0	0	0	0	0	0
Suicidal ideation	4	6*	10	3	3	3	1	2*	5
Suicide attempt	9	10*	12	3	4	4	0	0	0

Total AEs	**55**	**63**	**83**	**33**	**34**	**34**	**17**	**20**	**29**
Total patients	**35**			**23**			**12**		

* For the paroxetine group the total suicidal ideation/suicide attempt AEs were 16 from a total of 10 patients. For the placebo group the 2 suicidal ideation AEs were from 2 patients.

The post-audit estimated figures for rates of AEs in this table may be an overestimate, since the CRFs audited were those of participants who were withdrawn from the study or who were known to have become suicidal.

There was also a major difference between the frequency of suicidal thinking and events reported by Keller et al, and the frequency documented in the CSR. Our CRF audit adds even more cases (see table 8).

Table 8. Comparison of suicidality using different safety methodologies

	Keller et al.		**CSR recoded**		**CRF Audit**	
	Paroxetine	**Placebo**	**Paroxetine**	**Placebo**	**Paroxetine**	**Placebo**
Suicidal ideation/gesture	≤5*	≤2*	4	1	6	2
Suicide attempt	0	0	9	0	10	0
Total	≤5*	≤2*	13	1	16	2

* Classified under 'emotional liability (e.g., suicidal ideation/gestures)'

Severity Ratings

Keller et al. reported 11 serious AEs (defined as events that 'resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious') in the paroxetine group, five in the imipramine group, and two in the placebo group. Designating an AE as serious hinged on the judgement of the clinical investigator.

We are not able to make comparable judgements of seriousness, but there are two other methods to approach the issue of severity of AEs. One is to look at those rated as severe rather than moderate or mild at the time of the event. The second is to look at rates of discontinuation due to AEs. Table 9 presents the data broken down by severity ratings. In this table, the events are from the CSR, not from the audit, because new events detected in the audit do not include severity ratings. Note the high number and proportion of severe psychiatric events in the paroxetine group. In contrast, few of the many cardiovascular events in the imipramine group were rated as severe.

Table 9. Adverse events rated as 'severe' (acute phase plus taper)

System Organ Class (MedDRA)	Paroxetine N=93		Imipramine N=95		Placebo N=87	
	AEs in Appendix D	Severe AEs reported	AEs in Appendix D	Severe AEs reported	AEs in Appendix D	Severe AEs reported
Cardiovascular Disorders	45	1 (2.2%)	131	4 (3.1%)	32	0
Gastro-intestinal	112	25 (22.3%)	147	20 (13.6%)	79	4 (5.1%)
Psychiatric Disorders	101	32 (31.7%)	63	4 (6.3%)	24	5 (20.8%)
Respiratory & Thoracic disorders	42	2 (4.8%)	22	1 (4.5%)	39	4 (10.3%)
All Other Disorders	179	10 (5.8%)	189	21 (11.2%)	156	12 (7.7%)
Total AEs	**479**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**25 (7.6%)**

Discontinuations

Table 10 presents the data on rates of discontinuation due to AEs and other causes.

Table 10. Reasons for withdrawal during acute phase and taper

Reason for withdrawal		Paroxetine (n=93)*			Imipramine (n=95)			Placebo (n=87)		
		Keller et al.	Appendix G	Audit	Keller et al.	Appendix G	Audit	Keller et al.	Appendix G	Audit
Adverse Event	**Aggression**		1	0		0	0		0	0
	Mania		1	2		0	0		0	0
	Overdose		1	1		0	0		0	0
	Depression worsening		0	1		0	0		0	1

	Agitation		0	1		0	0		0	0
	Suicidality		0	5*		0	2		0	1
	Hallucinations		0	0		0	1		0	0
	Conduct disorder		1	1		0	0		0	0
	Hospitalisation/surgery		1	0		1	1		0	0
	Fatigue		0	0		1	1		0	0
	Sedation		0	1		0	1		0	0
	Nausea/vomiting		0	1		2	5		0	1
	Rash/acne		0	0		2	3		1	1
	Cardiac		0	1		9	15		3	2
	Accidental injury		0	0		1	0		0	0
	Urinary		0	0		1	1		0	0
	Pregnancy		0	0		1	1		0	0
	Intercurrent illness		6	0		12	0		2	0
	Total AE dropouts - n (%)	9 (9.7 %)	11 (11. 8%)	14 (15. 0%)	30 (31. 5%)	30 (31. 5%)	31 (32. 6%)	6 (6.9 %)	6 (6.9 %)	6 (6.9 %)
Protocol violation	**Non compliance with med**		3	1		4	4		6	4
	By investigator		0	0		0	0		0	4
	Recreational drug use		0	0		1	1		1	1
	Total		3 (3.2 %)	1 (1.1 %)		5 (5.3 %)	5 (5.3 %)		7 (8.0 %)	9 (10. 3%)
Lost to Follow-up			5 (5.4 %)	4 (4.3 %)		1 (1.1 %)	1 (1.1 %)		1 (1.1 %)	1 (1.1 %)
Lack of efficacy			3 (3.2 %)	3 (3.2 %)		1 (1.1 %)	0 (0%)		6 (6.9 %)	4 (4.6 %)

Withdrawn consent		4 (4.3 %)	5 (5.4 %)		1 (1.1 %)	1 (1.1 %)		1 (1.1 %)	1 (1.1 %)
Total dropout rate - n (%)	26 (28 %)	26 (28 %)	27 (29 %)	38 (40 %)	38 (40 %)	38 (40 %)	21 (24 %)	21 (24 %)	21 (24 %)

* During the audit, Patient **329.002.00058** was found to have stopped meds 3 days prior to attempting suicide. Originally this had been classed as a 'continuation phase' drop out, but has now been moved to '30 day discontinuation' period. Reason for withdrawal was originally 'AE including intercurrent illness' but was changed to 'suicide attempt'.

There are two points to note here. Firstly, we audited all records involving discontinuations due to 'Adverse Events: Intercurrent Illness' and replaced this term with more specific AE terms. Secondly, there were four patients enrolled in the study who violated the inclusion criterion; two patients had cardiovascular problems, one had a C-GAS score greater than 60, and one was 'extremely' suicidal at screening. All four were randomised to placebo. It was unclear how to categorize their reasons for discontinuation; we chose 'protocol violations'.

All changes of coding for discontinuation are laid out in our Appendix 2 (Table viii).

In a study that has a continuation phase, the assessment of AEs throws up a methodological difficulty not yet addressed by groups such as Consort. If a study only has an acute phase, then all AEs are counted for all patients on treatment as well as in any taper phase, and often for a 30-day follow-up period. When a study has a continuation phase, the taper and 30-day follow-up periods are displaced. To ensure comparable analysis of all participants, we have tallied the AEs across the acute phase and both taper and follow-up phases whether displaced or not. We have not been able to ascertain what GSK did in this regard.

Taking this approach in Study 329 revealed a conundrum. In addition to the 86 dropouts from the acute phase noted by GSK, there were 65 dropouts after week 8 ratings were completed. GSK regarded these patients as participants in the continuation phase, although none of them took a continuation phase pill or had a continuation phase rating. The coding for discontinuation was particularly ambiguous for this group.

The majority of patients stopped at this point were designated by GSK as lack of efficacy (see Table 11). Investigators in four centres reported lack of efficacy as a reason for stopping six placebo patients even though the HAM-D score was in the responder range and as low as 2 or 3 points in some instances.

In some cases there were clear protocol violations or factors such as the unavailability of further medication (placebo in particular). We have recategorized the lack of efficacy dropouts based on factors such as AEs and HAM-D scores.

Keller et al. stated that 69% of patients completed the acute phase. It would be wrong to assume that this meant that 69% continued. In fact only 45% went on to the continuation

phase. Our analysis of reasons for withdrawal at the end of the acute phase is shown in table 11.

Table 11. Reasons for withdrawal from Study 329 – patients discontinued at the end of the Acute Phase (n=65)

Reason for withdrawal		Paroxetine group (acute completers n=67)		Imipramine group (acute completers n= 56)		Placebo group (acute completers n=66	
		GSK App G	RIAT proposed	GSK App G	RIAT proposed	GSK App G	RIAT proposed
Adverse Event	Aggression/paranoia	1	1	0	0	0	0
	Mania	0	1	0	0	0	0
	Overdose	1	0	0	0	0	0
	Depression worsening	0	1	0	0	0	0
	Homicidality	0	0	1	1	0	0
	Suicidality	0	1	0	0	0	0
	Rash	1	1	0	0	0	0
	Cardiac	0	0	1	2	0	0
	Dry mouth	0	0	0	1	0	0
	TOTAL AE drop outs N (%)	**3**	**5**	**2**	**4**	**0**	**0**
Protocol violation	Non compliance with study meds	1	1	2	2	0	0
	Recreational drug use	0	0	0	0	1	1
	PV by Investigator	0	1	0	2	0	3
	TOTAL PV drop outs N (%)	**1**	**2**	**2**	**4**	**1**	**4**
Lost to Follow Up		**0**	**2**	**0**	**0**	**0**	**0**
Lack of Efficacy		**9**	**5**	**12**	**8**	**23**	**17**
Withdrawn consent		**1**	**1**	**0**	**0**	**4**	**5**
Other	Misc (HAM-D responder)	0	1	0	1	0	6
	General surgery	1	0	0	0	0	0
	No study meds	1	0	0	0	3	0

	available						
	ADHD symptoms	0	0	1	0	0	0
	Moved out of state	0	0	0	0	1	0
	TOTAL 'other' drop outs **N (%)**	**2**	**1**	**1**	**1**	**4**	**6**
TOTAL DISCONTINUED AT WEEK 8		**16**	**16**	**17**	**17**	**32**	**32**

Withdrawal Effects

The protocol for Study 329 called for a taper phase for all subjects and in addition a 30-day follow up period for all subjects who discontinued because of adverse events. The data in the CSR Appendix D makes it possible to identify adverse events happening in the taper and follow-up periods.

The data are presented in Table 12.

Table 12. Adverse events from taper phase

SOC	**Paroxetine N=19**		**Imipramine N=32**		**Placebo N=9**	
	AEs reported (CSR check)	**AEs reported as severe**	**AEs reported (CSR check)**	**AEs reported as sever**	**AEs reported (CSR check)**	**AEs reported as severe**
Cardiovascular Disorders	4	0	7	0	0	0
Gastrointestinal Disorders	9	4	18	4	4	0
Psychiatric disorders	15	7	2	0	1	1
Respiratory & thoracic disorders	3	0	1	0	0	0
All other SOCs	16	1	20	3	5	0
Total AEs	**47**	**12**	**48**	**9**	**10**	**1**

The Effect of Other Medications

In Table 13 we present data on the effects of other medications on the AEs recorded. It is clear that those taking other medications had more AEs than those who were not. This effect is slightly more marked in the placebo group, and as such works to the apparent benefit of the active drug treatments in minimizing any excess of effects over placebo.

Table 13. Use of other medications in the month prior to enrolment, and incidence of AEs

	Paroxetine (n=93)		Imipramine (n=95)		Placebo (n=87)	
	Other medications	**No other medications**	**Other medications**	**No other medications**	**No other medications**	**No other medications**
% patients	26% (n=24)	74% (n=69)	33% (n=31)	67% (n=64)	30% (n=26)	70% (n=61)
Psychiatric AEs subgroup (acute + taper)	15	38	13	21	6	11
Total AEs (acute + taper)	155	298	215	325	137	190

* PSYCH AEs included in this subgroup include: Abnormal dreams, aggravated depression, agitation, akathisia, anxiety, depersonalisation, disinhibition, hallucinations, paranoia, psychosis, suicidal ideation/gesture/attempt.

Discussion

We have reported Study 329 according to the original protocol and analysed the efficacy data accordingly. Appendix 1 shows the sources of information used in preparing this paper, which should aid other researchers who wish to access the data, either to check our analysis or to interrogate it in other ways. We draw minimal conclusions regarding efficacy and harms, inviting others to offer their own analysis.

The RIAT approach revealed different outcomes from those reported in the CSR and Keller et al. Re-examination of the data, including a non-random audit of 34% of the cases, revealed no significant discrepancies in the primary efficacy data. The marked difference in the reporting of efficacy outcomes was predominantly a product of our analysis keeping faith with the protocol methodology and its designation of primary and secondary outcome variables.

The authors/sponsors departed from protocol by performing pairwise comparisons of two of the three groups when the omnibus ANOVA showed no significance in either the continuous or dichotomous variables. They also reported four other variables as significant that had been unmentioned in the protocol or its amendments, without any acknowledgment that these measures were introduced post hoc.

The situation with AEs was different. There were large and clinically meaningful differences between the data as analysed by us and those reported in Keller et al. These differences arise both from inadequate entry of data from CRFs to summary data sheets in the CSR, and the analysis and reporting of these data sheets in Keller et al.

Our finding is consistent with other findings, including a recent study that examined 142 studies of six psychotropic drugs for which journal articles and clinical trial summaries were both available.[23,24] Most deaths (94/151, 62%) and suicides (8/15, 53%) cited in trial summaries were not reported in journal articles. Only one of nine suicides in olanzapine trials was reported in published papers.

Our reanalysis of study 329 revealed significant variations in the way AEs can be reported, demonstrating several ways in which the analysis and presentation of safety data can influence the apparent safety of a drug (see Box 2).

Box 2. Potential confounders of accurate reporting of harms

1. Use of an idiosyncratic coding system

The term 'emotional lability', as used in SKB's ADECS, masks discrepancies in suicidal behaviour between paroxetine and placebo.

2. Failure to transcribe all AEs from the clinical record to the side effect database

Our non-random audit of CRFs disclosed significant under-recording of AEs.

3. Filtering data on AEs through statistical techniques

For instance, Keller et al. (and GSK in subsequent correspondence) ignored unfavourable harms data on the grounds that the difference between paroxetine and placebo was not statistically significant. In our opinion, statistically significant or not, all relevant primary and secondary outcomes, and harms outcomes, should be explicitly reported. Testing for statistical significance is most appropriately undertaken for the primary outcome measures. We have not undertaken statistical tests for harms, since we know of no valid way of interpreting them. To get away from a dichotomous (statistically significant/non significant) presentation of evidence, we opted to present all original and recoded evidence to allow readers their own interpretation. The data presented in Appendix 2 and related worksheets lodged at www.xxx will, however, readily permit other approaches to data analysis for those interested, and we welcome other analyses.

4. Restriction of reporting to events that occurred above a given frequency in any one group

In the Keller et al. paper, reporting only AEs that occurred in more than 5% of patients obscured the harms burden. In contrast, we report all AEs that have been recorded. These are available in Table iii in Appendix 2 that accompanies this paper.

5. Coding an event under different headings for different patients (dilution)

The effect of reporting only AEs that have a frequency of more than 5% is compounded when, for instance, agitation may be coded under agitation, anxiety, nervousness, hyperkinesis and

emotional lability; thus, a problem occurring at a rate of >10% could vanish by being coded under different subheadings such that none of these reach a threshold rate of 5%.

Aside from making all the data available so that others can scrutinize it, one way to compensate for this possibility is to present all the data in broader SOC groups. We chose: psychiatric; cardiovascular; gastrointestinal; respiratory; and other. In Appendix 2, the data coded here under 'Other' is broken down under the following additional SOC headings - general, nervous system, metabolic, musculo-skeletal, endocrine, eye, renal, 'immune system, blood and lymphatic disorders, skin, infectious, reproductive system, ear, injuries, surgical, and pregnancy.

6. Grouping of AEs

Even when presented in broader system groups, grouping common and benign symptoms with more important ones can mask safety issues. For example, in the Keller paper, common AEs such as dizziness and headaches are grouped with psychiatric AEs in the 'nervous system' SOC heading. Since these AEs are frequent across treatment arms, this grouping has the effect of diluting the difference in psychiatric side effects between paroxetine, imipramine and placebo.

We have reported dizziness under 'cardiovascular' events and headache under 'other'. There may be better categorisations; our grouping is provisional rather than strategic. In Appendix 2, we have listed all events coded under each SOC heading and we invite others to further explore these issues, including alternative categorisation of these AEs.

7. Rating Severity

In addition to coding AEs, investigators rate them for severity. If no attempt is made to take severity into account, readers may get the impression that there was an equal AE burden in each arm, when in fact all events in one arm might be severe and enduring while those in the other might be mild and transient.

One way to manage this is to look specifically at those patients who drop out of the study because of AEs. Another method is to select those AEs coded as severe for each drug group while omitting those coded as mild or moderate. We used both approaches.

8. Relatedness coding

Judgements by investigators as to whether an AE is related to the drug can lead to discounting the importance of an effect. We have included these judgements in the worksheets lodged at www.xxx but have not analysed them, because it became clear that the blind had been broken in several cases before relatedness was adjudicated, and because some judgements were implausible. For instance, it is documented in the CSR (p 279) that an investigator, knowing the patient was on placebo, declared that a suicidal event was 'definitely related to treatment', on the grounds that 'the worsening of depression and suicidal thought were life threatening and definitely related to study medication [known to be placebo] in that there was a lack of effect'. Notably, of the 11 patients with serious AEs on paroxetine (compared to two on placebo) reported in the Keller paper, only one 'was considered by the treating investigator to be related

to paroxetine treatment', thus dismissing the clinically significant difference between the paroxetine and placebo groups for serious AEs.

9. Masking effects of concomitant medication

In almost all trials, patients will be on concomitant medications. The AEs from these other medications will tend to obscure differences between active drug treatment and placebo. This may be a very significant factor in trials of treatments such as statins, where patients are often on multiple medications.

Accordingly we also compared the list of AEs in those on concomitant medication versus those not on other medication. There are other medications instituted in the course of the study that we have not analysed, but the data are available in our Appendix 2 and worksheets lodged at www.xxx, and in Appendix B from the CSR. There are a number of other angles in the submitted data that could be further explored, such as the effects of withdrawal of concomitant medication on AE profiles as the spreadsheets submitted offer the day of onset of AEs and the dates of starting or stopping any concomitant medication. Another option to explore is the possibility of any prescribing cascades triggered by AEs related to study medication.

10 The Effects of Medication Withdrawal

The protocol included a taper phase lasting 7-17 days that investigators were encouraged to adhere to even in patients who were discontinued because of adverse events. The original paper did not analyse these data separately. We have done. They reveal evidence consistent with dependence on and withdrawal from paroxetine.

This RIAT exercise proved to be demanding of resources. We have logged (www.xxx) over 130,000 words of email correspondence amongst the team over a year. Gaining access to the CRFs required extensive correspondence with GSK.[10] Although GSK ultimately provided CRFs, the mode of access was excessively time-consuming. It required of the order of one thousand hours to audit only a third of the CRFs. Less restricted access to the CRFs would have significantly reduced the burden.

Our analysis indicates that while CSRs are useful, and in this case all that was needed to reanalyse efficacy, analysis of adverse events requires access to individual patient level data (CRFs).

Since we have been breaking new ground, we do not always have precedents to call on in analysis and reporting, and we are open to future collaborations to do things differently. We invite readers to contact us for clarification of any ambiguities through a public Q&A forum at www.xxx.com, where we will provide an initial response within two working days to any queries about our data or analysis, with further follow-up as required.

Conclusion

Study 329 showed no advantage of paroxetine or imipramine over placebo in adolescent depressive symptomatology on any of the specified parameters. There were clinically significant

increases in AEs in the paroxetine and imipramine arms, including serious, severe, and suicide related AEs.

As with most scientific papers, Keller et al. conveys an impression that 'the data has spoken'. This authoritative stance is only possible in the absence of access to the data. When the data becomes accessible to others, it become clear that scientific authorship is provisional rather than authoritative.

Box 3. Strengths and limitations of this study

Study 329 was a randomised controlled trial with a reasonable sample size.

The RIAT analysis included an audit of 34% of CRFs conducted by two investigators, using MedDRA (by far the most commonly used coding system today) to check AE data. The analysis generated a useful taxonomy of potential confounders of accurate reporting of AEs.

This study has significant limitations. There was evidence of protocol violations, including some cases of blind-breaking. Some AEs were miscoded, raising the possibility that some other data might be unreliable. The inability to access all CRFs may have introduced some error.

The trial participants had relatively chronic depression (mean duration more than one year), which would limit the generalizability of the results because many cases of adolescent depression have shorter durations.[25]

Trial Registration: Registration number and name of trial register: SmithKline Beecham study 29060/329.

Trial Protocol: SmithKline Beecham study 29060/329, Final Clinical Report Acute Phase, Appendix A, Protocol, from p. 531.[12]

Trial Funding: SmithKline Beecham study.

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Appendices/Supplementary material

1. RIATAR audit form, showing sources of data

2. Adverse event appendices

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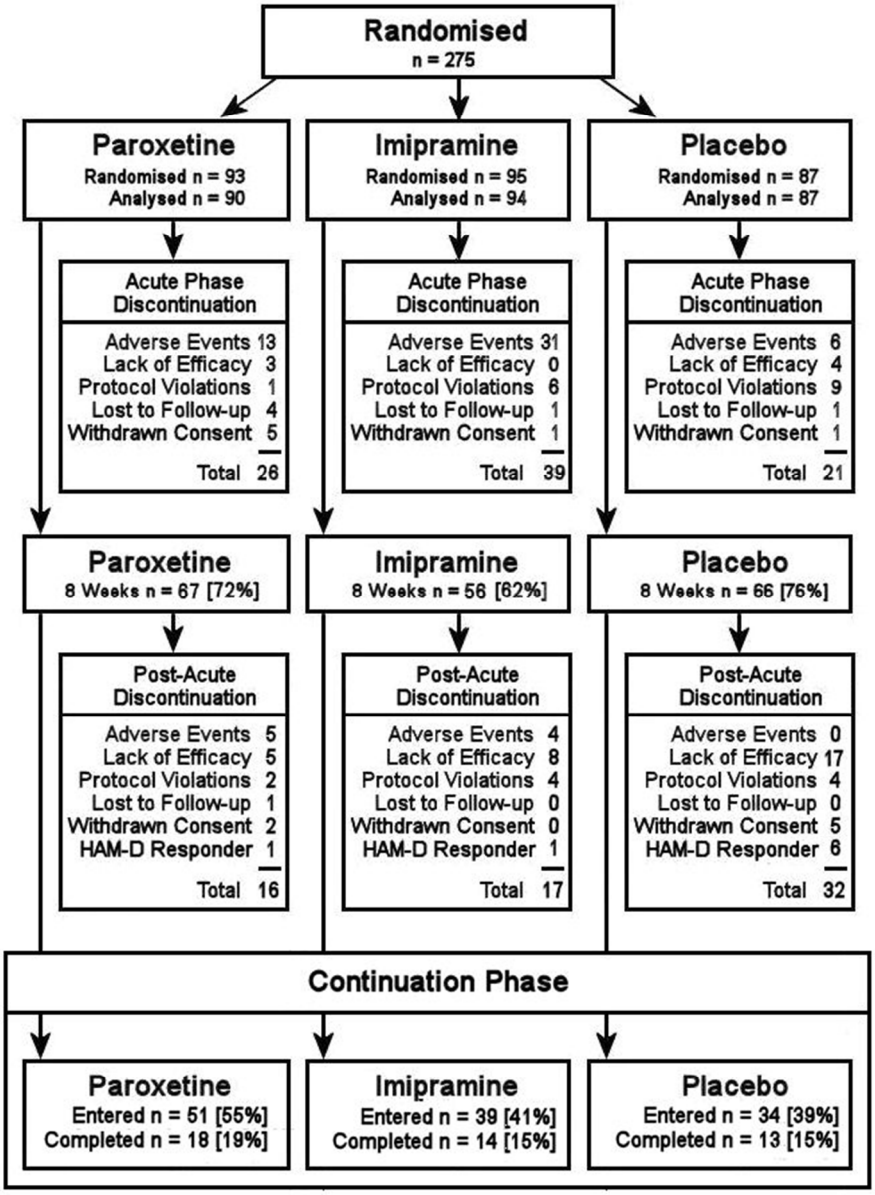

Figure 1. Randomisation and discontinuations.
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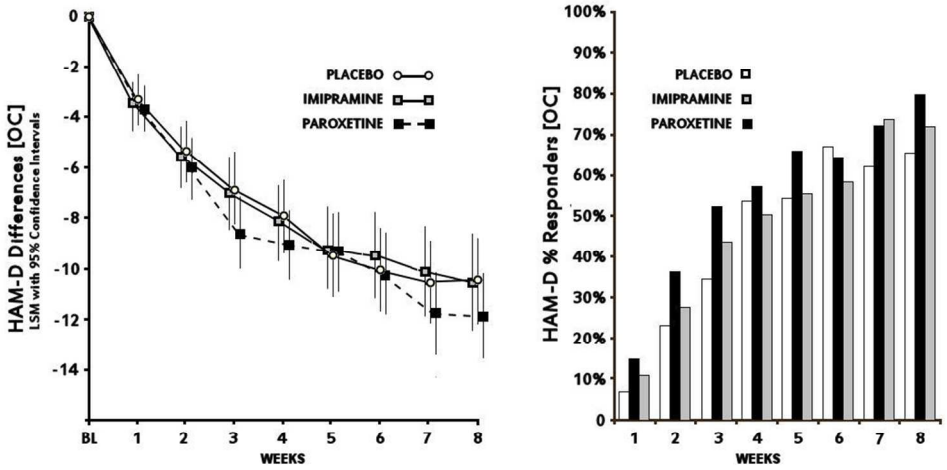

Figure 2. Primary Outcome

Figure 2. Primary Outcomes.
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RIAT Audit Record (RIATAR)

A tool for documenting the transformation from regulatory documents to journal publication, based on the CONSORT 2010 checklist of information to include when reporting a randomised trial*

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Title and abstract						
	1a	Identification as a randomised trial in the title	p.1			
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.1	CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9.	CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9.	
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Background and objectives	2a	Scientific background and explanation of rationale	p.2-3;	CSR Final Clinical Report Acute Phase; 1 Introduction, page 22, paragraphs 1-2; Appendix A, Protocol, 1.0 INTRODUCTION, page 545, paragraphs 1-2;	CSR Final Clinical Report Acute Phase; 1 Introduction, page 22, paragraph 1-2; Appendix A, Protocol, 1.0 INTRODUCTION, page 15, paragraph 1-2;	
	2b	Specific objectives or hypotheses	p.2-3	CSR Final Clinical Report Acute Phase; Report Synopsis, Objectives, page 14, paragraphs 1 to 3;2 Objectives, 2.1 Primary, page 24, paragraph 1; Objectives, 2.2 Secondary, page 24, paragraphs 2-4; Appendix A, Protocol, SYNOPSIS, OBJECTIVES OF STUDY,	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, SYNOPSIS, OBJECTIVES OF STUDY, page 10; 2.0 OBJECTIVES, Primary,	

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				page 540; 2.0 OBJECTIVES, 2.1 Primary, page 547 paragraph 1; 2.2 Secondary, page 547 paragraphs 2-4; Appendix A, Protocol, Appendices, APPENDIX G, CLINICAL MANAGEMENT FOR ADOLESCENT DEPRESSION, I. Purpose of Study, page 602; Continuation Study, Report Synopsis, Objectives, PDF page 1; Continuation Phase Final Clinical Report, 1 Introduction, page 17 paragraph 2; Continuation Phase Final Clinical Report, 2 Objectives, page 18;	page17; Appendix A, Protocol Appendices PDF page 72; Continuation Study, Report Synopsis no page numbers in the document; Continuation Phase Final Clinical Report same pages;	
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p.9;	CSR Final Clinical Report Acute Phase; Report Synopsis, Study Design, page 14, paragraph 4; 3 Methodology, 3.1 Study Design, page 25, paragraph 1; Figure 1 Study Design, page 26; 3.13.3 Method of Randomization, page 49 paragraph 4; Appendix A, Protocol, 3.0 STUDY PLAN, 3.1 Study Design, page 548 paragraph 1-3; Appendix A, Protocol, 5.0 CONDUCT OF STUDY, 5.2 Study Method, 5.2.2 Randomization, page 555; Continuation Study, Report Synopsis, Study Design, PDF page 1; Continuation Phase Final Clinical Report, 3 Methodology, 3.1 Overview, page 19-20;	CSR Final Clinical Report Acute Phase,Same pages; Appendix A Protocol, PDF page 18; Appendix A Protocol, 5.0 CONDUCT OF STUDY, 5.2 Study Method, 5.2.2 Randomization, page 25; Continuation Study, Report Synopsis no page numbers in the document;	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with	p.4;	CSR Final Clinical Report Acute Phase; Report Synopsis, Evaluation Criteria, page 15 paragraph 5; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 1 (approved 17 April, 1994), pages 26-27;	CSR Final Clinical Report Acute Phase,Same pages; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 1 (approved 17 April,	

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		reasons		Amendment 2 (approved 28 October 1996), pages 27-28; Amendment #1, page 536-537; Amendment #2, page 538-539;	1994), pages 26-27; Amendment 2 (approved 28 October 1996), pages 27-28; Appendix A, Protocol, PDF page 6-7; page 8-9;	
Participants	4a	Eligibility criteria for participants	p.3-4; Table 1;	CSR Final Clinical Report Acute Phase; Report Synopsis, Study Population, page 14, paragraph 5; 3 Methodology, 3.1 Study Design, page 25, paragraph 1,; page 26, Figure 1; 3.4 Eligibility Criteria, 3.4.1 Inclusion Criteria, page 30, paragraph 2; 3.4.2 Exclusion Criteria, pages 30, paragraph 3 to page 31; Appendix A, Protocol, 4.0 STUDY POPULATION, 4.2 Inclusion criteria, page 549 paragraph 2; 4.3 Exclusion Criteria, page 549 paragraph 2 to page 550; Continuation Study, Report Synopsis, Study Population, PDF page 2; Continuation Phase Final Clinical Report, 3.2 Inclusion Criteria: Continuation Phase, page 20 paragraph 1;4 Study Population, 4.1 Entry into the Continuation Phase, page 24; 4.2 Reasons for Not Entering the Continuation Phase, page 25 to page 26 paragraph 1;	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 19-20;	
	4b	Settings and locations where the data were collected	p.4	CSR Final Clinical Report Acute Phase; Report Synopsis, Investigators and Centers, page 13, paragraph 2; 3.2 Investigators, page 28, paragraph 3 to page 29;	Clinical Report Acute Phase,Same pages;	
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		for each group with sufficient details to allow replication, including how and when they were actually administered		Report Synopsis, Treatment and Administration, page 15, paragraphs 1 to 3; 3.5 Treatments and Administration, 3.5.1 Study Medication, page 32; 3.5.2 Dosage and Administration, page 33 to page 35 paragraph 1; 3.5.4 Other Protocol-specified Therapy, page 35, paragraph 4; 3.6 Compliance with Study Medication, page 36; 3.7 Prior and Concomitant Medication, 3.7.1 Prior Medication, page 36, paragraph 2; 3.7.2 Concomitant Medication, page 36, paragraph 3-5; Appendix A, Protocol, 6.0 DRUG SUPPLIES AND PACKAGING, 6.1 Formulations, page 559; 6.2 Study Drug Administration, page 559; 6.4 Concomitant Medication, page 560 paragraph 1-2; 6.5 Packaging, page 560; 6.6 Labeling and Preparation, page 560; 6.7 Storage, page 560; 6.8 Drug Accountability, page 560; 6.9 Assessment of Compliance, page 561; Appendix A, Protocol Appendices, APPENDIX G, CLINICAL MANAGEMENT FOR ADOLESCENT DEPRESSION, pages 599 to 623; Continuation Study, Report Synopsis, Treatment and Administration, PDF page2; Continuation Phase Final Clinical Report, 3.3 Study Medication and Administration, page 20 paragraph 2 to page 21 paragraphs 1-2;	Acute Phase,Same pages; Appendix A, Protocol, PDF page 29, 30-31; page 69-93; Continuation Study, Report Synopsis, Treatment and Administration, PDF page2; Continuation Phase Final Clinical Report, 3.3 Study Medication and Administration, page 20 paragraph 2 to page 21 paragraphs 1-2;	
Outcomes	6a	Completely defined pre-specified primary	p.4-9	CSR Final Clinical Report Acute Phase; Report Synopsis, Evaluation Criteria, Efficacy Parameters, Safety Parameters,	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol,	

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		and secondary outcome measures, including how and when they were assessed		Other Parameters, page 15, paragraphs 4-5, page 16, paragraphs 1-2; 3.9 Efficacy Assessments, pages 41-44; 3.9.1 Primary Efficacy Parameters, pages 43 paragraph 4 to page 44 paragraph 1; 3.9.2 Secondary Efficacy Parameters, page 44 paragraph 2;3.10 Safety Assessments, 3.10.1 Adverse Experiences, page 44 paragraph 4 to page 45 paragraphs 1-2; 3.13.4 Planned Efficacy Evaluations, page 49, paragraph 5, Primary Efficacy Variables, page 49 paragraph 6 to page 50 paragraphs 1-6; Appendix A, Protocol, 9.0 DATA EVALUATION, 9.1 Criteria for Efficacy, 9.1.1 Primary efficacy variables, page 571 paragraph 1; 9.1.2 Secondary efficacy variables, page 571 paragraph 2; Appendix A, APPENDIX F, INSTRUMENTS, pages 597-598. Continuation Study, Report Synopsis, Evaluation Criteria, PDF page 2; Continuation Phase Final Clinical Report, 3.6 Planned Efficacy Evaluations, page 22 paragraphs 2-4;	PDF page 41, 67-68; Continuation Study, Report Synopsis, Evaluation Criteria, PDF page 2; Continuation Phase Final Clinical Report, 3.6 Planned Efficacy Evaluations, page 22 paragraphs 2-4;	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	p.5	CSR Final Clinical Report Acute Phase; Report Synopsis, Evaluation Criteria, Efficacy Parameters, page 15, paragraph 5;	Clinical Report Acute Phase,Same pages;	
Sample size	7a	How sample size was determined	p.4,9	CSR Final Clinical Report Acute Phase; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 2 (approved 28 October 1996), pages 27-28; 3.13.2 Target Sample Size, page 49	Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF pages 3, 8-9. 42;	

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				paragraph 3; Appendix A, Protocol, Amendment #2 page 533, last line; Amendment #2, page 538-539; 9.2.2 Sample size determination, page 572 paragraphs 1-2;		
	7b	When applicable, explanation of any interim analyses and stopping guidelines	4	CSR Final Clinical Report Acute Phase; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 2 (approved 28 October 1996), pages 27-28; 3.13.2 Target Sample Size, page 49 paragraph 3; 3.13.4 Planned Efficacy Evaluations, page 49; Appendix A, Protocol, Amendment #2, page 538-539;	Clinical Report Acute Phase,Same pages; Appendix A Protocol, PDF pages 8-9;	
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49 paragraph 4; Appendix A, Protocol, 5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 555 paragraph 2;Appendix A, Randomisation Code, page 1431 to 1434; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 25; Appendix A, Protocol PDF pages 901-904; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	Clinical Report Acute Phase,Same pages; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; 3.5.3 Methods of	Clinical Report Acute Phase,Same pages; Appendix A, Protocol,	

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		sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		Blinding, page 35, paragraph 2-3; Appendix A, Protocol, 5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 555 paragraph 2; Blank Case Report Form (CRF), QUALIFICATION FOR ENTRY TO DOUBLE-BLIND PHASE, page 734; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 25 paragraph 2; Blank Case Report Form (CRF), QUALIFICATION FOR ENTRY TO DOUBLE-BLIND PHASE, page 204; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	Clinical Report Acute Phase,Same pages; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	p.9	CSR Final Clinical Report Acute Phase; 3.1.1 Protocol Amendments, Amendment 1, page 27, paragraph 3; Amendment 2, page 28, paragraph 2; 3.5.3 Methods of Blinding, page 35, paragraph 2-3; Final Clinical Report, Treatment and Administration, page 15, paragraph 3; Appendix A, Protocol, 5.2.3 Treatment Phase, Termination at end of acute study for non-responders, page 557, paragraph 5; 6.3 Blinding, page 559 paragraph 3;	Clinical Report Acute Phase,Same pages; PDF page Appendix A, pages 27, 29;	
	11b	If relevant, description of the	p.9	CSR Final Clinical Report Acute Phase; Report Synopsis, Treatment and	CSR Final Clinical Report Acute Phase,Same pages;	

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Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.10	CSR Final Clinical Report Acute Phase; Report Synopsis, Statistical Methods, page 16, paragraph 3; 3.13 Statistical Evaluation, page 48, paragraphs 6-7; 3.13.1 Comparison of Interest, page 49; 3.13.5 Methods of Analysis, page 50 paragraph 7-8 to page 51 paragraph 1-6; 3.13.6 Populations/Data Sets to be Evaluated, page 51 paragraph 7 to page 54 paragraph 1-3; 5.1 Efficacy Evaluation, 5.1.1 Data Sets Analyzed, page 71 paragraph 1-2; 5.2.4 Sustained Response, page 78 paragraph 1; Appendix A, Protocol, 9.2 Statistical Methods, 9.2.1 Comparisons of interest, page 571 paragraph 3; Protocol, 9.3 Efficacy Analysis, 9.3.1 Intent to Treat Analysis, 9.3.2 Patients Valid For The EfficacyAnalysis, page 572 paragraph 2	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 41; pages 42-43; page 43; pages 43-44; Statistical Report PDF pages 922-927; pages 928-949;	

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	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p.6-9 (methods for additional harms analysis);	CSR Final Clinical Report Acute Phase; page 15, paragraph 5; 3.1.1 Amendments, Amendment 2, page 27 paragraph 6 to page 28 paragraph 1; page 44, paragraph 3; 3.13.5 Methods of Analysis, page 50 paragraph 3; 5.1.1 Data Sets Analyzed, page 71 paragraph 1; 5.4 Efficacy Subgroup Analysis, page 89 paragraph 1 to page 90 paragraph 1-2; Appendix A, Statistical Report, 2.5 Covariate Analyses, page 1456 paragraph 6;	Clinical Report Acute Phase,Same pages; Appendix A, PDF page 926;	
Results						
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for	p.11 , Figure 1;	Final Clinical Report, Acute Phase, Report Synopsis, Patient Disposition and Key Demographic Data page 16 paragraph 4; Table Demographic and Clinical Characteristics at Entry page 17; Table Patient Disposition page 17; 4 Study Populations, 4.2 Patient Disposition, 4.2.1 Number and	Same page numbersin the PDF of Final Clinical Report, Acute Phase, Final Clinical Report, Continuation Phase, and Appendix B;	

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	13b	For each group, losses and exclusions after randomisation,together with reasons	p.11; Figure 1;	Final Clinical Report, Acute Phase, Report Synopsis, Patient Disposition and Key Demographic Data page 16 paragraph 4; Table Patient Disposition,page 17; 4 Study Populations, 4.2 Patient Disposition, 4.2.1 Number and Distribution of Patients, page 56 paragraph 2; Table 7, page 57; Table 8, page 58; 4.2.3 Withdrawal Reasons, page 58; Table 9, Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal, page 59; page 59; Table 10, Number and Cumulative Percentage of Patients Withdrawn from the Study by Reason and by Week, page 60; 4.3 Protocol Violations, pages 60-62; 6.7 Withdrawals for Adverse Experiences, page 110; Table 49,Treatment-emergent Adverse Experiences, Regardless of Attribution,	Same page numbersin the PDF of Final Clinical Report, Acute Phase, Final Clinical Report, Continuation Phase, and Appendix B;	

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				Experiences by Age Group-Non-gender Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 211-216; Table 16.10.2 Summary of Treatment-Emergent Adverse Experiences by Age Group-Male Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 217-219; 16.10.3 Summary of Treatment-Emergent Adverse Experiences by Age Group-Female Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 220-222; 16.12 Summary of Clinically Significant Abnormal Vital Signs by Treatment Group (Continuation Phase) (Intent to Treat Population) page 232; Table 16.12.1 Narratives for Patients with Vital Signs of Potential Clinical Concern pages 233-246; Table 16.14 Summary of Clinically Significant Abnormal Laboratory Values (Continuation Phase) (Intent to Treat Population) pages 259-260; Table 16.14.1 Narratives for Patients with Laboratory Values of Potential Clinical Concern pages 261-262;		
Discussion				Final Clinical Report, Acute Phase, Report Synopsis, Statistical Methods page 16 paragraph 3 (“No comparisons were made between paroxetine and imipramine.”); 3.13.1 Comparison of Interest page 49 paragraph 2 (“No comparisons were made between paroxetine and imipramine.”);	Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase;	

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				Continuation Study, Final Clinical Report, Report Synopsis, Efficacy Results, page 8 paragraph 6 (“The continuation phase of this study was not designed to analyze efficacy, as patients were not rerandomized at the end of the acute phase. In addition, only responders were to enter the continuation phase.”); Conclusion page 9 paragraph 2 (“However, with such a small sample size, in the absence of pre- and post-dose body mass index data, the clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.”); 7 Discussion, page 61 paragraph 1 (“However, the number of patients completing the additional six months of study medication in the continuation phase was small (18 in the paroxetine group and 13 each in the imipramine and placebo groups), which limits any conclusions that can be drawn regarding long-term efficacy.”);paragraph 2 (“Additionally, compliance in the continuation phase, defined as taking 80% to 120% of study medication over the course of the continuation phase, was less than ideal in all three treatment groups: 78.8% among paroxetine patients, 82.5% among imipramine patients and 72.7% among placebo patients. The small sample size along with poor compliance makes it difficult to draw meaningful conclusions about the results of the study.”); Safety:, page 62, paragraph 4 (“It is not unexpected for some adolescents to experience this degree of weight gain in an eight-month		

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				period."); Efficacy:, page 63 paragraph 1 ("In this continuation phase of the study, patients were not re-randomized, which would be necessary in order to establish long-term efficacy."), paragraph 3 ("Since the number of patients in each group was small, it is difficult to draw meaningful conclusions about any differences between the groups."); 8 Conclusions, page 64 ("However, with such a small sample size, in the absence of pre- and post-dose body mass index data, the clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.");		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p.4; p. 6-7; p. 8, Box 1; p.22-23; p.23-25, Box 2; p. 25; p.25-26, Box 3;			
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p.23-25, Box 2; p.25-26, Box 3;	Final Clinical Report, Acute Phase, Report Synopsis, Conclusions, page 21; 8 Conclusions, page 124; Continuation Study, Final Clinical Report, Report Synopsis, Conclusions, page 9; 8 Conclusions, page 64;	Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase;	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other	p.22-23; p. 25;	Final Clinical Report, Acute Phase, Report Synopsis, Conclusions page 21 paragraph 2; 7 Discussion, page 121-123;8 Conclusions, page 124; Continuation Study, Final Clinical Report, Report Synopsis, Conclusions, page 9; 7 Discussion, pages 61-63; 8 Conclusions,	Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase;	

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		relevant evidence		page 64;		
Other information						
Registration	23	Registration number and name of trial registry	p.26;	SmithKline Beecham study 29060/329, Final Clinical Report Acute Phase, page 1; SmithKline Beecham study 29060/329, Final Clinical Report, Addendum to Study Report–Continuation Phase, page 1;	Final Clinical Report Acute Phase, page 1; Final Clinical Report, Continuation Phase, page 1;	
Protocol	24	Where the full trial protocol can be accessed, if available	p.2, 26, 27 (references 7 and 8);	SmithKline Beecham study 29060/329, Final Clinical Report Acute Phase, Appendix A, Protocol, from page 531;	Final Clinical Report Acute Phase, Appendix A, Protocol, from PDF page 1;	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p.26;	SmithKline Beecham study 29060/329, Final Clinical Report Acute Phase, page 1; Supply of drugs: Final Clinical Report, Report Synopsis, Treatment and Administration, Test product, Reference therapies, page 15, paragraph 1-2; 3 Methodology, 3.5 Treatments and Administration,3.5 Treatments and Administration, 3.5.1 Study Medication, Table 2 Appearance, Formulation, Dosage Strengths, and Batch Numbers of Study Medication, page 32, paragraph 1; Role of funders: Final Clinical Report, 3.2 Investigators, page 28, paragraph 3-5 to page 29, paragraph 1; Role of funders:3 Methodology, 3.5 Treatments and Administration,3.5.3 Methods of Blinding, page 35, paragraph 3; Role of funders: 3.10 Safety Assessments, 3.10.1 Adverse Experiences, Serious Adverse Experiences, page 45 paragraph 2; 3.12 Data Quality Assurance, page 47 paragraph 5 to page 48 paragraph 1-5; Role of funders: Final Clinical Report Acute Phase, Appendix	Same page numbers for PDF Final Clinical Report Acute Phase andFinal Clinical Report, Continuation Phase;Final Clinical Report Acute Phase, Appendix A, Protocol, PDF pages 7, 9, 21;Appendix A, Protocol, PDF page 25; Final Clinical Report Acute Phase, Appendix A, Protocol, PDF page 26; Appendix A, Protocol, PDF pages 36, 37; Clinical Report Acute Phase, Appendix A, Protocol, PDF page 38; Clinical Report Acute Phase, Appendix A, Protocol, PDF page 38; Clinical Report Acute Phase, Appendix A, Protocol,	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
				A, Protocol,Amendment #1 Approved: April17, 1994, Section 7.5.2, page 537; Amendment #2 Approved: October 28, 1996, Section 7.5.2, page 539, paragraph 5; 5.0 CONDUCT OF STUDY,5.1 Ethical Considerations, 5.1.1 Ethics Review Committee (ERC)/Institutional Review Board (IRB), page 551, paragraphs 3, 4;Appendix A, Protocol, 5.2.2 Randomization, page 555 paragraph 2; Final Clinical Report Acute Phase, Appendix A, Protocol, 5.2.3 Treatment Phase, Assessments during study visits, Serum Levels, page 556 paragraph 3-4; 7.0 ADVERSE EXPERIENCES, 7.4 Following-up of Adverse Experiences, page 566; 7.5 Serious Adverse Experiences, 7 .5.2 Reporting Serious Adverse Experiences, page 567; Final Clinical Report Acute Phase, Appendix A, Protocol, 7.6 Overdosage, page 568 paragraph 1; Final Clinical Report Acute Phase, Appendix A, Protocol, 7.7 Pregnancy, page 568 paragraph 4; Final Clinical Report Acute Phase, Appendix A, Protocol, 7.8 Breaking the Study Blind, page 568 paragraph 5; 10.0 ADMINISTRATIVE MATTERS, page 575; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, II. PROTOCOL AMENDMENTS, page 585 paragraph 5; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, III. SPONSOR'S TERMINATION OF STUDY, page 585 paragraph 7; Final Clinical Report Acute Phase, Appendix	PDF page 38;Appendix A, Protocol, PDF page 45; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, II. PROTOCOL AMENDMENTS, PDF page 55 ; PDF pages 56-57; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, MONITORING BY SMITHKLINE BEECHAM (i.e. the Sponsor), PDF page 57; PDF pages 57; pages 57-58; PDF pages 58-59; PDF page 905-916; PDF page 950-952;	

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				A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, IV. CASE REPORT FORM INSTRUCTIONS, page 586 to page 587 paragraph 1-2; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, V. MONITORING BY SMITHKLINE BEECHAM (i.e. the Sponsor), page 587 paragraph 3-4; VI. ARCHIVING OF DATA, page 587 paragraph 6-7; VII. AUDITS, page 587 paragraph 8 to page 588 paragraph 1-4; VIII. CONFIDENTIALITY AND PUBLICATION, page 588 paragraph 5-6 to page 589 paragraph 1-3; Certificates of Analysis, page 1435-1446; Audited Investigator Sites, page 1480-1482;SmithKline Beecham study 29060/329, Final Clinical Report, Addendum to Study Report Continuation Phase, page 1; 3.3 Study Medication and Administration, page 20; 3.5 Method of Randomization, page 22;		

*The aim of this audit tool is provide a permanent record of the parts of text, tables and figures of the source Clinical Study Report (CSR) selected for inclusion into the RIAT manuscript submitted for publication. This tool is based upon checklist items described in the CONSORT 2010 statement, which is a widely adopted standard for reporting randomised trials. RIAT authors should consult the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. Similar audit records can be created for other types of trials by adapting other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See www.consort-statement.org for more details.

**Note that Appendix A contains the study Protocol, which itself includes APPENDIX A to APPENDIX G. The CSR appendices are written with lower case letters except for the first letter, which is upper case (Appendix A, Appendix B, etc.); the appendices of Appendix A are written with upper case letters entirely (ex. APPENDIX A, APPENDIX B, etc.).

***All CSR Final Clinical Report PDF page numbers are the same as the document page numbers.

Appendix 2

List of tables

Table i – Breakdown of new adverse events found during Study 329 audit by System Organ Class (SOC) (MedDRA)

SOC	Adverse event	Paroxetine N=31		Imipramine N=40		Placebo N=22	
		No. found in audit	Estimate of total additional AEs	No. found in audit	Estimate of total additional AEs	No. found in audit	Estimate of total additional AEs
Psychiatric disorders	Suicidal ideation	2	+6	0	0	1	+4
	Feelings of hopelessness	1	+3	0	0	0	0
	Self harm/suicidal gesture	1	+3	0	0	0	0
	Depression worsening	2	+6	0	0	1	+4
	Psychosis	1	+3	0	0	0	0
	Increased anger/aggression	1	+3	0	0	0	0
	Insomnia	1	+3	0	0	0	0
	Agitation	1	+3	0	0	0	0
	Somnolence	0	0	0	0	0	0
	Nervousness	0	0	1	+2.4	0	0
	Decreased concentration	0	0	0	0	1	+4
	Mutism/soft speech	2	+6	0	0	0	0
	Increased anxiety	0	0	0	0	1	+4
	Total	**12**	**+36**	**1**	**+2.4**	**4**	**+16**
Gastrointestinal disorders	Nausea	1	+3	1	+2.4	2	+8
	Gastrointestinal complaints	1	+3	0	0	0	0
	Increased sickness	1	+3	0	0	0	0
	Diarrhoea	1	+3	1	+2.4	0	0
	Vomiting	0	0	1	+2.4	0	0
	Heartburn	0	0	1	+2.4	0	0
	Total	**4**	**+12**	**4**	**+10**	**2**	**+8**
Metabolism and nutrition disorders	Loss of appetite	1	+3	0	0	0	0
	Weight loss	2	+6	0	0	0	0
	Dehydration	0	0	1	+2.4	0	0
	Total	**3**	**+9**	**1**	**+2.4**	**0**	**0**
Musculoskeletal and connective tissue disorders	Neck pain	0	0	0	0	1	+4
	Joint pain	0	0	0	0	1	+4
	Total	**0**	**0**	**0**	**0**	**2**	**+8**
General disorders and administration site conditions	Fatigue	4	+12	1	+2.4	0	0
	Headache	0	0	2	+5	0	0
	Body shakes	0	0	1	+2.4	0	0
	Fever	0	0	0	0	1	+4
	Total	**4**	**+12**	**4**	**+10**	**1**	**+4**
Respiratory, thoracic and mediastinal disorders	Chest congestion	0	0	1	+2.4	0	0
	Cough	0	0	0	0	1	+4
	Total	**0**	**0**	**1**	**+2.4**	**1**	**+4**
Cardiac disorders	Tachycardia	0	0	0	0	0	0
	Dizziness	0	0	3	+7	0	0
	Low systolic BP	0	0	1	+2.4	0	0
	High BP	0	0	1	+2.4	0	0
	Total	**0**	**0**	**5**	**+12**	**0**	**0**
Skin and subcutaneous tissue disorders	Sweating	0	0	1	+2.4	0	0
	Total	**0**	**0**	**1**	**+2.4**	**0**	**0**
Total Psychiatric disorders		**12**	**+36**	**1**	**+2.4**	**4**	**+16**
TOTAL ALL OTHER AES		**11**	**+33**	**16**	**+39**	**6**	**+24**
GRAND TOTAL		**23**	**+69**	**17**	**+42**	**10**	**+40**

NB. All AEs found for the paroxetine and imipramine patients were reported during the acute phase. For the placebo group, 2 additional AEs were found during the continuation phase (these were ‘depression worsening’ & ‘increased irritability’).

Table ii – Summary of all adverse events by SOC (plus estimate of total AEs based on findings from audit)

	Paroxetine N=93		Imipramine N=95		Placebo N=87	
System Organ Class (MedDRA)	Reanalysis – CSR check only	Estimate following CRF audit	Reanalysis – CSR check only	Estimate following CRF audit	Reanalysis – CSR check only	Estimate following CRF audit
Cardiac disorders & Vascular disorders	45	45	131	143	32	32
GI disorders	112	124	147	157	79	87
Psychiatric disorders	101	137	63	65	24	40
Nervous system disorders	41	41	54	54	21	21
Respiratory, thoracic and mediastinal disorders	42	42	22	24.4	39	43
General disorders	74	86	69	79	73	77
Skin and subcutaneous tissue disorders	10	10	17	19.4	10	10
Renal and urinary disorders	5	5	9	9	4	4
Immune system disorders	2	2	2	2	3	3
Endocrine disorders	1	1	1	1	1	1
Blood and lymphatic system disorders	1	1	4	4	3	3
Musculoskeletal disorders	8	8	7	7	16	24
Reproductive system and breast disorders	4	4	4	4	4	4
Infections	6	6	5	5	4	4
Eye disorders	5	5	4	4	1	1
Metabolism and nutrition disorders	17	26	6	8.4	10	10
Ear and labyrinth disorders	1	1	0	0	0	0
Injury, poisoning and procedural complications	3	3	3	3	6	6
Pregnancy, puerperium and perinatal conditions	0	0	2	2	0	0
Surgical and medical procedures	1	1	2	2	0	0
TOTAL NUMBER OF AEs	**479**	**548**	**552**	**593**	**330**	**370**

Table iii – Full breakdown of all adverse events within each SOC

SOC	MedDRA Term	Paroxetine N=93		Imipramine N=95		Placebo N=87	
		Reanalysis – CSR check only	Estimate following CRF audit	Reanalysis – CSR check only	Estimate following CRF audit	Reanalysis – CSR check only	Estimate following CRF audit
Cardiac disorders & Vascular disorders	Atrial ectopic	0	0	0	0	1	1
	AV block	1	1	2	2	2	2
	Bradycardia	0	0	0	0	1	1
	Bundle branch block	0	0	1	1	1	1
	Chest pain	2	2	5	5	2	2
	Dizziness	35	35	57	64	18	18
	ECG/ T-ECG abnormal	0	0	7	7	2	2
	Hot flush	0	0	6	6	2	2
	NIL	0	0	2	2	1	1
	Postural hypotension/ hypotension	3	3	17	19.4	1	1
	QT interval prolonged	0	0	3	3	0	0
	Tachycardia	3	3	28	28	1	1
	Hypertension	0	0	2	4.4	0	0
	Migraine	1	1	1	1	0	0
	TOTAL	**45**	**45**	**131**	**143**	**32**	**32**
Gastrointestinal disorders	Abdominal pain	0	0	0	0	2	2
	Constipation	7	7	10	10	4	4
	Cramps	14	14	11	11	14	14
	Diarrhea	12	15	8	10.4	9	9
	Dry Mouth	20	20	48	48	12	12
	Dyspepsia/ heartburn	8	8	12	14.4	4	4
	Food poisoning	1	1	0	0	1	1
	Gastroenteritis/ GI complaints	0	3	1	1	0	0
	Nausea/ sickness	37	43	43	45.4	27	35
	Reflux	1	1	0	0	0	0
	Retching	0	0	1	1	0	0
	Sores	0	0	0	0	1	1
	Stomatitis	0	0	2	2	0	0
	Ulcer	1	1	0	0	0	0
	Vomiting	11	11	11	13.4	5	5
	TOTAL	**112**	**124**	**147**	**157**	**79**	**87**
Psychiatric disorders	Abnormal dreams	3	3	5	5	2	2
	Aggravated depression	5	11	3	3	2	6
	Aggression/ increased anger	7	10	3	3	0	0
	Agitation	0	3	1	1	0	0
	Akathisia	18	18	12	12	8	8
	Anorgasmia	1	1	0	0	0	0
	Anxiety	2	2	0	0	1	5
	Concentration low	2	2	1	1	0	4
	Depersonalisation	0	0	1	1	1	1

	Disinhibition	4	4	1	1	2	2
	Drug withdrawal syndrome	2	2	0	0	0	0
	Hallucination	1	1	1	1	0	0
	Hopelessness (feelings of)	0	3	0	0	0	0
	Insomnia	16	19	14	14	4	4
	Nervousness	0	0	0	2.4	0	0
	Mutism/soft speech	0	6	0	0	0	0
	Paranoia	1	1	0	0	0	0
	Psychosis	1	4	0	0	0	0
	Somnolence	24	24	14	14	3	3
	Substance abuse	1	1	1	1	0	0
	Suicidal ideation	4	10	3	3	1	5
	Suicide attempt	9	12	3	3	0	0
	TOTAL	**101**	**137**	**63**	**65**	**24**	**40**
Nervous System Disorders	Bad taste	0	0	3	3	0	0
	Convulsion	0	0	1	1	0	0
	Dystonia	5	5	7	7	3	3
	Laryngitis dystonia	1	1	0	0	0	0
	Memory loss	0	0	1	1	0	0
	Myoclonus	4	4	1	1	0	0
	Paresthesia	1	1	1	1	0	0
	Sore throat-dystonia	10	10	12	12	11	11
	Tics	1	1	1	1	0	0
	Tinnitus	0	0	2	2	0	0
	Toothache dystonia	6	6	0	0	3	3
	Tremor	11	11	20	20	2	2
	Vision blurred	2	2	5	5	2	2
	TOTAL	**41**	**41**	**54**	**54**	**21**	**21**
Respiratory, thoracic and mediastinal disorders	Chest cold/ congestion	11	11	6	8.4	14	14
	Coughing	6	6	4	4	6	10
	Dyspnea	3	3	5	5	2	2
	Epistaxis	1	1	1	1	0	0
	Nasopharyngitis	3	3	0	0	1	1
	Respiratory disorder	0	0	0	0	2	2
	Rhinitis	10	10	3	3	5	5
	Sinusitis	8	8	3	3	8	8
	Sneezing	0	0	0	0	1	1
	TOTAL	**42**	**42**	**22**	**24.4**	**39**	**43**
General disorders and administration site conditions	Body Shakes	0	0	0	2.4	0	0
	Fatigue	15	27	8	10.4	11	11
	Fever	0	0	2	2	4	8
	Headache	59	59	59	64	56	56
	Pain	0	0	0	0	2	2
	TOTAL	**74**	**86**	**69**	**79**	**73**	**77**
Skin and subcutaneous tissue disorders	Acne	3	3	2	2	1	1
	Dermatitis	1	1	2	2	1	1
	Itchy	0	0	1	1	1	1
	Rash	4	4	5	5	4	4
	Scabies	0	0	0	0	1	1
	Sweating	2	2	7	9.4	1	1
	Syncope	0	0	0	0	1	1

	TOTAL	**10**	**10**	**17**	**19.4**	**10**	**10**
Renal and urinary disorders	Albuminuria	0	0	0	0	4	4
	Cystitis	1	1	0	0	0	0
	Nocturia	0	0	1	1	0	0
	Polyuria	0	0	1	1	0	0
	Pyuria	0	0	1	1	0	0
	Urinary abnormality	3	3	0	0	0	0
	Urinary retention	0	0	6	6	0	0
	UTI	1	1	0	0	0	0
	TOTAL	**5**	**5**	**9**	**9**	**4**	**4**
Immune system disorders	Allergy	1	1	1	1	3	3
	Urticaria	1	1	1	1	0	0
	TOTAL	**2**	**2**	**2**	**2**	**3**	**3**
Endocrine disorders	Amenorrhea	1	1	0	0	0	0
	Hyperglycemia	0	0	1	1	1	1
	TOTAL	**1**	**1**	**1**	**1**	**1**	**1**
Blood and lymphatic system disorders	Anemia	1	1	1	1	0	0
	Eosinophilia	0	0	1	1	1	1
	Leukopenia	0	0	2	2	0	0
	Lymphadenopathy	0	0	0	0	1	1
	Thrombocythemia	0	0	0	0	1	1
	TOTAL	**1**	**1**	**4**	**4**	**3**	**3**
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1	1	4	8
	Back pain	5	5	2	2	10	14
	Chills	0	0	3	3	0	0
	Myalgia	2	2	1	1	2	2
	TOTAL	**8**	**8**	**7**	**7**	**16**	**24**
Reproductive system and breast disorders	Breast enlargement	1	1	0	0	0	0
	Dysmenorrhea	3	3	4	4	4	4
	TOTAL	**4**	**4**	**4**	**4**	**4**	**4**
Infections	Herpes zoster	0	0	0	0	1	1
	Infection	4	4	3	3	3	3
	Otitis media	2	2	2	2	0	0
	TOTAL	**6**	**6**	**5**	**5**	**4**	**4**
Eye disorders	Conjunctivitis	2	2	0	0	1	1
	Itchy eyes	2	2	1	1	0	0
	Mydriasis	0	0	1	1	0	0
	Photosensitivity	1	1	1	1	0	0
	Photopsia	0	0	1	1	0	0
	TOTAL	**5**	**5**	**4**	**4**	**1**	**1**
Metabolism and nutrition disorders	Decreased appetite	9	12	2	2	4	4
	Dehydration	0	0	0	2.4	0	0
	Increased appetite	4	4	1	1	1	1
	Thirst	0	0	2	2	3	3
	Weight gain	2	2	0	0	0	0
	Weight loss	2	8	1	1	2	2
	TOTAL	**17**	**26**	**6**	**8.4**	**10**	**10**
Ear and	Ear pain	1	1	0	0	0	0

labyrinth disorders	**TOTAL**	**1**	**1**	**0**	**0**	**0**	**0**
Injury, poisoning and procedural complications	Head injury	0	0	1	1	0	0
	Overdose	0	0	1	1	0	0
	Trauma	3	3	1	1	6	6
	TOTAL	**3**	**3**	**3**	**3**	**6**	**6**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0	2	2	0	0
	TOTAL	**0**	**0**	**2**	**2**	**0**	**0**
Surgical and medical procedures	Tooth extraction	1	1	2	2	0	0
	TOTAL	**1**	**1**	**2**	**2**	**0**	**0**
TOTAL NUMBER OF AEs		**479**	**548**	**552**	**593**	**330**	**370**

Table iv – Adverse events during taper phase only

SOC	MedDRA Term	Paroxetine N=19		Imipramine N=32		Placebo N=9	
		No. AEs reported (CSR check)	No. reported as 'Severe'	No. AEs reported (CSR check)	No. reported as 'Severe'	No. AEs reported (CSR check)	No. reported as 'Severe'
Cardiac disorders & Vascular disorders	AV block	1	0	0	0	0	0
	Chest pain	0	0	1	0	0	0
	Dizziness	3	0	2	0	0	0
	ECG/ T-ECG abnormal	0	0	1	0	0	0
	QT interval prolonged	0	0	1	0	0	0
	Tachycardia	0	0	2	0	0	0
	TOTAL	**4**	**0**	**7**	**0**	**0**	**0**
Gastrointestinal disorders	Constipation	1	0	2	0	0	0
	Dry mouth	0	0	1	0	0	0
	Diarrhea	0	0	2	0	0	0
	Dysepsia	0	0	3	0	0	0
	Cramps	1	0	0	0	1	0
	Gastroenteritis	0	0	1	1	0	0
	Nausea/ sickness	4	2	6	1	1	0
	Sores	0	0	0	0	1	
	Ulcer	1	1	0	0	0	0
	Vomiting	2	1	3	2	1	0
	TOTAL	**9**	**4**	**18**	**4**	**4**	**0**
Psychiatric disorders	Aggravated depression	0	0	0	0	1	1
	Aggression	2	1	0	0	0	0
	Akathisia	2	1	1	0	0	0
	Concentration low	1	0	0	0	0	0
	Drug withdrawal syndrome	2	1	0	0	0	0
	Insomnia	1	0	0	0	0	0
	Paranoia	1	0	0	0	0	0
	Somnolence	1	0	0	0	0	0
	Substance abuse	1	1	0	0	0	0
	Suicidal ideation/gesture	2	2	1	0	0	0
	Suicide attempt	2	1	0	0	0	0
	TOTAL	**15**	**7**	**2**	**0**	**1**	**1**
Nervous System Disorders	Convulsion	0	0	1	1	0	0
	Sore throat-dystonia	1	0	1	0	0	0
	Tremor	1	0	0	0	0	0
	Vision blurred	1	0	0	0	0	0
	TOTAL	**3**	**0**	**2**	**1**	**0**	**0**
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	0	0	0	0	0
	Rhinitis	2	0	0	0	0	0
	Sinusitis	0	0	1	0	0	0
	TOTAL	**3**	**0**	**1**	**0**	**0**	**0**
General disorders and administration	Fatigue	1	0	1	0	0	0
	Headache	4	1	7	1	0	0
	TOTAL	**5**	**1**	**8**	**1**	**0**	**0**

site conditions							
Renal and urinary disorders	Albuminuria	0	0	0	0	2	0
	Pyuria	0	0	1	0	0	0
	Urinary abnormality	2	0	0	0	0	0
	UTI	1	0	0	0	0	0
	TOTAL	**3**	**0**	**1**	**0**	**2**	**0**
Immune system disorders	Urticaria	0	0	1	0	0	0
	TOTAL	**0**	**0**	**1**	**0**	**0**	**0**
Endocrine disorders	Hyperglycemia	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
Blood and lymphatic system disorders	Anemia	1	0	1	0	0	0
	Eosinophilia	0	0	1	0	0	0
	Thrombocythemia	0	0	0	0	1	0
	TOTAL	**1**	**0**	**2**	**0**	**1**	**0**
Musculoskeletal and connective tissue disorders	Arthralgia	0	0	1	0	0	0
	Back pain	0	0	0	0	1	0
	Myalgia	0	0	1	0	0	0
	TOTAL	**0**	**0**	**2**	**0**	**1**	**0**
Reproductive system and breast disorders	Dysmenorrhea	1	0	0	0	0	0
	TOTAL	**1**	**0**	**0**	**0**	**0**	**0**
Infections	Otitis media	0	0	1	0	0	0
	TOTAL	**0**	**0**	**1**	**0**	**0**	**0**
Metabolism and nutrition disorders	Decreased appetite	0	0	0	0	1	0
	Increased appetite	1	0	0	0	0	0
	Weight gain	2	0	0	0	0	0
	TOTAL	**3**	**0**	**0**	**0**	**1**	**0**
Injury, poisoning and procedural complications	Overdose	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0	1	1	0	0
	TOTAL	**0**	**0**	**1**	**1**	**0**	**0**
		Total AEs	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**
TOTAL NUMBER OF AEs		**47**	**12**	**48**	**9**	**10**	**1**

Table v – Summary of adverse events occurring during taper phase only

SOC	Paroxetine N=19		Imipramine N=32		Placebo N=9	
	No. AEs reported (CSR check)	No. reported as 'Severe'	No. AEs reported (CSR check)	No. reported as 'Severe'	No. AEs reported (CSR check)	No. reported as 'Severe'
Cardiac disorders & Vascular disorders	4	0	7	0	0	0
Gastrointestinal disorders	9	4	18	4	4	0
Psychiatric disorders	15	7	2	0	1	1
Nervous System Disorders	3	0	2	1	0	0
Respiratory, thoracic and mediastinal disorders	3	0	1	0	0	0
General disorders and administration site conditions	5	1	8	1	0	0
Renal and urinary disorders	3	0	1	0	2	0
Immune system disorders	0	0	1	0	0	0
Endocrine disorders	0	0	1	1	0	0
Blood and lymphatic system disorders	1	0	2	0	1	0
Musculoskeletal and connective tissue disorders	0	0	2	0	1	0
Reproductive system and breast disorders	1	0	0	0	0	0
Infections	0	0	1	0	0	0
Metabolism and nutrition disorders	3	0	0	0	1	0
Injury, poisoning and procedural complications	0	0	1	1	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1	1	0	0
	Total AEs	TOTAL SAEs	Total AEs	TOTAL SAEs	Total AEs	TOTAL SAEs
TOTAL NUMBER OF AEs	47	12	48	9	10	1

Table vi – Total number of adverse events classed as 'Severe' by investigator – events provided in Appendix D only

SOC	MedDRA Term	Paroxetine N=93		Imipramine N=95		Placebo N=87	
		No. reported in Appendix D	No. reported as 'Severe'	No. reported in Appendix D	No. reported as 'Severe'	No. reported in Appendix D	No. reported as 'Severe'
Cardiac disorders & Vascular disorders	Atrial ectopic	0	-	0	-	1	0
	AV block	1	0	2	0	2	0
	Bradycardia	0	-	0	-	1	0
	Bundle branch block	0	-	1	0	1	0
	Chest pain	2	1	5	1	2	0
	Dizziness	35	0	57	1	18	0
	ECG/ T-ECG abnormal	0	-	7	0	2	0
	Hot flush	0	-	6	0	2	0
	NIL	0	-	2		1	
	Postural hypotension/ hypotension	3	0	17	0	1	0
	QT interval prolonged	0	-	3	0	0	-
	Tachycardia	3	0	28	1	1	0
	Hypertension	0	-	2	0	0	-
	Migraine	1	0	1	1	0	-
	TOTAL	**45**	**1**	**131**	**4**	**32**	**0**
Gastrointestinal disorders	Abdominal pain	0	-	0	-	2	0
	Constipation	7	0	10	2	4	0
	Cramps	14	1	11	0	14	0
	Diarrhea	12	6	8	3	9	0
	Dry Mouth	20	0	48	2	12	1
	Dyspepsia/ heartburn	8	0	12	0	4	0
	Food poisoning	1	0	0	-	1	1
	Gastroenteritis/ GI complaints	0	-	1	1	0	-
	Nausea/ sickness	37	10	43	5	27	2
	Reflux	1	0	0	-	0	-
	Retching	0	-	1	0	0	-
	Sores	0	-	0	-	1	0
	Stomatitis	0	-	2	2	0	-
	Ulcer	1	1	0	0	0	0
	Vomiting	11	7	11	5	5	0
	TOTAL	**112**	**25**	**147**	**20**	**79**	**4**
Psychiatric disorders	Abnormal dreams	3	0	5	0	2	0
	Aggravated depression	5	3	3	0	2	1
	Aggression/ increased anger	7	3	3	2	0	-
	Agitation	0	-	1	0	0	-
	Akathisia	18	1	12	1	8	0
	Anorgasmia	1	1	0	-	0	-
	Anxiety	2	1	0	-	1	1
	Concentration low	2	0	1	0	0	-
	Depersonalisatio	0	-	1	0	1	0

	n						
	Disinhibition	4	3	1	0	2	1
	Drug withdrawal syndrome	2	1	0	-	0	-
	Hallucinations	1	1	1	1	0	-
	Hopelessness (feelings of)	0	-	0	-	0	-
	Insomnia	16	2	14	0	4	1
	Nervousness	0		0	-	0	-
	Paranoia	1	0	0	-	0	-
	Psychosis	1	1	0	-	0	-
	Somnolence	24	6	14	0	3	0
	Substance abuse	1	1	1	0	0	-
	Suicidal ideation/gesture	4	4	3	0	1	1
	Suicide attempt	9	4	3	0	0	-
	TOTAL	**101**	**32**	**63**	**4**	**24**	**5**
Nervous System Disorders	Bad taste	0	-	3	0	0	-
	Convulsion	0	-	1	1	0	-
	Dystonia	5	0	7	0	3	0
	Laryngitis dystonia	1	0	0	-	0	-
	Memory loss	0	-	1	0	0	-
	Myoclonus	4	1	1	0	0	-
	Paresthesia	1	0	1	0	0	-
	Sore throat-dystonia	10	1	12	1	11	2
	Tics	1	0	1	0	0	-
	Tinnitus	0	-	2	0	0	-
	Toothache dystonia	6	1	0	-	3	1
	Tremor	11	1	20	1	2	0
	Vision blurred	2	0	5	1	2	0
	TOTAL	**41**	**4**	**54**	**4**	**21**	**3**
Respiratory, thoracic and mediastinal disorders	Chest cold/ congestion	11	1	6	0	14	1
	Coughing	6	0	4	0	6	0
	Dyspnea	3	1	5	1	2	0
	Epistaxis	1	0	1	0	0	-
	Nasopharyngitis	3	0	0	-	1	0
	Respiratory disorder	0		0	-	2	0
	Rhinitis	10	0	3	0	5	1
	Sinusitis	8	0	3	0	8	2
	Sneezing	0	-	0	-	1	0
	TOTAL	**42**	**2**	**22**	**1**	**39**	**4**
General disorders and administration site conditions	Body Shakes	0	-	0	-	0	-
	Fatigue	15	2	8	1	11	1
	Fever	0	-	2	0	4	0
	Headache	59	3	59	9	56	4
	Pain	0	-	0	-	2	0
	TOTAL	**74**	**5**	**69**	**10**	**73**	**5**
Skin and subcutaneous tissue disorders	Acne	3	0	2	0	1	0
	Dermatitis	1	0	2	0	1	0
	Itchy	0	-	1	0	1	1
	Rash	4	0	5	1	4	0
	Scabies	0	-	0	-	1	0
	Sweating	2	0	7	0	1	0
	Syncope	0	-	0	-	1	0

	TOTAL	**10**	**0**	**17**	**1**	**10**	**1**
Renal and urinary disorders	Albuminuria	0	-	0	-	4	0
	Cystitis	1	0	0	-	0	-
	Nocturia	0	-	1	0	0	-
	Polyuria	0	-	1	0	0	-
	Pyuria	0	-	1	0	0	-
	Urinary abnormality	3	0	0	-	0	-
	Urinary retention	0	-	6	1	0	-
	UTI	1	0	0	-	0	-
	TOTAL	**5**	**0**	**9**	**1**	**4**	**0**
Immune system disorders	Allergy	1	0	1	0	3	0
	Urticaria	1	0	1	0	0	-
	TOTAL	**2**	**0**	**2**	**0**	**3**	**0**
Endocrine disorders	Amenorrhea	1	0	0	-	0	-
	Hyperglycemia	0	-	1	1	1	0
	TOTAL	**1**	**0**	**1**	**1**	**1**	**0**
Blood and lymphatic system disorders	Anemia	1	0	4	0	0	-
	Eosinophilia	0	-	1	0	1	0
	Leukopenia	0	-	2	0	0	-
	Lymphadenopathy	0	-	0	-	1	0
	Thrombocythemia	0	-	0	-	1	0
	TOTAL	**1**	**0**	**4**	**0**	**3**	**0**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0	1	0	4	0
	Back pain	5	0	2	0	10	0
	Chills	0	-	3	0	0	-
	Myalgia	2	0	1	0	2	0
	TOTAL	**8**	**0**	**7**	**0**	**16**	**0**
Reproductive system and breast disorders	Breast enlargement	1	0	0	-	0	-
	Dysmenorrhea	3	0	4	1	4	1
	TOTAL	**4**	**0**	**4**	**1**	**4**	**1**
Infections	Herpes zoster	0	-	0	-	1	0
	Infection	4	0	3	1	3	1
	Otitis media	2	1	2	0	0	-
	TOTAL	**6**	**1**	**5**	**1**	**4**	**1**
Eye disorders	Conjunctivitis	2	0	0	-	1	0
	Itchy eyes	2	0	1	0	0	-
	Mydriasis	0	-	1	0	0	-
	Photosensitivity	1	0	1	0	0	-
	Photopsia	0	-	1	0	0	-
	TOTAL	**5**	**0**	**4**	**0**	**1**	**0**
Metabolism and nutrition disorders	Decreased appetite	9	0	2	0	4	0
	Dehydration	0	-	0	-	0	-
	Increased appetite	4	0	1	0	1	0
	Thirst	0	-	2	0	3	0
	Weight gain	2	0	0	-	0	-
	Weight loss	2	0	1	0	2	1
	TOTAL	**17**	**0**	**6**	**0**	**10**	**1**
Ear and	Ear pain	1	0	0	-	0	-

labyrinth disorders	**TOTAL**	**1**	**0**	**0**	**-**	**0**	**-**
Injury, poisoning and procedural complications	Head injury	0	-	1	0	0	-
	Overdose	0	-	1	1	0	-
	Trauma	3	0	1	0	6	0
	TOTAL	**3**	**0**	**3**	**1**	**6**	**0**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	-	2	1	0	-
	TOTAL	**0**	**-**	**2**	**1**	**0**	**-**
Surgical and medical procedures	Tooth extraction	1	0	2	0	0	-
	TOTAL	**1**	**0**	**2**	**0**	**0**	**-**
		Total AEs	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**	**Total AEs**	**TOTAL SAEs**
TOTAL NUMBER OF AEs		**479**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**25 (7.6%)**

Table vii – Summary of 'Severe' adverse events (all SOCs)

SOC	Paroxetine N=93		Imipramine N=95		Placebo N=87	
	Total no. AEs reported in Appendix D	No. reported as 'Severe'	Total no. AEs reported in Appendix D	No. reported as 'Severe'	Total no. AEs reported in Appendix D	No. reported as 'Severe'
Cardiac disorders & Vascular disorders	45	1 (2.2%)	131	4 (3.1%)	32	0
Gastrointestinal disorders	112	25 (24%)	147	20 (13.6%)	79	4 (5.1%)
Psychiatric disorders	101	32 (31.7%)	63	4 (6.3%)	24	5 (20.8%)
Nervous System Disorders	41	4 (9.8%)	54	4 (7.4%)	21	3 (14.3%)
Respiratory, thoracic and mediastinal disorders	42	2 (4.8%)	22	1 (4.5%)	39	4 (10.3%)
General disorders and administration site conditions	74	5 (6.8%)	69	10 (14.5%)	73	5 (6.8%)
Skin and subcutaneous tissue disorders	10	0	17	1 (5.9%)	10	1 (10%)
Renal and urinary disorders	5	0	9	1 (11.1%)	4	0
Immune system disorders	2	0	2	0	3	0
Endocrine disorders	1	0	1	1 (100%)	1	0
Blood and lymphatic system disorders	1	0	4	0	3	0
Musculoskeletal and connective tissue disorders	8	0	7	0	16	0
Reproductive system and breast disorders	4	0	4	1 (25%)	4	1 (25%)
Infections	6	1 (16.7%)	5	1 (20%)	4	1 (25%)
Eye disorders	5	0	4	0	1	0
Metabolism and nutrition disorders	17	0	6	0	10	1 (10%)
Ear & Labyrinth Disorders	1	0	0	-	0	-
Injury, poisoning and procedural complications	3	0	3	1 (33.3%)	6	0
Pregnancy, puerperium and perinatal conditions	0	-	2	1 (50%)	0	-
Surgical and medical procedures	1	0	2	0	0	-
TOTAL NUMBER OF AEs	**479**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**25 (7.6%)**

Table viii – Changes to 'reasons for discontinuation' during acute (plus taper) phase

a) Paroxetine group

TAPER PHASE: In total, 67 patients completed the 8 week acute phase. Of these, 16 were discontinued at the 8 week visit. The proposed changes to the reasons for discontinuation are given for each below:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.001.00068	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00206	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00081	Lack of Efficacy	OTHER (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00089	Lack of Efficacy	AE (mania)	Became manic around wk4 (04 Apr 95), dose reduced wk7 (26 Apr 95) with note 'side effect manic' – p222 CRF), down-titrated & withdrawn week 8.
329.003.00248	Lack of Efficacy	Lack of Efficacy	Abnormal blood around same time as down-titration- but investigator deemed 'mild' & 'unrelated'. Experienced 'severe' withdrawal symptoms.
329.003.00250	AE (overdose)	AE (suicidal)	End of week 58 dose reduced, while patient was 'waiting to start phase II meds'. During this interim period, patient was hospitalised for attempted suicide and subsequently withdrawn.
329.005.00258	Other (going for general surgery)	Lost to FU	Patient eligible for continuation but scheduled for general surgery.
329.005.00300	Lack of Efficacy	Lost to FU	Patient never turned up for final visit during down titration (see page 222 of CRF)
329.005.00336	Other (no study meds)	PV (investigator)	No meds
329.008.00188	PV (non compliance)	PV (non compliance)	Migraine & Anxiety 9dys 48 & 52), 'over-compliance 128%' day 55.
329.009.00193	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00196	Withdrawn Consent	Withdrawn Consent	No acute phase conclusion page in CRF. Info from Appendix G
329.009.00201	AE (paranoia & aggression)	AE (paranoia & aggression)	
329.009.00324	AE (rash)	AE (rash)	
329.009.00329	Lack of Efficacy	AE (depression worsening)	Worsening of depression reported as AE just prior to initiating down titration
329.012.00025	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)

AUDITED CRFs: Out of 31 CRFs audited, 9 changes were proposed for reasons for withdrawal. These are given below:

	Patient ID	GSK reason for withdrawal (as per Appendix G)	RIAT reason for withdrawal
Reason for withdrawal changes	329.001.00065	AE (aggression)	AE (suicidal)
	329.002.00058	AE (overdose)	AE (suicidal gesture/attempt) – OD (Tylenol x 80 pills) 3 days after discontinuing meds
	329.003.00313	AE (hospitalisation)	AE (suicidal)
	329.004.00015 *	Other (conflict with school and study)	Withdrawn consent
	329.004.00212	PV (non compliance)	AE (sedation)
	329.005.00333	Lack of Efficacy	AE (suicidal)
	329.009.00133	Lost to Follow Up	Lack of Efficacy
	329.011.00288	Lack of Efficacy	AE (agitation, possibly suicidal)
	329.012.00228	PV	Withdrawn consent

In addition a further 8 participants in the audited cohort, who were originally described as having withdrawn for 'AE including intercurrent illness' according to Appendix G, were further defined. These were as follows:

	Patient ID	GSK reason for withdrawal (as per App G)	RIAT reason for withdrawal
Adverse events further defined	329.001.00063	AE inc intercurrent illness	AE (mania)
	329.002.00058	AE inc intercurrent illness	AE (suicidal)
	329.002.00245	AE inc intercurrent illness	AE (intentional overdose)
	329.003.00250 *	AE inc intercurrent illness	AE (suicidal)
	329.005.00011 *	AE inc intercurrent illness	AE (suicidal)
	329.005.00152	AE inc intercurrent illness	AE (GI – nausea/vomit/diarrhoea)
	329.009.00240	AE inc intercurrent illness	AE (worsening depression)
	329.012.00226	AE inc intercurrent illness	AE (cardiac)

* withdrawn during CONTINUATION phase

b) Imipramine group

TAPER PHASE: In total 56 patients completed the 8 week acute phase. Of these 17 were discontinued at the 8 week visit. Proposed changes to the 'reasons for discontinuation' (if any) for these patients are given below:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.002.00098	Lack of Efficacy	Adverse Event (dry mouth)	Patient reported ongoing 'dry mouth' and 'tremor'. Note on pages 222 and 226 showing a dose reduction/ down titration due to these AEs.
329.002.00244	Lack of Efficacy	PV (investigator)	Week 8 meds unavailable. (p250)
329.003.00090	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00249	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00314	PV non compliance	PV non compliance	
329.003.00317	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00009	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00117	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.005.00255	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00295	Adverse Event (homicidal)	Adverse Event (homicidal)	Wanted to kill parents
329.005.00332	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00335	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.008.00187	Lack of Efficacy	AE (tachycardia)	Pt experiencing 'persistent side effects' at time of withdrawal (p222), including pulse rate >110 for 2 consecutive weeks.
329.009.00134	AE (tachycardia/ inc QT/ QTc)	AE (tachycardia/ inc QT/ QTc)	
329.009.00137	Other (ADHD)	PV (investigator)	'Team felt due to continuing ADHD symptoms pt needed treatment with stimulant'. Patient had 'severe' symptoms of ADHD at baseline (p69).
329.009.00199	PV non compliance	PV non compliance	77% and 71% compliance
329.009.00262	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)

AUDITED CRFs: Out of 40 CRFs checked, 3 changes were proposed for reasons for withdrawal:

		GSK Reason for withdrawal (as per App G)	RIAT reason for withdrawal
'Reason for withdrawal' changes	329.002.00243	AE (accident/trauma)	AE (postural hypotension)
	329.004.00211	AE (dehydration)	AE (nausea/vomiting)
	329.012.00223	Lack of Efficacy	AE (suicidal gesture)

A further 10 participants from the audited cohort, who were described as having withdrawn for 'AE including intercurrent illness' according to Appendix G, were further defined. These were as follows:

Adverse events further defined	329.001.00061	AE inc intercurrent illness	AE (widened QTc)
	329.001.00066	AE inc intercurrent illness	AE (tachycardia)
	329.001.00067	AE inc intercurrent illness	AE (postural hypotension)
	329.001.00070	AE inc intercurrent illness	AE (tachycardia)
	329.003.00073	AE inc intercurrent illness	AE (vomiting)
	329.004.00014	AE inc intercurrent illness	AE (nausea)
	329.005.00003	AE inc intercurrent illness	AE (tachycardia)
	329.004.00215	AE inc intercurrent illness	AE (hallucinations/nightmares)
	329.005.00113	AE inc intercurrent illness	AE (suicidal)
	329.009.00236	AE inc intercurrent illness	AE (dizziness/sedation)

c) Placebo group

TAPER PHASE: In total 66 patients completed the 8 week acute phase. Of these 32 were discontinued at the 8 week visit. A number of changes to the 'reason for discontinuation' are proposed:

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.001.00069	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00071	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.001.00207	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.002.00049	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.002.00059	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.002.00246	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00078	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00080	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00085	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00094	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.003.00252	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00315	Withdrawn consent	Withdrawn consent	
329.003.00316	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.004.00018	Withdrawn consent	Withdrawn consent	
329.005.00001	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00120	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.005.00253	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.005.00293	Other (no study meds)	PV (investigator)	

329.005.00331	Other (no study meds)	PV (investigator)	
329.006.00259	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.007.00266	Other 'moved out of state'	Withdrawn consent	
329.007.00267	PV (positive drug test)	PV (positive drug test)	
329.009.00136	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00198	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00238	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.009.00276	Lack of Efficacy	Other (misc)	HAM-D scores indicate patient a 'Responder'
329.009.00306	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.009.00312	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.010.00263	Withdrawn consent	Withdrawn consent	
329.010.00282	Other (no study meds)	PV (investigator)	
329.011.00285	Lack of Efficacy	Lack of Efficacy	Non-responder (HAM-D)
329.011.00287	Withdrawn consent	Withdrawn consent	

AUDITED CRFs: Out of 22 CRFs checked, 6 changes were made to reasons for withdrawal. A further 1 participant who was described as having withdrawn for 'AE including intercurrent illness' according to Appendix G was further defined. These were as follows:

		GSK reason for withdrawal (as per App G)	**RIAT reason for withdrawal**
'Reason for withdrawal' changes	329.006.00037	PV non compliance (pt refused FU safety evaluation)	PV by investigator (screening error)
	329.007.00141	AE (angina)	PV by investigator (screening error)
	329.009.00129	Lack of Efficacy	AE (suicidal)
	329.009.00237	PV non compliance	PV by investigator (screening error)
	329.009.00327	Lack of Efficacy	AE (anxiety/depression worse)
	329.012.00217	AE (ambivalence about meds)	PV by investigator (screening error)
Adverse Events further defined	329.009.00330	AE inc intercurrent illness	AE (nausea/vomiting)

Table ix - Baseline screening errors (found during audit)

Four 'Protocol violations by investigator' were found in the placebo group:

Patient ID number	Inclusion criteria error
329.006.00037	Patient had a severity score HIGHER than 60 on the Clinical Global Assessment Scale (C-GAS). Reported as a PV in CRF query logs.
329.007.00141	Patient was withdrawn for ANGINA however angina was reported as a presenting condition at screening. CRF states comments on reason for withdrawal *'physician discretion due to comparator arm, vis-à-vis AE of chest pain.'*
329.009.00237	ELIGIBILITY CHECKLIST *'Is patient currently in episode of Major Depression for at least 8 weeks?'* 'NO' is checked – therefore not meeting criteria for MDD. In addition patient found to have SINUS BRADYCARDIA at screening.
329.012.217	Has been re-coded as 'PV by investigator'. Patient was 'extremely' suicidal at screening with no suicidal acts (see Kiddie-SADs & HAM-D). Patient showed 'worsening depression' during the study, was admitted to hospital during week 4 and given Zoloft. GSK reason for withdrawal was AE 'ambivalence towards meds'. Alternatively could argue was withdrawn for 'AE worsening depression'.

No similar protocol violations 'by investigator' were found for patients in the paroxetine or imipramine groups during the audit.

Table x – Suicidality at screening (Kiddie-SADS)

From the audit sample, 27% of patients were reported as having severe (or extreme) suicidal ideation at screening, compared with 13% in the paroxetine group and 3% in imipramine (see table 5).

a) Kiddie-SADS items 108 to 117 'SUICIDAL IDEATION' at screening visit (-1 week)

		Paroxetine N=31	Imipramine N=40	Placebo N=22
Suicidal Ideation	**Current episode**	2.9	2.7	3.1
	Last 2 weeks	2.2	2.3	2.6
Number of Suicidal Acts	**Current episode**	0.0	0.1	0.3
	Last 2 weeks	0.0	0.0	0.0
Seriousness of Suicidal acts	**Current episode**	0.7	0.6	0.7
	Last 2 weeks	0.5	0.5	0.5
Medical lethality of suicidal acts	**Current episode**	0.6	0.5	0.6
	Last 2 weeks	0.5	0.4	0.4
Number of non suicidal self harm	**Current episode**	1.7	1.3	0.9
	Last 2 weeks	1.3	1.1	0.7

NB. Rating scale from 0 (n/a) to 7 (very extreme)

b) Kiddie-SADS item 108 'SUICIDAL IDEATION' in 'Current Episode' at screening (-1 week)

	Paroxetine N=31	Imipramine N=40	Placebo N=22
0 - N/A	0	0	0
1 - None	6 (19%)	7 (18%)	4 (18%)
2 - Min	7 (23%)	12 (30%)	4 (18%)
3 - Mild	7 (23%)	10 (25%)	6 (27%)
4 - Moderate	7 (23%)	10 (25%)	2 (9%)
5 + - Severe/EXTREME/ V EXTREME	4 (13%)	1 (3%)	6 (27%)

c) Kiddie-SADS item 109 'SUICIDAL IDEATION' in 'Last Two Weeks' at Screening (-1 week)

	Paroxetine N=31	Imipramine N=40	Placebo N=22
0 - N/A	0	0	0
1 - None	14 (45%)	13 (33%)	6 (27%)
2 - Min	7 (23%)	9 (23%)	5 (23%)
3 - Mild	3 (10%	12 (30%)	4 (18%)
4 - Moderate	5 (16%)	5 (13%)	5 (23%)
5 + - Severe/EXTREME/ V EXTREME	2 (6%)	1 (3%)	2 (9%)

Table xi - Types of medications taken within 1 month prior to enrolment

ATC Level 2 drug type grouping	Drug	Paroxetine N=24	Imipramine N=31	Placebo N=26
Analgesics	Acetylsalicyclic acid (aspirin)	1	1	0
	cinnamedrine hydrochloride (midol)	1	0	0
	paracetamol	10	9	4
	Paracetamol plus (tylenol/benadryl cold/flu)	2	1	1
	Codeine phosphate	0	1	0
	Diphenhydramine citrate (exedrine pm)	0	1	0
	Mepyramine maleate (pamprin)	0	0	1
	Analgesic unknown	0	1	1
	Unknown Chinese medicine	0	1	0
	Total	**14**	**15**	**7**
Antibiotics	amoxicillin	1	2	4
	tetracycline	1	0	0
	erythromycin	0	1	2
	azithromycin	0	0	1
	Total	**2**	**3**	**7**
Psychoanaleptics	Fluoxetine (Prozac)	1	0	0
	Sertraline	1	0	0
	Amitriptyline	0	0	1
	Total	**2**	**0**	**1**
Psycholeptics	diazepam	0	0	1
	Total	**0**	**0**	**1**
Ophthalmologicals	Polymyxin b sulphate (eye drops)	1	0	0
	Sulfacetamide sodium	0	1	0
	Total	**1**	**1**	**0**
Systemic antihistamine	loratadine	1	0	0
	Total	**1**	**0**	**0**
Antipruritics	Diphendydramine hydrochloride	1	0	2
	Total	**1**	**0**	**2**
GI Antispas/ anticholin	Phenobarbitall, hyocyamine, atropine (Donnatal)	1	0	0
	Total	**1**	**0**	**0**
Vaccines	Hepatitis B vaccine	1	0	0

	Total	**1**	**0**	**0**
Nasal prep	Clemastine fumarate (Travist-d)	1	0	0
	Total	**1**	**0**	**0**
Antianaemic prep	Vit B 12	0	1	0
	Total	**0**	**1**	**0**
Sex hormones/stimulants	Ethinylestradiol (desogen28; loestrin or ovcon)	0	3	1
	Oral contraceptive unknown	0	1	0
	Injectable contraceptive (NOS)	0	0	1
	Total	**0**	**4**	**2**
Antimycotics	Ketoconazole (nizoral)	0	1	0
	Total	**0**	**1**	**0**
Anti inflammatory	ibuprofen	0	3	1
	Naproxen sodium	0	0	1
	oxaprozin	0	0	1
	Total	**0**	**3**	**3**
Cough & cold prep	Dextromethorphan hydrobromide (Nyquil)	0	1	0
	Guaifenesin (robitussin)	0	1	0
	Total	**0**	**2**	**0**
Antidiarrhea	Loperamide hydrochloride	0	1	0
	Total	**0**	**1**	**0**
Antiasthmatics	salbutamol	0	0	1
	Total	**0**	**0**	**1**
Chemotherapeutics	Trimethoprim (bactrim)	0	0	1
	Total	**0**	**0**	**1**
Antiepileptics	clonazepam	0	0	1
	Total	**0**	**0**	**1**

Table xii - AEs occurring in patients taking other medication during month prior to enrolment vs those taking no other medication

a) Paroxetine

		Patients taking 'other Medications' during month pre-enrolment	Patients taking 'No Medication' during month pre-enrolment
SOC	**MedDRA Term**		
Gastrointestinal disorders	Abdominal pain	0	0
	Constipation	0	6
	Cramps	3	10
	Diarrhea	1	11
	Dry Mouth	5	15
	Dyspepsia	1	7
	Food poisoning	1	0
	Gastroenteritis	0	0
	Nausea	7	26
	Reflux	1	0
	Retching	0	0
	Sores	0	0
	Stomatitis	0	0
	Vomiting	2	7
	TOTAL	**21**	**82**
Vascular Disorders	Hypertension	0	0
	Migraine	0	1
	TOTAL	**0**	**1**
Nervous System Disorders	Bad taste	0	0
	Convulsion	0	0
	Dystonia	4	1
	Laryngitis dystonia	0	1
	Memory loss	0	0
	Myoclonus	3	1
	Paresthesia	0	1
	Sore throat-dystonia	7	2
	Tics	0	1
	Tinnitus	0	0
	Toothache dystonia	4	2
	Tremor	4	6
	Vision blurred	0	1
	TOTAL	**22**	**16**
General disorders and administration site conditions	Headache	25	32
	Fatigue	6	8
	Fever	0	0
	Pain	0	0
	TOTAL	**31**	**40**
Psychiatric disorders	Abnormal dreams	0	3
	Aggravated depression	0	5
	Aggression	1	6
	Agitation	0	0
	Akathisia	10	8
	Anorgasmia	1	0
	Anxiety	0	2

	Concentration low	1	1
	Depersonalisation	0	0
	Disinhibition	1	3
	Drug withdrawal syndrome	0	2
	Hallucination	0	1
	Insomnia	3	12
	Paranoia	1	0
	Psychosis	0	1
	Somnolence	9	14
	Substance abuse	0	1
	Suicidal ideation/gesture	0	4
	Suicide attempt	2	5
	TOTAL	**29**	**68**
Respiratory, thoracic and mediastinal disorders	Coughing	4	2
	Chest cold	2	9
	Epistaxis	0	0
	Dyspnea	0	3
	Nasopharyngitis	2	1
	Respiratory disorder	0	0
	Rhinitis	4	5
	Sinusitis	3	5
	Sneezing	0	0
	TOTAL	**15**	**25**
Cardiac Disorders	Atrial ectopic	0	0
	AV block	0	1
	Bradycardia	0	0
	Bundle branch block	0	0
	Dizziness	13	19
	Chest pain	0	2
	ECG/ T-ECG abnormal	0	0
	Hot flush	0	0
	NIL	0	0
	Postural hypotension	1	2
	QT interval prolonged	0	0
	Tachycardia	1	2
	TOTAL	**15**	**26**
Skin and subcutaneous tissue disorders	Acne	1	2
	Dermatitis	0	1
	Itchy	0	0
	Rash	1	3
	Scabies	0	0
	Sweating	1	1
	Syncope	0	0
	TOTAL	**3**	**7**
Renal and urinary disorders	Albuminuria	0	0
	Cystitis	0	1
	Nocturia	0	0
	Polyuria	0	0
	Pyuria	0	0
	Urinary abnormality	1	2
	Urinary retention	0	0
	UTI	0	1

	TOTAL	**1**	**4**
Immune system disorders	Allergy	0	1
	Urticaria	0	1
	TOTAL	**0**	**2**
Endocrine disorders	Amenorrhea	1	0
	Hyperglycemia	0	0
	TOTAL	**1**	**0**
Blood and lymphatic system disorders	Anemia	0	1
	Eosinophilia	0	0
	Leukopenia	0	0
	Lymphadenopathy	0	0
	Thrombocythemia	0	0
	TOTAL	**0**	**1**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0
	Back pain	5	0
	Chills	0	0
	Myalgia	0	2
	TOTAL	**6**	**2**
Reproductive system and breast disorders	Breast enlargement	0	1
	Dysmenorrhea	2	0
	TOTAL	**2**	**1**
Infections	Herpes zoster	0	0
	Infection	2	2
	Otitis media	0	2
	TOTAL	**2**	**4**
Eye disorders	Conjunctivitis	2	0
	Itchy eyes	1	1
	Mydriasis	0	0
	Photosensitivity	0	1
	Photopsia	0	0
	TOTAL	**3**	**2**
Metabolism and nutrition disorders	Decreased appetite	3	6
	Increased appetite	0	3
	Thirst	0	0
	Weight gain	1	1
	Weight loss	0	2
	TOTAL	**4**	**12**
Ear and labyrinth disorders	Ear pain	0	1
	TOTAL	**0**	**1**
Injury, poisoning and procedural complications	Head injury	0	0
	Overdose	0	0
	Trauma	0	3
	TOTAL	**0**	**3**
Pregnancy, puerperium and	Pregnancy	0	0
	TOTAL	**0**	**0**

perinatal conditions			
Surgical and medical procedures	Tooth extraction	0	1
	TOTAL	**0**	**1**
Total number of AEs		**155**	**298**

b) imipramine

		Patients taking 'other Medications' during month pre-enrolment	**Patients taking 'No Medication' during month pre-enrolment**
SOC	**MedDRA Term**		
Gastrointestinal disorders	Abdominal pain	0	0
	Constipation	2	8
	Cramps	1	10
	Diarrhea	6	1
	Dry Mouth	15	33
	Dyspepsia	4	7
	Food poisoning	0	0
	Gastroenteritis	0	1
	Nausea	14	27
	Reflux	0	0
	Retching	0	1
	Sores	0	0
	Stomatitis	0	2
	Vomiting	6	5
	TOTAL	**48**	**95**
Vascular Disorders	Hypertension	0	2
	Migraine	1	0
	TOTAL	**1**	**2**
Nervous System Disorders	Bad taste	1	2
	Convulsion	1	0
	Dystonia	2	5
	Laryngitis dystonia	0	0
	Memory loss	0	1
	Myoclonus	0	1
	Paresthesia	0	1
	Sore throat-dystonia	7	5
	Tics	0	1
	Tinnitus	0	2
	Toothache dystonia	0	0
	Tremor	12	6
	Vision blurred	1	4
	TOTAL	**24**	**28**
General disorders and administration site conditions	Headache	32	27
	Fatigue	5	3
	Fever	0	2
	Pain	0	0
	TOTAL	**37**	**32**

Psychiatric disorders	Abnormal dreams	1	4
	Aggravated depression	2	1
	Aggression	1	2
	Agitation	0	1
	Akathisia	6	6
	Anorgasmia	0	0
	Anxiety	0	0
	Concentration low	1	0
	Depersonalisation	0	1
	Disinhibition	0	1
	Drug withdrawal syndrome	0	0
	Hallucination	1	0
	Insomnia	3	11
	Paranoia	0	0
	Psychosis	0	0
	Somnolence	3	11
	Substance abuse	0	1
	Suicidal ideation/gesture	0	3
	Suicide attempt	1	2
	TOTAL	**19**	**44**
Respiratory, thoracic and mediastinal disorders	Coughing	2	2
	Chest cold	0	6
	Epistaxis	0	1
	Dyspnea	4	1
	Nasopharyngitis	0	0
	Respiratory disorder	0	0
	Rhinitis	1	2
	Sinusitis	1	2
	Sneezing	0	0
	TOTAL	**8**	**13**
Cardiac Disorders	Atrial ectopic	0	0
	AV block	1	1
	Bradycardia	0	0
	Bundle branch block	0	1
	Dizziness	19	37
	Chest pain	4	1
	ECG/ T-ECG abnormal	3	3
	Hot flush	3	3
	NIL	0	2
	Postural hypotension	7	10
	QT interval prolonged	2	1
	Tachycardia	12	16
	TOTAL	**51**	**75**
Skin and subcutaneous tissue disorders	Acne	2	0
	Dermatitis	2	0
	Itchy	0	1
	Rash	2	3
	Scabies	0	0
	Sweating	5	2
	Syncope	0	0
	TOTAL	**11**	**6**
Renal and urinary	Albuminuria	0	0
	Cystitis	0	0

disorders	Nocturia	1	0
	Polyuria	0	1
	Pyuria	0	1
	Urinary abnormality	0	0
	Urinary retention	1	5
	UTI	0	0
	TOTAL	**2**	**7**
Immune system disorders	Allergy	0	1
	Urticaria	1	0
	TOTAL	**1**	**1**
Endocrine disorders	Amenorrhea	0	0
	Hyperglycemia	1	0
	TOTAL	**1**	**0**
Blood and lymphatic system disorders	Anemia	0	0
	Eosinophilia	1	0
	Leukopenia	1	0
	Lymphadenopathy	0	0
	Thrombocythemia	0	0
	TOTAL	**2**	**0**
Musculoskeletal and connective tissue disorders	Arthralgia	1	0
	Back pain	0	2
	Chills	0	3
	Myalgia	0	0
	TOTAL	**1**	**5**
Reproductive system and breast disorders	Breast enlargement	0	0
	Dysmenorrhea	2	2
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	0
	Infection	2	1
	Otitis media	1	1
	TOTAL	**3**	**2**
Eye disorders	Conjunctivitis	0	0
	Itchy eyes	0	1
	Mydriasis	1	0
	Photosensitivity	1	0
	Photopsia	0	1
	TOTAL	**2**	**2**
Metabolism and nutrition disorders	Decreased appetite	1	1
	Increased appetite	0	1
	Thirst	0	2
	Weight gain	0	0
	Weight loss	1	0
	TOTAL	**2**	**4**
Ear and labyrinth disorders	Ear pain	0	0
	TOTAL	**0**	**0**
Injury,	Head injury	0	1

poisoning and procedural complications	Overdose	0	1
	Trauma	0	1
	TOTAL	**0**	**3**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	2
	TOTAL	**0**	**2**
Surgical and medical procedures	Tooth extraction	0	2
	TOTAL	**0**	**2**
Total number of AEs		**215**	**325**

c) placebo

		Patients taking 'other Medications' during month pre-enrolment	**Patients taking 'No Medication' during month pre-enrolment**
SOC	**MedDRA Term**		
Gastrointestinal disorders	Abdominal pain	2	0
	Constipation	1	3
	Cramps	3	11
	Diarrhea	6	3
	Dry Mouth	4	8
	Dyspepsia	0	4
	Food poisoning	0	1
	Gastroenteritis	0	0
	Nausea	14	12
	Reflux	0	0
	Retching	0	0
	Sores	0	1
	Stomatitis	0	0
	Vomiting	2	2
	TOTAL	**32**	**45**
Vascular Disorders	Hypertension	0	0
	Migraine	0	0
	TOTAL	**0**	**0**
Nervous System Disorders	Bad taste	0	0
	Convulsion	0	0
	Dystonia	2	1
	Laryngitis dystonia	0	0
	Memory loss	0	0
	Myoclonus	0	0
	Paresthesia	0	0
	Sore throat-dystonia	3	8
	Tics	0	0
	Tinnitus	0	0
	Toothache dystonia	1	2
	Tremor	1	1
	Vision blurred	2	0
	TOTAL	**9**	**12**

General disorders and administration site conditions	Headache	29	27
	Fatigue	3	8
	Fever	1	3
	Pain	1	1
	TOTAL	**34**	**39**
Psychiatric Disorders	Abnormal dreams	0	2
	Aggravated depression	1	1
	Aggression	0	0
	Agitation	0	0
	Akathisia	2	6
	Anorgasmia	0	0
	Anxiety	1	0
	Concentration low	0	0
	Depersonalisation	1	0
	Disinhibition	0	2
	Drug withdrawal syndrome	0	0
	Hallucination	0	0
	Insomnia	2	2
	Paranoia	0	0
	Psychosis	0	0
	Somnolence	1	2
	Substance abuse	0	0
	Suicidal ideation/gesture	1	0
	Suicide attempt	0	0
	TOTAL	**9**	**15**
Respiratory, thoracic and mediastinal disorders	Coughing	1	5
	Chest cold	8	6
	Epistaxis	0	0
	Dyspnea	0	2
	Nasopharyngitis	0	1
	Respiratory disorder	1	1
	Rhinitis	2	3
	Sinusitis	5	3
	Sneezing	0	1
	TOTAL	**17**	**22**
Cardiac Disorders	Atrial ectopic	1	0
	AV block	1	1
	Bradycardia	1	0
	Bundle branch block	0	1
	Dizziness	5	13
	Chest pain	1	1
	ECG/ T-ECG abnormal	2	0
	Hot flush	1	1
	NIL	0	1
	Postural hypotension	1	0
	QT interval prolonged	0	0
	Tachycardia	0	1
	TOTAL	**13**	**19**
Skin and subcutaneous tissue disorders	Acne	1	0
	Dermatitis	0	1
	Itchy	1	0
	Rash	3	1

	Scabies	0	1
	Sweating	1	0
	Syncope	0	1
	TOTAL	**6**	**4**
Renal and urinary disorders	Albuminuria	0	3
	Cystitis	0	0
	Nocturia	0	0
	Polyuria	0	0
	Pyuria	0	0
	Urinary abnormality	0	0
	Urinary retention	0	0
	UTI	0	0
	TOTAL	**0**	**3**
Immune system disorders	Allergy	3	0
	Urticaria	0	0
	TOTAL	**3**	**0**
Endocrine disorders	Amenorrhea	0	0
	Hyperglycemia	0	1
	TOTAL	**0**	**1**
Blood and lymphatic system disorders	Anemia	0	0
	Eosinophilia	0	1
	Leukopenia	0	0
	Lymphadenopathy	1	0
	Thrombocythemia	0	1
	TOTAL	**1**	**2**
Musculoskeletal and connective tissue disorders	Arthralgia	2	2
	Back pain	3	7
	Chills	0	0
	Myalgia	1	1
	TOTAL	**6**	**10**
Reproductive system and breast disorders	Breast enlargement	0	0
	Dysmenorrhea	2	2
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	1
	Infection	1	2
	Otitis media	0	0
	TOTAL	**1**	**3**
Eye disorders	Conjunctivitis	0	1
	Itchy eyes	0	0
	Mydriasis	0	0
	Photosensitivity	0	0
	Photopsia	0	0
	TOTAL	**0**	**1**
Metabolism and nutrition disorders	Decreased appetite	1	3
	Increased appetite	0	1
	Thirst	2	1
	Weight gain	0	0

	Weight loss	1	1
	TOTAL	**4**	**6**
Ear and labyrinth disorders	Ear pain	0	0
	TOTAL	**0**	**0**
Injury, poisoning and procedural complications	Head injury	0	0
	Overdose	0	0
	Trauma	0	6
	TOTAL	**0**	**6**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	0
	TOTAL	**0**	**0**
Surgical and medical procedures	Tooth extraction	0	0
	TOTAL	**0**	**0**
Total number of AEs		**137**	**190**