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

Journal:	*BMJ*
Manuscript ID:	BMJ.2014.022376.R2
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
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Keywords:	child and adolescent psychiatry, antidepressant, RCT, selective reporting, critical appraisal, pharmaceutical industry, paroxetine, medical fraud

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

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Jon Jureidini affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests

Dr. Healy has been and is an expert witness for plaintiffs in legal cases involving GlaxoSmithKline's drug paroxetine. He is also a witness for plaintiffs in actions involving other antidepressants with the same mechanism of action as paroxetine.

Dr Jureidini has been paid by Baum, Hedlund, Aristei & Goldman, Los Angeles, California to provide expert analysis and opinion about documents obtained from GlaxoSmithKline in a class action over study 329, and from Forest in relation to paediatric citalopram RCTs.

Drs Le Noury, Nardo, Raven, Tufanaru and Abi-Jaoude have nothing to declare.

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

Abstract

Objectives: The primary objective of GSK's Study 329 (published by Keller et al. in 2001) was to compare the efficacy and safety of paroxetine and imipramine to placebo in the treatment of adolescents with unipolar major depression. The objective of this restoration under the Restoring Invisible and Abandoned Trials (RIAT) initiative was to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

Design: Double- blind randomised placebo-controlled trial.

Setting: 12 North American academic psychiatry centres, from 20 April 1994 to 15 February 1998.

Participants: 275 adolescents with major depression of at least 8 weeks in duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality.

Interventions: Participants were randomised to 8 weeks double-blind treatment with paroxetine (20–40 mg), imipramine (200–300 mg), or placebo.

Main outcome measures: The pre-specified primary efficacy variables were: change from baseline to the end of the 8-week 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-SADS-L; Clinical Global Impression; 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 efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any pre-specified primary or secondary efficacy outcome. HAM-D scores decreased by 10.73 [9.134, 12.328], 8.95 [7.356, 10.541] and 9.08 [7.450, 10.708] points, LS MEAN [95%CI], respectively, for the paroxetine, imipramine and placebo groups (p = 0.204). Clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events, were observed in the paroxetine group, and cardiovascular problems in the imipramine group.

Conclusions: Neither paroxetine nor high-dose imipramine demonstrated efficacy for major depression in adolescents, and there was an increase in harms with both drugs. Access to primary data from trials has important implications for both clinical practice and research, including that published conclusions about efficacy and safety should not be read as authoritative. The reanalysis of Study 329 illustrates the necessity of making primary trial data available to increase the rigour of the evidence base.

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

Funding of Study 329: SmithKline Beecham/GlaxoSmithKline. No funding was obtained to support this restoration.

Supplementary material / data can be found at [URL TBA]

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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 had been identified as unpublished or misreported, independent groups were 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. The original study was funded by SmithKline Beecham (SKB; subsequently GlaxoSmithKline, GSK) and led by Dr Martin Keller. We acknowledge the work of the original investigators. 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 asked GSK whether it had any intention to restore any of the trials it sponsored. GSK did not signal any intent to publish a corrected version of any of its trials. 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]

Study 329 was a multicenter eight-week double-blind RCT (acute phase), followed by a six-month continuation phase. SKB's stated 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.[7] Very few previously published RCTs have been reported in published papers by different teams of authors.[8]

Methods

We have reanalysed Study 329 according to the RIAT recommendations. To this end, we have used the Clinical Study Report (CSR; SKB's 'Final Clinical Report') available on the GSK website,[9] other publically available documents,[10] and the individual participant level data access Solutions OnDemand,[11] on which GSK subsequently also posted some Study 329 documents (available only to users approved by GSK). Following negotiation,[12] GSK posted de-identified individual case report forms (CRFs) on that website. A table of sources of data consulted in preparing each part of this paper is available as Appendix 1.

Except where indicated, in accordance with RIAT recommendations, our methods are those set out in the 1994/1996 Study 329 protocol,[13] 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 (replacement of the K-SADS-P with the K-SADS-L and reduction in required sample size). Furthermore, the CSR reported some procedures that varied from those specified in the protocol, and we have noted variations wherever they were considered significant.

Participants

275 adolescents between the ages of 12 and 18 years, meeting *DSM-IV* criteria[14] for a current episode of major depression of at least 8 weeks duration, were recruited for the study (the protocol specified *DSM-III-R* 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.

An undisclosed number of patients identified by telephone screening as potential participants were subsequently evaluated at the study site by a senior clinician (psychiatrist or psychologist). Multiple meetings and teleconferences were held by the sponsoring company with site study investigators to ensure standardization across sites. 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, the study informed consent form was signed by both patient and parent; there is no mention of a separate assent form in the protocol or in the clinical study report. A 7 to 10 day screening period was used to obtain past clinical records and to document that the depressive symptoms were stable. At the end of the screening period, only patients continuing to meet the inclusion criteria (DSM-III-R major depression and the HAM-D total score of 12 or greater) were randomised. There was no placebo lead-in phase.

The number of study sites was originally 6 but was increased to 12 (10 in the United States and 2 in Canada). The centres were affiliated with either a university or a hospital psychiatry department and had experience with adolescent patients. The investigators were selected for their interest in the study and their ability to recruit study patients.

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 February 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 (those failing to reach responder criteria) 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.

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.

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.

Recruitment was slower than expected, and reportedly medication supplies (mainly placebo) ran short due to expiry. Therefore 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 to 275 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.

Randomisation

A computer-generated randomisation 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. The identity of the study medication was not otherwise disclosed to the investigator or SKB staff associated with the study.

Outcomes

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

1. Efficacy Endpoints

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 (longer than many antidepressant trials). *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. (Scores on the HAM-D can vary from 0 to 52.)

Secondary Efficacy Variables

The pre-specified secondary efficacy variables were:

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

- Depression items in K-SADS-L
- Clinical Global Impression (CGI)
- 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.

Box 1: Challenges in carrying out RIAT

This is the first RIAT effort by an external team of authors, so there are no clear precedents or guides. **Challenges** included:

Potential or perceived bias

A RIAT report is not intended to be a critique of a previous publication. The point is rather to produce a thorough independent analysis of a trial that has remained unpublished or called into question. We acknowledge, however, that any RIAT team may be seen as having an intrinsic bias, in that questioning the earlier published conclusions is what brought some members of the team together. Consequently, we took all appropriate procedural steps to avoid such putative bias. In addition, we have made the data available for others to analyse.

Correction for testing multiple variables

We had multiple sources of information: The protocol; the published paper; the documents posted on the GSK web site including the CSR and Individual Patient Data; and the raw primary data in the CRFs provided by GSK on a remote desk-top for this project. The protocol declared

two primary and six secondary variables for the three treatment groups in two differing datasets (OC [observed case] and LOCF [last observation carried forward)]. The CSR contained statistical comparisons on 28 discrete variables using two comparisons [paroxetine vs placebo and imipramine vs placebo] in the two datasets [OC and LOCF]. The published paper listed eight variables with two statistical comparisons each in one dataset [LOCF]. But the original authors nowhere addressed the need for corrections for multiple variables - a standard requirement when there are multiple outcome measures. In the final analysis, there were no statistically or clinically significant findings, so corrections were not needed for this analysis.

Statistical testing

The protocol called for ANOVA testing [GLM] for continuous variables using a model that included the effects of SITE, TREATMENT, and SITE x TREATMENT interaction, with the latter dropped if p≥0.10. Logistical Regression [chi Square 2x3] was prescribed for categorical variables under the same model. Both methods begin with an omnibus statistic for the overall significance of the dataset, then progress to pairwise testing if and only if the omnibus statistic meets alpha [0.05]. Yet all statistical outcomes in the CSR and published paper were reported only as the pairwise values for only two of the three possible comparisons [paroxetine vs placebo and imipramine vs placebo] with no mention of the omnibus statistic. Therefore, we conducted the needed omnibus analyses, which are negative as shown. The pairwise values are available in the online Appendix 2 (table i).

Missing values

The protocol called for evaluation of the OC and LOCF datasets, with the latter being definitive. The LOCF method for correcting missing values was the standard at the time the study was conducted. It continues to be widely used, though newer models such as Multiple Imputation or Mixed Models are superior. We chose to adhere to the protocol and use the LOCF method rather than introduce a *post hoc* analytic tool.

Non-protocol specified outcome variables

There were four outcome variables in the CSR and in the published paper that were not specified in the protocol. These were the only outcome measures reported as significant. They were in no version of the protocol as amendments nor were they submitted to the Institutional Review Board. The CSR (section 3.9.1) states they were part of an 'analysis plan' developed some two months before the blind was broken. No such plan appears in the CSR and we have no contemporaneous documentation of that claim, despite having repeatedly requested it from GSK.

Conclusions

After prolonged discussions, we decided that the best and most unbiased course of action was to analyse the efficacy data in the IPD based on the last guaranteed *a priori* version of SKB's own protocol [1994, amended in 1996 to accept a reduced sample size]. Although the protocol omitted a discussion of corrections which we would have thought necessary, correction for multiple variables is designed to prevent false positives and there were no positives. We agreed with the statistical mandates of the protocol, but while we saw pairwise comparisons in the

absence of overall significance as inappropriate, we recognize that this is not a universal opinion, so we included them in the online Appendix 2, table i.

Finally, although investigators can explore the data however they wish, additional outcome variables outside those in the protocol cannot be legitimately declared once the study is underway, except as 'exploratory variables' - appropriate for the discussion or as material for further study, but not for the main analysis. The *a priori* protocol and blinding are the bedrock of a randomised controlled trial - guaranteeing that there is not even the possibility of the HARK phenomenon ['hypothesis after results known']. While we can readily demonstrate that none of the reportedly 'positive' four non-protocol outcome variables stands up to scrutiny, the primary mandate of the RIAT enterprise is to reaffirm essential practices in RCTs, so we did not include these variables in our efficacy analysis.

2. Harm Endpoints

An adverse experience/event (AE) was defined in the 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.
> 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'.

Vital 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. Additional information was available from the summary narratives in the body of the CSR 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.) However, the large number of other patients discontinued because of AEs that were not regarded as serious, or discontinued for lack of efficacy or protocol violations (see Figure 1), did not generate patient narratives. The tables laid out in Appendix D of the CSR give the clinical descriptors used by the blind investigators along with Adverse Drug Events Coding System (ADECS) codes used to code these clinical descriptions, 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),[10] which made it difficult and extremely time-consuming to inspect the records properly.[20] Effectively only one person could undertake the task, with backup for ambiguous cases. Accordingly we could not examine all CRFs. Instead we decided to focus on those 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 reviewer (MN) is a clinician, untrained in this system. There was agreement between these two reviewers 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 total AEs were compared with the AE totals reported in CSR Appendix D.

This review 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 ii, iii and x in Appendix 2 accompanying this paper.

At least 1000 pages were missing from the CRFs reviewed with no discernible pattern to missing information; for example, one CRF came with a page inserted stating that pages 114 to 223 were missing, without indicating reasons.

Coding of Adverse Events

All of the initial coding from the clinical descriptions in the CSR was done blind, as was coding from the CRFs.

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, because it is by far the most commonly used coding system today, and it is not possible to access ADECS. 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 SKB, 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'.

Box 2: Coding Challenges

Most recoding was straightforward. Patient 00039, who had a severe (but not serious) AE, 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 SKB 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 SKB 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' as the correct coding for what SKB had coded as trauma at week 2 (see above).

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; HAM-D 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)'. Had SKB coded this way, the patient would have required a patient narrative.

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); the MedDRA system groups events into broader system-organ-class (SOC) groups – psychiatric, cardiovascular, gastrointestinal, respiratory and other (consistent with the published paper); 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.

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 (amended in 1996 to accept a reduced sample size). 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.

One of the two primary efficacy variables, proportion of responders (response), and one secondary efficacy variable, proportion of patients relapsing, were treated as categorical variables. The second 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 [22] so we included them in the online Appendix 2 for completeness). 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)[23] 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

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. 28 patients reached the highest permissible dose of 40 mg of paroxetine, and 20 patients were titrated to the maximum 300 mg of imipramine.

Efficacy

There were no discrepancies between any of our analyses and those contained in the CSR. Figure 2 illustrates the longitudinal values for the two primary efficacy variables: mean change from baseline in the HAM-D score; 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. 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. There was no statistical significance (considered at $p<0.05$) or clinical significance demonstrated for any of the pre-specified primary or secondary efficacy variables in either the OC or LOCF datasets, so pairwise analysis was considered unjustified. The results at week 8 are shown in Table 3. HAM-D scores decreased by 10.73 [9.134, 12.328], 8.95 [7.356, 10.541] and 9.08 [7.450, 10.708] points (LS MEAN [95%CI]), for the paroxetine, imipramine and placebo groups, respectively.

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

Primary Efficacy Variables [8 Weeks]

		Paroxetine				Imipramine				Placebo				*p*
	Data	LSMean	95% CI	SEM	n	LSMean	95% CI	SEM	n	LSMean	95% CI	SEM	n	ANOVA
HAM-D Change	OC	-12.18	-13.91 , -10.45	0.88	67	-10.59	-12.52 , -8.67	0.97	56	-10.51	-12.25 , -8.77	0.88	66	0.255
	LOCF	-10.73	-12.33 , -9.13	0.81	90	-8.95	-10.54 , -7.36	0.81	94	-9.08	-10.71 , -7.45	0.83	87	0.204

		criteria met	[+/-]	criteria met	[+/-]	criteria met	[+/-]	X^2
HAM-D Response ≥50% drop or ≤8	OC	80.6%	54/13	73.2%	41/15	65.2%	43/23	0.131
	LOCF	66.7%	60/30	58.5%	55/39	55.2%	48/39	0.269

Secondary Efficacy Variables [8 Weeks]

		Paroxetine				Imipramine				Placebo				*p*
		LSMean	95% CI	SEM	n	LSMean	95% CI	SEM	n	LSMean	95% CI	SEM	n	ANOVA
K-SADS-L Change	OC	-12.05	-13.84 , -10.26	0.91	67	-10.70	-12.68 , -8.73	1.00	56	-10.71	-12.52 , -8.90	0.92	65	0.459
	LOCF	-11.43	-13.08 , -9.79	0.84	83	-9.47	-11.10 , -7.85	0.82	88	-9.39	-11.02 , -7.76	0.83	85	0.131
CGI Mean Score	OC	1.89	1.59 , 2.19	0.15	68	2.16	1.82 , 2.50	0.17	56	2.36	2.05 , 2.66	0.16	66	0.086
	LOCF	2.36	2.05 , 2.67	0.16	90	2.69	2.39 , 3.00	0.15	94	2.72	2.41 , 3.04	0.16	87	0.155
Autonomous Function Check List Change	OC	14.35	8.76 , 19.94	2.83	58	13.34	7.34 , 19.35	3.04	52	9.29	3.75 , 14.84	2.81	60	0.325
	LOCF	14.68	9.15 , 20.21	2.80	60	11.55	5.77 , 17.32	2.92	57	9.27	3.83 , 14.71	2.76	62	0.367
Self Perception Profile Change	OC	12.89	8.34 , 17.46	2.31	60	13.24	8.37 , 18.11	2.46	55	12.68	8.13 , 17.21	2.30	60	0.875
	LOCF	13.22	8.62 , 17.83	2.33	61	13.06	8.30 , 17.81	2.41	60	11.38	6.89 , 15.86	2.27	63	0.877
Sickness Impact Profile Change	OC	-11.18	-14.29 , -8.07	1.57	62	-13.51	-16.87 , -10.15	1.70	55	-10.63	-13.72 , -7.53	1.57	62	0.244
	LOCF	-11.36	-14.42 , -8.29	1.55	63	-12.98	-16.18 , -9.78	1.62	60	-9.87	-12.86 , -6.88	1.51	65	0.233

LSMean - Least Square Means adjusted over the site covariate. (Using arithmetic means did not alter the findings.)
SEM – Standard Error of the Mean.
ANOVA – All Treatment [Omnibus] Analysis of Variance with Treatment and Site Effects in the model
X^2 - Logistical Regression with Treatment and Site Effects in the model
OC – Observed Case
LOCF – Last Observation Carried Forward
Note - All p values uncorrected for multiple variable sampling

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

Review of Clinical Records Forms

The review of 34% of CRFs produced the data shown in Table 4.

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%

*In considering adverse effects from imipramine, it should be noted that doses (mean 205.8 mg) were 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.[24]

Recoding and Representation of Adverse Event Data

Table 5 presents AEs found in this study according to System-Organ-Class (SOC) recoded from the CSR Appendix D (RIAT MedDRA recoded), and additional AEs found in our reanalysis of 93 CRFs. Table 5 also presents the AEs rated as severe by the original investigator (only from the CSR, because new events detected in the review of 93 CRFs do not include severity ratings). A full listing of AEs can be found in table iii in Appendix 2 to this paper.

Table 5. Adverse events in CSR and 93 CRFs (acute phase plus taper)

	Paroxetine N=93			Imipramine N=95			Placebo N=87		
Type of Adverse Event	CSR RIAT MedDRA recoded	Severe AEs reported	additional AEs found in 31 CRFs	CSR RIAT MedDRA recoded	Severe AEs reported	additional AEs found in 40 CRFs	CSR RIAT MedDRA recoded	Severe AEs reported	additional AEs found in 22 CRFs
Cardiovascular SOC*	45	1 (2.2%)	0	131	4 (3.1%)	5	32	0	0
Gastrointestinal SOC	112	25 (22.3%)	4	147	20 (13.6%)	4	79	4 (5.1%)	2
Psychiatric SOC*	101	32 (31.7%)	12	63	4 (6.3%)	1	24	5 (20.8%)	4
Respiratory SOC	42	2 (4.8%)	0	22	1 (4.5%)	1	39	4 (10.3%)	1
All other SOCs	179	10 (5.8%)	7	189	21 (11.2%)	6	156	12 (7.7%)	3
TOTAL	**479**	**70 (14.6%)**	**23**	**552**	**50 (9.1%)**	**17**	**330**	**25 (7.6%)**	**10**

* In the Keller et al paper the AEs 'dizziness' and 'headache' were grouped with psychiatric AEs under the heading 'Nervous System'. In the CSR recoding and CRF review these AEs have been reported under 'Cardiovascular SOC' for dizziness and 'Other/General SOC' for headaches. See also Appendix 2, table iii

Behavioural adverse events are further broken down in Table 6.

Table 6. Behavioural adverse events (acute phase plus taper)

Psychiatric disorders	**Paroxetine N=93**		**Imipramine N=95**		**Placebo N=87**	
	CSR RIAT MedDRA recoded	additional AEs found in 31 CRFs	**CSR** RIAT MedDRA recoded	additional AEs found in 40 CRFs	**CSR** RIAT MedDRA recoded	additional AEs found in 22 CRFs
Abnormal dreams	3	0	5	0	2	0
Depression worsening	5	2	3	0	2	1
Aggression/ anger	7	1	3	0	0	0
Agitation	0	1	1	0	0	0
Akathisia	18	0	12	0	8	0

Anxiety	2	0	0	0	1	1
Depersonalisation	0	0	1	0	1	0
Disinhibition	4	0	1	0	2	0
Hallucinations	1	0	1	0	0	0
Paranoia	1	0	0	0	0	0
Psychosis	1	1	0	0	0	0
Suicidal ideation	4	2*	3	0	1	1*
Suicide attempt	9	1*	3	1	0	0
Total AEs	**55**	**8**	**33**	**1**	**17**	**3**
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.

Severity Ratings

The CSR 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 therefore 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 (see table 5; 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).

Discontinuations

A second method of approaching the issue of severity of AEs is to look at rates of discontinuation due to AEs. Table 7 presents reasons for withdrawal during the acute phase and taper due to AEs and other causes. Note that we examined all discontinuation CRFs.

Table 7. Reasons for withdrawal during acute phase and taper

Reason for withdrawal		**Paroxetine (n=93)***		**Imipramine (n=95)**		**Placebo (n=87)**	
		Appendix G	**Appendix H**	**Appendix G**	**Appendix H**	**Appendix G**	**Appendix H**
Adverse	**Aggression**	1	0	0	0	0	0

Event	**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 (%)	11 (11.8%)	14 (15.0%)	30 (31.5%)	31 (32.6%)	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%)	27 (29%)	38 (40%)	38 (40%)	21 (24%)	21 (24%)

*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'.
**We replaced the term 'Adverse Events: Intercurrent Illness' with more specific AE terms.
***Four patients enrolled in the study violated the inclusion criterion. Two 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 x).

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 SKB 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 SKB, there were 65 dropouts after week 8 ratings were completed. SKB 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 SKB as lack of efficacy (see Table 9). 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 recategorised the lack of efficacy dropouts based on factors such as AEs and HAM-D scores.

Our analysis of reasons for withdrawal at the end of the acute phase is shown in table 8.

Table 8. 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	
		SKB/GSK coded, **App G**	**RIAT proposed***	SKB/GSK coded, **App G**	**RIAT proposed***	SKB/GSK coded, **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 available	1	0	0	0	3	0

	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**

*Following a review of the codes given for reasons for withdrawal from the study that were found in the CSR (Appendix G), along with a review of patient narratives and CRFs where applicable, we proposed changes to these reasons for withdrawal in a proportion of those discontinued.

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 make it possible to identify adverse events happening in the taper and follow-up periods.

The data are presented in Table 9.

Table 9. Adverse events from taper phase

System Organ Class (MedDRA)	**Paroxetine N=19**		**Imipramine N=32**		**Placebo N=9**	
	AEs reported (RIAT MedDRA recoded)	**AEs reported as severe**	**AEs reported** (RIAT MedDRA recoded)	**AEs reported as severe**	**AEs reported** (RIAT MedDRA recoded)	**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 10 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 AEs over placebo.

Table 10. 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**	**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 (with approved amendments) 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 review 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 their study protocol in the CSR itself 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. This contravened

provision II of Appendix B Administrative Matters, according to which any changes to the study protocol were required to be filed as amendments/modifications.

With regard to AEs, 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 and incomplete 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. Keller et al reported 265 adverse events with paroxetine, while we identified 479 from our analysis of the CSR, and found a further 23 that had been missed from the 93 CRFs that we reviewed. 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.

One reason why Keller et al.'s 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 other figures quoted in Keller et al, because Keller et al did not report a category of psychiatric AEs, but instead grouped psychiatric events together with 'dizziness' and 'headache' under Nervous System. Since dizziness is more likely to be attributable to 'cardiovascular' while headaches most commonly stem from muscles and blood vessels to the scalp, we did not group them together with psychiatric AEs. The effect of this change was to unmask a clinically important difference in psychiatric AE profiles between paroxetine and placebo.

Keller et al. tabulated only 51 psychiatric AEs for paroxetine and 38 for placebo (6 vs 3 for Emotional lability, 7 vs 3 for Hostility, 14 vs 13 for Insomnia, 8 vs 6 for Nervousness, and 16 vs 13 for Somnolence). We found 101 psychiatric AEs with paroxetine vs 24 with placebo (see table 5), making the differences between placebo and paroxetine more salient in the primary datasets than in Keller et al.

There was 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 review added even more cases.

Table 11. Comparison of suicidality using different safety methodologies

	Keller et al.		RIAT MedDRA recoded		additional AEs found in 93 CRFs	
	Paroxetine	**Placebo**	**Paroxetine**	**Placebo**	**Paroxetine**	**Placebo**
Suicidal ideation/gesture	≤5*	≤2*	4	1	2	1
Suicide attempt	0	0	9	0	1	0
Total suicidality	≤5*	≤2*	13	1	3	1

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

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.[25, 26] 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.

With regard to dropouts, 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 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 3).

Box 3. Potential barriers to 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 AE database

Our review 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 v 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. MedDRA offers the following higher levels: psychiatric; cardiovascular; gastrointestinal; respiratory; and other. In Appendix 2, table v, the data coded here under 'Other' is broken down under the additional MedDRA SOC headings - general, nervous system, metabolic, musculoskeletal, 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, table v, we have listed all events coded under each SOC heading and we invite others to further explore these issues, including alternative higher level 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 [TBA] but have not analysed them, because it became clear that the blind had been broken in several cases before relatedness was adjudicated by the original investigators, 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 [TBA]) over 130,000 words of email correspondence amongst the team over a year. The single screen remote desktop interface (we called the "periscope") proved to be an enormous challenge. The efficacy analysis required multiple spreadsheet tables be opened simultaneously, with much copying, pasting, cross-checking, and the space was highly restrictive. Gaining access to the CRFs required extensive correspondence with GSK.[11] Although GSK ultimately provided CRFs, they were even harder to manage, given that could we see only one page at a time. It required of the order of one thousand hours to examine only a third of the CRFs. Being unable to print was a significant handicap. There were no means to prepare packets for multiple independent

coders to decrease bias; to make annotations or use marginalia; or to sort and collate the AE reports. Our experience highlights that hard copies are crucial for an enterprise like this.

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 in the form of 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 [TBA], 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 pre-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 become accessible to others, it becomes clear that scientific authorship is provisional rather than authoritative.

Box 4. Strengths and limitations of this study

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

The RIAT analysis included a review 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 barriers to 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 by the original investigators, raising the possibility that some other data might be unreliable. Time and resources prevented access to all CRFs because of the difficulties in using the portal for accessing the study data and because significant data were missing.

The trial duration was only eight weeks. Participants had relatively chronic depression (mean duration more than one year), which would limit the generalizability of the results, particularly to primary care, because many cases of adolescent depression have shorter durations.[27] Generalizability to primary care would also be limited by the fact that participants were recruited via tertiary settings.

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.[13]

Trial Funding: SmithKline Beecham study.

Funding of the RIAT reanalysis: No funding received.

Data Analysis Protocol for RIAT reanalysis: Submitted to GSK on 28 October 2013. Approved by GSK on 4 December 2013.

We thank Tom Jefferson and Leemon McHenry for comments on various drafts.

Appendices/Supplementary material

1. RIATAR audit record, showing sources of data
2. Adverse event appendices

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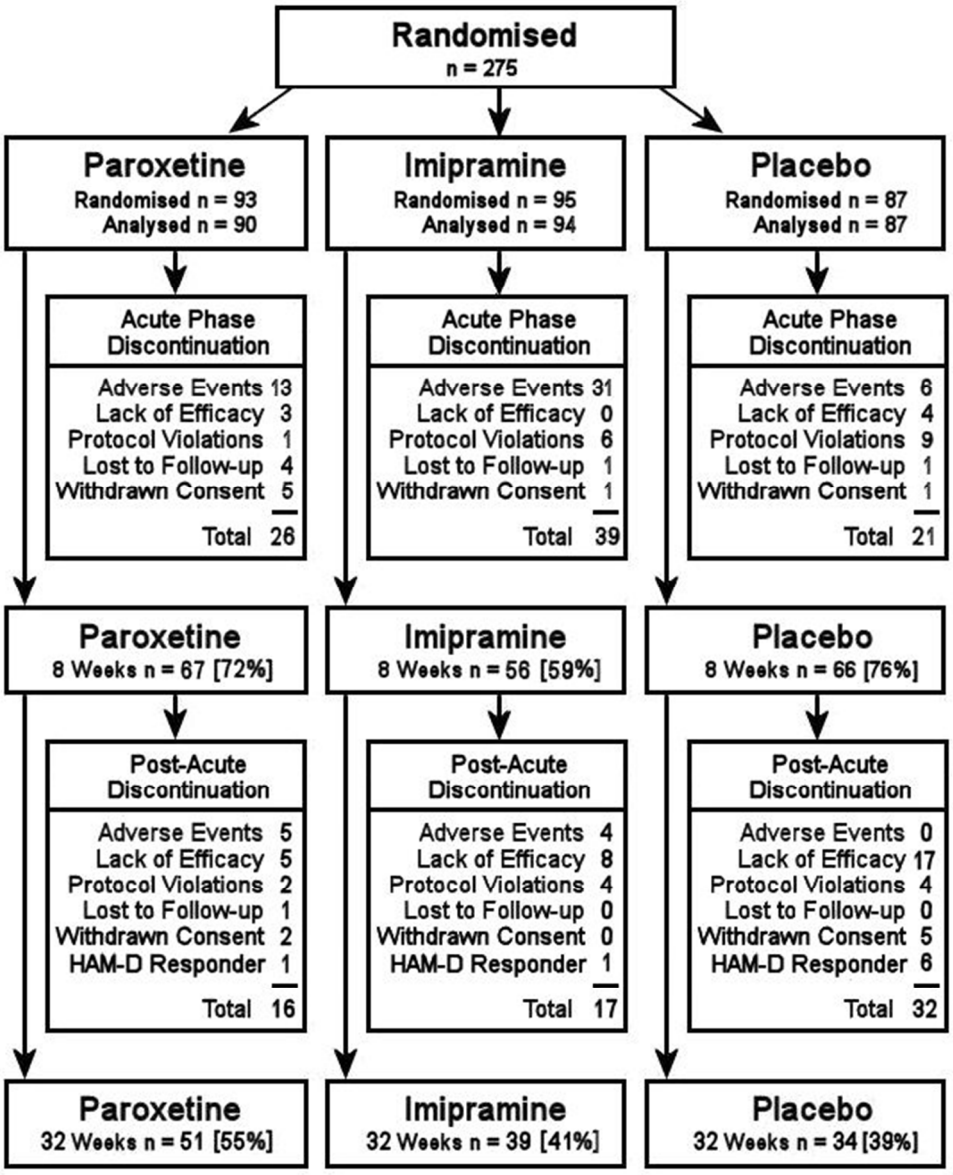

Figure 1. Randomisation and discontinuations.
82x100mm (200 x 200 DPI)

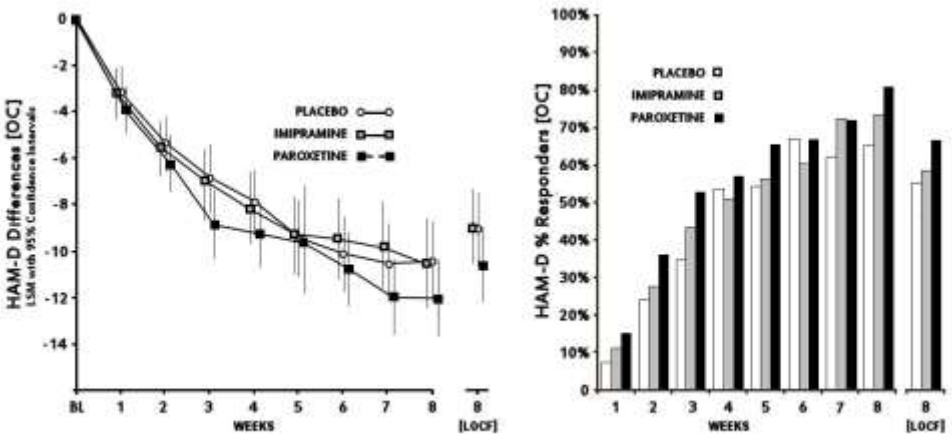

Figure 2: Primary Outcome
152x76mm (200 x 200 DPI)

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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.	
Introduction				CSR Final Clinical Report Acute Phase; 1 Introduction, pages 22-23; Appendix A, Protocol, 1.0 INTRODUCTION, page 545-546; Continuation Study, Final Clinical Report,Introduction, page 17.	CSR Final Clinical Report Acute Phase, Same pages; Appendix A, Protocol, PDF pages 15-16;Continuation Study, Final Clinical Report,Introduction, page 17.	
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,	

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
		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;	
Interventions	5	The interventions	p.4	CSR Final Clinical Report Acute Phase;	CSR Final Clinical Report	

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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,	

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
		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;	

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
				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,	

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
		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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		similarity of interventions		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; 3.7 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, 6.4 Concomitant Medication, page 560 paragraph 1-2; Protocol Appendices, APPENDIX G, CLINICAL MANAGEMENT FOR ADOLESCENT DEPRESSION, pages 599 to 623;	Appendix A, Protocol, PDF page 30; page 69-93;	
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				Change from Baseline (+/- SE) in TotalScore on the Self Perception Profile for the Week 8 OC and Week 8 LOCF Datasets, page 88; 5.3.3 Sickness Impact Profile, Table 38 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Scoreand Subscores on the Sickness Impact Profile for the Week 8 OC and Week 8 LOCFDatasets, page 89; 5.4 Efficacy Subgroup Analysis, Table 39 Summary of Responders by Subgroup at Endpoint, page 90; 10 Data Source Tables: Study Population, Table 12.1 Summary of Patient Distribution by Investigator byTreatment (Intent-to-Treat Population), page 130;Table 12.2 Summary of Patients Remaining in the Study at WeeklyIntervals (Intent-to-Treat Population), pages 131-132; 11 Data Source Tables: Efficacy Results, pages 189-221; Continuation Study, Final Clinical Report, Report Synopsis, Patient Disposition and Key Demographic Data, page 6; 4 Study Population4.1 Entry into the Continuation Phase, page 24, Figure 2 Disposition of Patients, page 25; Table 3 Number (%) of Randomized Patients Who Completed the Acute Phase ButDid Not Participate in the Continuation Phase, by Reason (ITT Population), page 26; 4.3 Disposition of Patients in the Continuation Phase, page 26; 6 Efficacy Results, 6.3 Hamilton Depression Scale, Table 20 Baseline Mean (±SE) and Mean Change from		

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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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*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

[CHANGES FROM INITIAL SUBMISSION INDICATED IN RED]

List of Tables

Table i – Pairwise comparison tables – Primary and secondary efficacy variables (8 weeks)

		Omnibus	Paroxetine v. Placebo	Imipramine v. Placebo	Paroxetine v. Imipramine
Primary Efficacy Variables [8 Weeks]					
Analysis of Variance					
HAM-D Change	OC	0.255	0.106	0.673	0.261
	LOCF	0.204	0.153	0.895	0.109
Logistical Regression					
HAM-D Response ≥50% drop or ≤8	OC	0.131	0.044	0.337	0.332
	LOCF	0.269	0.117	0.651	0.253
Secondary Efficacy Variables [8 Weeks]					
Analysis of Variance					
K-SADS-L Change	OC	0.459	0.209	0.679	0.447
	LOCF	0.131	0.072	0.902	0.084
CGI Mean Score	OC	0.086	0.034	0.269	0.289
	LOCF	0.155	0.084	0.836	0.124
Autonomous Function Check List Change	OC	0.325	0.166	0.243	0.903
	LOCF	0.367	0.145	0.498	0.490
Self Perception Profile Change	OC	0.875	0.904	0.702	0.619
	LOCF	0.788	0.711	0.489	0.761
Sickness Impact Profile Change	OC	0.244	0.752	0.070	0.191
	LOCF	0.233	0.504	0.055	0.302

Analysis of Variance - with Treatment and Site Effects in the model
Logistical Regression - with Treatment and Site Effects in the model
OC – Observed Cases
LOCF – Last Observation Carried Forward
Note - All p values uncorrected for mutiple variable sampling

Table ii – Additional AEs found during review 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**

Table iii – Breakdown of new adverse events found during CRF review by System Organ Class (SOC) (MedDRA)

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

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 iv - Summary of all adverse events by SOC

	Paroxetine N=93	Imipramine N=95	Placebo N=87
System Organ Class (MedDRA)	**Reanalysis- CSR check only**	**Reanalysis- CSR check only**	**Reanalysis- CSR check only**
Cardiac and vascular disorders	45	131	32
Gastrointestinal disorders	112	147	79
Psychiatric disorders	101	63	24
Nervous system disorders	41	54	21
Respiratory, thoracic and mediastinal disorders	42	22	39
General disorders and administration site conditions	74	69	73
Skin and subcutaneous tissue disorders	10	17	10
Renal and urinary disorders	5	9	4
Immune system disorders	2	2	3
Endocrine disorders	1	1	1
Blood and lymphatic system disorders	1	4	3
Musculoskeletal disorders	8	7	16
Reproductive system and breast disorders	4	4	4
Infections	6	5	4
Eye disorders	5	4	1
Metabolism and nutrition disorders	17	6	10
Ear and labyrinth disorders	1	0	0
Injuries, poisoning and procedural complications	3	3	6
Pregnancy, puerperium and perinatal conditions	0	2	0
Surgical and medical procedures	1	2	0
TOTAL NUMBER OF AEs	**479**	**552**	**330**

Table v – 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	Reanalysis- CSR check only	Reanalysis- CSR check only
Cardiac and vascular disorders	Atrial ectopic	0	0	1
	AV block	1	2	2
	Bradycardia	0	0	1
	Bundle branch block	0	1	1
	Chest pain	2	5	2
	Dizziness	35	57	18
	ECG/ T-ECG abnormal	0	7	2
	Hot flush	0	6	2
	NIL	0	2	1
	Postural hypotension/ hypotension	3	17	1
	QT interval prolonged	0	3	0
	Tachycardia	3	28	1
	Hypertension	0	2	0
	Migraine	1	1	0
	TOTAL	**45**	**131**	**32**
Gastrointestinal disorders	Abdominal pain	0	0	2
	Constipation	7	10	4
	Cramps	14	11	14
	Diarrhea	12	8	9
	Dry Mouth	20	48	12
	Dyspepsia/ heartburn	8	12	4
	Food poisoning	1	0	1
	Gastroenteritis/ GI compliants	0	1	0
	Nausea/ sickness	37	43	27
	Reflux	1	0	0
	Retching	0	1	0
	Sores	0	0	1
	Stomatitis	0	2	0
	Ulcer	1	0	0
	Vomiting	11	11	5
	TOTAL	**112**	**147**	**79**
Psychiatric disorders	Abnormal dreams	3	5	2
	Aggravated depression	5	3	2
	Aggression/ increased anger	7	3	0
	Agitation	0	1	0
	Akathisia	18	12	8
	Anorgasmia	1	0	0
	Anxiety	2	0	1
	Concentration low	2	1	0
	Depersonalisati	0	1	1

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

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

	Weight gain	2	0	0
	Weight loss	2	1	2
	TOTAL	**17**	**6**	**10**
Ear and labyrinth disorders	Ear pain	1	0	0
	TOTAL	**1**	**0**	**0**
Injuries, poisoning and procedural complications	Head injury	0	1	0
	Overdose	0	1	0
	Trauma	3	1	6
	TOTAL	**3**	**3**	**6**
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	2	0
	TOTAL	**0**	**2**	**0**
Surgical and medical procedures	Tooth extraction	1	2	0
	TOTAL	**1**	**2**	**0**
TOTAL NUMBER OF AEs		**479**	**552**	**330**

Table vi – Breakdown of 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 and 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 site conditions	Fatigue	1	0	1	0	0	0
	Headache	4	1	7	1	0	0
	TOTAL	**5**	**1**	**8**	**1**	**0**	**0**
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 disorder	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 nutritional 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**
Injuries, 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 vii – 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 and 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 disorder	1	0	0	0	0	0
Infections	0	0	1	0	0	0
Metabolism and nutritional disorders	3	0	0	0	1	0
Injuries, 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 viii – 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 and 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	Abnormal	3	0	5	0	2	0

disorders	dreams						
	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	-
	Depersonalisation	0	-	1	0	1	0
	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	Body Shakes	0	-	0	-	0	-
	Fatigue	15	2	8	1	11	1

administration site conditions	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 disorder	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 nutritional 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 labyrinth disorders	Ear pain	1	0	0	-	0	-
	TOTAL	**1**	**0**	**0**	**-**	**0**	**-**
Injuries, 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 ix – Summary of 'Severe' adverse events (all SOCs)

SOC	Paroxetine N=93		Imipramine N=95		Placebo N=87	
	Total No. AEs reported in App D	No. reported as 'Severe'	Total No. AEs reported in App D	No. reported as 'Severe'	Total No. AEs reported in App D	No. reported as 'Severe'
Cardiac and 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 & 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 & nutritional disorders	17	0	6	0	10	1 (10%)
Ear and labyrinth disorders	1	0	0	-	0	-
Injuries, poisoning & 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 x – 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 pg 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)

CRF REVIEW: Out of 31 reviewed CRFs, 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 of those reviewed, 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)

CRF REVIEW: 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 cohort of reviewed CRFs, 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	

REVIEWED 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 xi - Baseline screening errors (found during safety check)

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 & HamD). 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 xii – Suicidality at screening (Kiddie-SADS)

From the sample of reviewed CRFs, 27% of patients were reported as having severe (or extreme) suicidal ideation at screening, compared to 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'- '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 - LAST 2 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 xiii - Types of medication taken 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 phophate	0	1	0
	Diphenhydramine citrate (exedrine pm)	0	1	0
	Mepyramine maleate (pamprin)	0	0	1
	Analgesic unknown	0	1	1
	Unknown chineses 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**
Opthalmologicals	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 xiv - AEs occurring in patients taking other medication 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 disorder	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**
Injuries, poisoning and procedural complications	Head injury	0	0
	Overdose	0	0
	Trauma	0	3
	TOTAL	**0**	**3**
Pregnancy, puerperium and perinatal	Pregnancy	0	0
	TOTAL	**0**	**0**

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 PRE ACUTE	**Patients taking 'No Medication' during PRE ACUTE**
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	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 tissues 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 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 disorder	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**
Injuries, poisoning and	Head injury	0	1
	Overdose	0	1

procedural complications	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 PRE ACUTE	**Patients taking 'No Medication' during PRE ACUTE**
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 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 disorder	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**
Injuries, 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**

Table xiv - Attrition of patients by week

TREATMENT	EFFICACY [RANDOMIZED]	STATUS	WEEK 1	2	3	4	5	6	7	8
IMIPRAMINE	94 [95]	total	94	90	81	77	74	64	58	56
		data	91	88	77	69	68	63	57	56
PAROXETINE	90 [93]	total	90	84	80	78	76	73	71	67
		data	88	81	77	76	72	72	68	67
PLACEBO	87 [87]	total	87	85	79	77	74	68	66	66
		data	84	82	75	73	70	66	63	66

Four of the randomized subjects had no post-treatment visits [1 Imipramine, 3 Paroxetine]. “total” is the number of subjects in the study for each week. “data” is the number with data for each week.