# 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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THE UNIVERSITY of ADELAIDE

10 June 2015

Dear Dr Loder

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

We are now resubmitting our paper for your in-house review. This response should be read in the context of the letter that I wrote to you dated 8 May 2015. We have made all the changes that we agreed to make in that letter, and several more that we did not agree to at that time. You will also see in our response to reviews that we have complied with requests in your email from 21 May.

As noted in our 'response to review' we accept your view that our attempts to lay open our most ambiguous example are not working as part of the paper. Our reflection about Box 2 and your concerns about its apparent bias has led us to create what we think is an important table that makes clear all of our coding decisions in relation to suicidal and self injurious behaviour. Because that table is probably too big to include in the paper proper, we have included it as RIAT Appendix 3, which also includes a modified version of the previous Box 2.

With regard to legal review, two of us have had experiences with BMJ with papers that have been commissioned, accepted and then rejected on legal review, and I think it is understandable that we are wary about last minute rejection of this paper. We therefore request that legal review will be transparent and immediate and not be delayed until the galley phase.

There are some issues unrelated to your decision about the publication of our manuscript that we want to discuss with you in more detail in this letter.

1. You asked that we specify what was done to make the coding reliable, unbiased and reproducible by providing references and other information. To our knowledge, there is not a single other article about a clinical trial in the published literature that specifies these steps, and little useful guidance is provided in the Consort-Harms document, a fact that underscores the novelty and utility of what we are doing. This state of affairs arises for two reasons. Firstly, it seems that medicine and medical journals seem to have been unaware of the issue. Secondly, coding is inherently open to revision – it is never going to, and never should, produce 100% replication. Our paper will provide a basis for future researchers to specify what the processes should be, and arguably should make it impossible for journals to feel comfortable publishing any clinical trial ever again without access to the trials data.

**CEMH: Critical and Ethical Mental Health research group**
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2. We note that you were unsettled by the example of our ambiguous coding incident, which was intentionally the most ambiguous we could find. Although we have now removed it from the body of the paper, we do want to take the time to discuss this issue. We think discomfort is exactly the hoped-for response to the challenges of coding, supporting demands to 'show us the data'. We are attempting to show that coding events need constant and repeated scrutiny. The book should never be closed on any of these events. But it gets closed when the data are sequestered.[1]

3. With regard to your request that we specify a process that would allow others to reproduce what we have done, and your reviewers apparent belief that there can be some mechanical procedure by which bias can be eliminated, the solution is to make the data available for scrutiny by others. Researchers who do so would be fully aware that their judgement calls might reveal their biases, but their commitment to the transparency of the data and the integrity of data analysis and interpretation would be such that they were happy to have their bias revealed and dissected in the process. Coding and the overall interpretation of adverse event data cannot be something that is left to a sponsoring company, and cannot be sorted out definitively in the manner some reviewers seem to want. Different investors (including patients and doctors), faced with the adverse event profile of a drug, might choose different options.

   Where the data have been thoroughly exposed, as in our Study 329 case, there is a better chance that a point can be reached where a majority of investors will take the same view as to what it means, but there will never be unanimity on these things and it may well turn out to be that the minority view is correct. Some of the most important science is about is about someone's hunch leading them to overturn a consensus.
4. We note that GSK almost certainly could not specify a process that would allow others to reproduce what they did. Three examples:

   a. In the process of looking at the data (without access to the drug names), we found that there were a large number of sore throats that GSK had in almost all instances coded as pharyngitis. At the time Study 329 was recruiting patients, and long before anything was coded, there were a number of publications showing that SSRIs can cause sore throats, but that these are dystonic in origin for the most part. GSK leapt to a diagnosis (pharyngitis) here rather than retaining the verbatim term.

[1] The United States Supreme Court has made a ruling that supports us in a 2011 judgement against Matrixx Pharmaceuticals. Matrixx shareholders took an action against the company for withholding adverse event data on their nasal spray Zircam. Zircam causes anosmia, and when this became clear, the share price of the company dropped. The shareholders argued that they should have been provided with the adverse event data. The company argued that none of the adverse event data regarding anosmia was statistically significant and that, on the basis that nothing had been proven, there was as such no need to inform the shareholders. The shareholders argued that it was not for the company to decide what the adverse event data meant; they had a right to access the data and make their own mind up as to whether their money was well invested or not. The Supreme Court sided with the shareholders.

b. In the original Appendix D, there were instances where GSK had lumped three side effects together under the one verbatim term, making diagnoses such as pneumonia. The only instance in which we thought that bringing together multiple AEs was justified was the ambiguous case in box 2 that made you feel uncomfortable. There is no way around this discomfort. While it would be a mistake to jump from sore throat to dystonia or pharyngitis without extra material to warrant this leap, in this instance there is a large amount of material in the record that clamours for coding as 'suicide attempt'.

c. In looking through the CRFs, it was clear to us that there were other AEs mentioned that did not get transferred from the CRF to Appendix D. An extreme case arose in a serious adverse event narrative where the coding term at the very top of the page in bold and large font was **DRUG WITHDRAWAL SYNDROME** and yet this was not transferred into Appendix D.

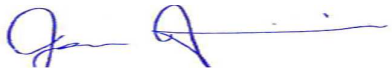
5. Your insistence on adhering to items of the protocol (while at the same time introducing imputation, which is not part of the protocol) demonstrates the real trap we face, journals face, and the field faces in the absence of access to the data. This is a trap which could allow companies to design protocols in such a manner that the evidence from the trial can never come to light, as threatens to be the case here, when our attempts to bring out the shortcomings in reporting of adverse events are described by one of your editors as 'the tail wagging the dog'.

   The only way to resolve these issues is through data access. We have attempted to make clear that making the data fully available allows others not only to interpret the data but also to judge the bias of our and other written reports based on them.

As I noted at the start of my letter, most of what I have set out here does not relate directly to your decision about our paper, but we did think it important to document our point of view.

I look forward to hearing from you soon

Yours sincerely



Jon Jureidini
on behalf of the RIAT 329 group

**Restoring Study 329: Efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: restoration of a randomised controlled trial**

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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.

v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and,
vi) licence any third party to do any or all of the above.

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 randomised controlled trials.

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

***Restoring Study 329: Efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: restoration of a randomised controlled trial***

**Abstract**

Objectives: This is a reanalysis of GSK's Study 329 (published by Keller et al. in 2001), the primary objective of which 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 to 12.328], 8.95 [7.356, to 10.541] and 9.08 [7.450 to 10.708] points, least-squares mean [95%Confidence Interval], 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]

***Restoring Study 329: Efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: restoration of a randomised controlled trial.***

**Background**

In 2013, in the face of the selective reporting of outcomes of randomised controlled trials , 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 randomised controlled trial 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* 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, including Study 329. GSK did not signal any intent to publish a corrected version of any of its trials. In later correspondence, GSK stated that Keller et al. 'accurately reflects the honestly-held views of the clinical investigator authors' and that it did 'not agree that the article is false, fraudulent or misleading'), including Appendices A-G,.[6]

Study 329 was a multicenter eight-week double-blind randomised controlled trial (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. The study was not designed to compare paroxetine with imipramine. 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 randomised controlled trials 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'), including Appendices A-G, 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, Appendix H) on that website. A table of sources of data consulted in preparing each part of this paper is available as RIAT 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) (RIAT Appendix 1). In cases where the methodology used and published by Keller et al. diverged from the protocol, we followed the protocol. Because the protocol-specified method of correction for missing values, Last Observation Carried Forward (LOCF), has been questioned in the intervening years, we also included a more modern method, Multiple Imputation (MI), at the request of the reviewers. This is a post hoc method added for comparison only, not part of our formal reanalysis. 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 Clinical Study Report reported some procedures that varied from those specified in the protocol, and we have noted variations that we 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;<br>Child Global Assessment Scale severity score < 60;<br>Hamilton Depression Scale (17-item) score ≥ 12;<br>Medically healthy;<br>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;<br>Current (within 12 months) *DSM-III-R* diagnosis of post-traumatic stress disorder;<br>Adequate antidepressant trial within 6-months;<br>Suicidal ideation with a definite plan, suicide |

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|---|---|
| | attempt during current depressive episode, or history of suicide attempt by medication overdose;<br>Medical illness which contraindicates the use of heterocyclic antidepressants;<br>Current use of psychotropic medications (including anxiolytics, antipsychotics, mood stabilizers), or illicit drugs;<br>Organic brain disease, epilepsy or mental retardation;<br>Patients who are pregnant or lactating;<br>Sexually active females not using reliable contraception;<br>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 20 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.

*Patient involvement*

So far as we can ascertain, there was no patient involvement in SKB's study design.

*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 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. A midcourse evaluation of 189 patients was carried out, without breaking the blind, revealing less variability in HAM-D scores (Standard Deviation 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 Clinical Study Report, treatments were balanced in blocks of 6 consecutive patients; however, there is an inconsistency in that in Clinical Study Report 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 Adverse Event 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 Clinical Study Report 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, to our knowledge, so there are no clear precedents or guides. **Challenges** we have encountered include:

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 Clinical Study Report and Individual Patient Data; and the raw primary data in the Case Report Forms 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 (observed case and last observation carried forward). The Clinical Study Report contained statistical comparisons on 28 discrete variables using two comparisons [paroxetine vs placebo and imipramine vs placebo] in the two datasets [OC and last observation carried forward]. The published paper listed eight variables with two statistical comparisons each in one dataset [last observation carried forward]. 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 [generalized linear model] for continuous variables using a model that included the effects of SITE, TREATMENT, and SITE x TREATMENT interaction, with the latter dropped if $p \geq 0.10$. 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 Clinical Study Report 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 RIAT Appendix 2 (table i).

Missing values

The protocol called for evaluation of the observed case and last observation carried forward datasets, with the latter being definitive. The last observation carried forward method for correcting missing values was the standard at the time the study was conducted. It continues to be widely used, although newer models such as Multiple Imputation or Mixed Models are superior. We had chosen to strictly adhere to the protocol and use the last observation carried forward method rather than introduce a post hoc analytic tool. Our reviewers, however, encouraged us to also report a Multiple Imputation analysis.

Non-protocol specified outcome variables

There were four outcome variables in the Clinical Study Report 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 Clinical Study Report (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 Clinical Study Report and we have no contemporaneous documentation of that claim, despite having repeatedly requested it from GSK.

**Conclusions**

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 RIAT 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 randomised controlled trials, so we did not include these variables in our efficacy analysis.

2. Harm Endpoints

An adverse experience/event 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.'

Adverse Events 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 Adverse Events, 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.

Adverse Event data come from the Clinical Study Report 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 Clinical Study Report for patients who had Adverse Events that were designated as serious or led to withdrawal. (Of the eleven paroxetine patients with Adverse Events designated as serious, nine discontinued because of Adverse Events.) However, the large number of other patients discontinued because of Adverse Events 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 Clinical Study Report 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 Adverse Events that led to discontinuation from the trial contained Adverse Events that had not been coded or assembled within the tables of Adverse Events.

Therefore we approached GSK for access to Case Report Forms (Appendix H). GSK made available all 275 Case Report Forms for patients entered into Study 329. However, the Case Report Forms 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 Case Report Forms. Instead we decided to focus on those 85 participants identified in Clinical Study Report Appendix H who were withdrawn from the study, along with 8 further participants who were known from prior inspection of the Clinical Study Reports to have become suicidal. 31 of the Case Report Forms that were checked were from the paroxetine group, 40 from the imipramine group and 22 from placebo.

All Case Report Forms 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), endorsed by the FDA and now used by GSK[1]. The second reviewer (JN), a clinician, is untrained in the MedDRA system, but training is not necessary for drop-out coding. 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 Case Report Forms were scrutinised for all AEs occurring during the acute, taper and follow-up phases, and total Adverse Events were compared with the Adverse Event totals reported in Clinical Study Report Appendix D.

This review process gave rise to additional Adverse Events. It also led to recoding of a number of the reasons for discontinuation. The new Adverse Events and the reasons for changing discontinuation category are recorded in Tables ii, iii and ix in RIAT Appendix 2 accompanying this paper.

At least 1000 pages were missing from the Case Report Forms reviewed with no discernible pattern to missing information; for example, one Case Report Form 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 Clinical Study Report was done blind, as was coding from the Case Report Forms. Information from Appendix D was transcribed into spreadsheets (available at www.TBA). The verbatim terms and the ADECS coding terms were transcribed first into these sheets, allowing all coding to be done before the drug names were added in. The transcription was carried out by a research assistant who was a MedDRA trained coder, who took no part in the actual coding. All coding was carried out by JLN, and checked by DH, or vice versa.

The original protocol for Study 329 makes no mention of how Adverse Events from this trial would be coded. The Clinical Study Report specifies that the Adverse Events 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 ADECS is not itself a recognized system.

We coded Adverse Events 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 into the Clinical Study Report, 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,

[1] Winter C. MedDRA in clinical trials – industry perspective SFDA-ICH MedDRA Workshop, Beijing, 13-14 May 2011. https://www.meddra.org/sites/default/files/page/documents_insert/christina_winter_2_meddra_in_clinical_trials_industry_perspective.pdf

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 Adverse Event profile of a drug. In staying closer to the original description of events, MedDRA codes suicidal events as ‘suicidal ideation’ or ‘self-harm/attempted suicide’ rather than the ADECS option of ‘emotional lability’; similarly, aggression is more clearly flagged as ‘aggressive events’ rather than ‘hostility’.

Most recoding was straightforward. The vast majority of the verbatim terms simply mapped onto coding terms in MedDRA. Coding challenges most often related to cases where there were significant Adverse Events, but the patients were designated by SKB/GSK to have discontinued for lack of efficacy. There was no patient narrative for such patients, in contrast to patients deemed to have discontinued because of the Adverse Event occurring at discontinuation. Our most challenging coding decision is described in RIAT Appendix 3.

*Analysis of harms data*

In analysing the harms data for the safety population, we have explored the discrepancies in the number of events between Case Report Forms and the Clinical Study Report. We present all Adverse Events 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; Table iv in RIAT Appendix 2 summarises adverse events by SOC. We break down events by severity, selecting Adverse Events coded as severe, and utilising the listing in Clinical Study Report 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 Adverse Events experienced by patients on concomitant medication (from Appendix B) versus those not on other medication. In addition, 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 Clinical Study Report 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 Clinical Study Report Appendix G, and in a proportion of cases changed these.

*Statistical Methods*

The primary population of interest was the intent-to-treat 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 (i.e. the last on-therapy assessment during the acute phase) and observed case datasets. Paroxetine and imipramine were each to be compared with placebo; there was no comparison of paroxetine with imipramine.

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 RIAT 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. Statistical testing was done using the Linear Model (LM) and General Linear Models (GLM) procedures of the R statistical package (version 2.15.2) as provided by GSK. Imputation was performed using the Multiple Imputation by Chained Equations (MICE) package also in R. [23]

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 | 77 (83%) | 83 (87%) | 70 (81%) |
| African American | 5 (5%) | 3 (3%) | 6 (7%) |
| Asian American | 1 (1%) | 2 (2%) | 2 (2%) |
| Other | 10 (11%) | 7 (7%) | 9 (10%) |
| 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 (0%) | 2 (2%) | 0 (0%) |
| 1 | 75 (81%) | 75 (79%) | 68 (77%) |
| 2 | 11 (12%) | 13 (14%) | 12 (14%) |
| >3 | 7 (7%) | 5 (6%) | 7 (8%) |
| Comorbidity | | | |
| Any comorbid disorder | 42 (41%) | 47 (50%) | 39 (41%) |
| Current Anxiety disorder | 24 (19%) | 24 (26%) | 24 (19%) |
| ODD, CD, or ADHD | 23 (25%) | 24 (26%) | 17 (20%) |
| Baseline Scores LSM [SEM] | | | |
| HAM-D | 18.9 [0.44] | 18.1 [0.43] | 19.0 [0.44] |
| K-SADS-L | 28.3 [9.5] | 27.5 [0.51] | 28.3 [0.52] |
| Autonomous Function | 93.4 [3.1] | 97.0 [3.1] | 94.2 [3.2] |
| Self Perception Profile | 64.0 [2.2] | 63.5 [2.2] | 63.4 [2.3] |
| Sickness Impact Profile | 32.4 [1.2] | 30.8 [1.2] | 32.9 [1.3] |

§ 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.

[legend] Allocations and discontinuations

The flow chart covers the intent-to-treat 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% (51/93) moving to a higher dose (mean 28.0 mg/day, Standard Deviation 8.4 mg) by week 8. The imipramine group was titrated to 200 mg/day by week 4, with 40% (38/95) going higher (mean 205.8 mg/day, Standard Deviation 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 Clinical Study Report. 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 for any dataset during the acute phase.

Insert Figure 2 here.

[legend] Primary outcome measures

The formal reanalysis included both observed case and last observation carried forward datasets. As mentioned above, the Multiple Imputation dataset is included for comparison. 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 observed case or last observation carried forward datasets, so pairwise analysis was considered unjustified. The results at week 8 are shown in Table 3. HAM-D scores decreased by 10.7 [9.1 to 12.3], 9.0 [7.4 to 10.5] and 9.1 [7.5 to, 10.7] points (least–squares mean [95%Confidence Interval]), for the paroxetine, imipramine and placebo groups, respectively.

Insert Table 3 here

Table 3. Datasets for primary and secondary outcomes: Observed case, Last Observation Carried Forward, and Multiple Imputation

**ANOVA** - with Treatment and Site Effects in the model
**OC** – Observed Case
**LOCF** – Last Observation Carried Forward
**MI** – Multiple Imputation
**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 Clinical Study Report 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% (93 of 275) of Case Report Forms in Appendix H produced the data shown in Table 4.

Table 4. Adverse Events found in Case Report Forms vs. Adverse Events listed in Appendix D

| | **Paroxetine (n=31)** | **Imipramine* (n=40)** | **Placebo (n=22)** |
|---|---|---|---|
| **Adverse Events found in CRFs (Appendix H)**** | 159 | 257 | 77 |
| **Adverse Events 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]

**Most frequent categories of additional adverse events found in CRFs were psychiatric for paroxetine (12/23) and placebo (4/10), and cardiovascular for imipramine (5/17) – see RIAT Appendix 2, table ii.

**Recoding and Representation of Adverse Event Data**

Table 5 presents Adverse Events found in this study according to System-Organ-Class (SOC) recoded from the Clinical Study Report Appendix D (RIAT MedDRA recoded), and additional Adverse Events found in our reanalysis of 93 Case Report Forms. Table 5 also presents the Adverse Events rated as severe by the original investigator (only from the Clinical Study Report,

because new events detected in the review of 93 Case Report Forms do not include severity ratings). A full listing of Adverse Events can be found in table iii in RIAT Appendix 2.

Table 5. Adverse events in Clinical Study Report (acute phase plus taper)

| | Paroxetine N=93 | | | Imipramine N=95 | | | Placebo N=87 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Type of Adverse Event** | CSR RIAT MedDRA coded | Severe AEs reported | | CSR RIAT MedDRA coded | Severe AEs reported | | CSR RIAT MedDRA coded | Severe AEs reported | |
| **Cardiovascular SOC*** | 45 | 1 (2%) | | 131 | 4 (3%) | | 32 | 0 | |
| **Gastrointestinal SOC** | 112 | 25 (22%) | | 147 | 20 (14%) | | 79 | 4 (5%) | |
| **Psychiatric SOC*** | 100 | 32 (32%) | | 63 | 4 (6%) | | 24 | 5 (21%) | |
| **Respiratory SOC** | 42 | 2 (5%) | | 22 | 1 (5%) | | 39 | 4 (10%) | |
| **All other SOCs** | 179 | 10 (6%) | | 189 | 21 (11%) | | 156 | 12 (8%) | |
| **TOTAL** | **479** | **70 (15%)** | | **552** | **50 (9%)** | | **330** | **25 (8%)** | |

* In the Keller et al paper, the Adverse Events 'dizziness' and 'headache' were grouped with psychiatric Adverse Events under the heading 'Nervous System'. In the MedDRA coding, these Adverse Events have been reported under 'Cardiovascular SOC' for dizziness and 'Nervous System SOC' for headaches. See also RIAT 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 CSR** RIAT MedDRA coded | **Paroxetine N=93** | **Imipramine N=95** | **Placebo N=87** |
|---|---|---|---|
| **Abnormal dreams** | 3 | 5 | 2 |
| **Depression worsening** | 5 | 3 | 2 |
| **Aggression/ anger** | 7 | 3 | 0 |

| | | | |
|---|---|---|---|
| **Agitation** | 0 | 1 | 0 |
| **Akathisia** | 18 | 12 | 8 |
| **Anxiety** | 2 | 0 | 1 |
| **Depersonalisation** | 0 | 1 | 1 |
| **Disinhibition** | 4 | 1 | 2 |
| **Hallucinations** | 1 | 1 | 0 |
| **Paranoia** | 1 | 0 | 0 |
| **Psychosis** | 1 | 0 | 0 |
| **Suicidal ideation** | 4 | 3 | 1 |
| **Suicide attempt** | 8 | 3 | 0 |
| **Total AEs** | **54** | **33** | **17** |
| **Total patients** | **35** | **23** | **12** |

* For the paroxetine group, the total suicidal ideation/suicide attempt Adverse Events were 15 from a total of 10 patients. For the placebo group, the 2 suicidal ideation Adverse Events were from 2 patients.

There were no noteworthy changes in physiological data.

**Severity Ratings**

The Clinical Study Report reported 11 serious Adverse Events (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 Adverse Event 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 Adverse Events. 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 Adverse Events is to look at rates of discontinuation due to Adverse Events. Table 7 presents reasons for withdrawal during the acute phase and taper due to Adverse Events and other causes. Note that we examined all discontinuation Case Report Forms.

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 medications 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 'Adverse Event including intercurrent illness' but was changed to 'suicide attempt'.
**We replaced the term 'Adverse Events: Intercurrent Illness' with more specific Adverse Event 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 RIAT Appendix 2 (Table ix).

In a study that has a continuation phase, the assessment of Adverse Events throws up a methodological difficulty not yet addressed by groups such as CONSORT. If a study only has an acute phase, then all Adverse Events 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 Adverse Events 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 Adverse Events 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 Adverse Event drop outs** | **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** | **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** | **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 Clinical Study Report (Appendix G), along with a review of patient narratives and Case Report Forms 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 Clinical Study Report 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 coded) | **AEs reported as severe** | **AEs reported** (RIAT MedDRA coded) | **AEs reported as severe** | **AEs reported** (RIAT MedDRA coded) | **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 Adverse Events** | **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 Adverse Events 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 Adverse Events over placebo.

Table 10. Use of other medications in the month prior to enrolment, and incidence of Adverse Events

| | 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 Adverse Events subgroup* (acute + taper)** | 15 | 39 | 12 | 21 | 6 | 11 |
| **Total Adverse Events (acute + taper)** | 158 | 320 | 220 | 332 | 137 | 193 |

* Psychiatric Adverse Events included in this subgroup include: abnormal dreams, aggravated depression, agitation, akathisia, anxiety, depersonalisation, disinhibition, hallucinations, paranoia, psychosis, suicidal ideation/gesture/attempt.

## Discussion

*Principal findings and comparison with original paper*

Our RIAT analysis of Study 329 revealed that neither paroxetine nor high-dose imipramine demonstrated efficacy for major depression in adolescents, and there was an increase in harms with both drugs. This analysis contrasts with both Keller et al.'s published findings and the way that the outcomes were reported and interpreted in the Clinical Study Report.

We analysed and reported Study 329 according to the original protocol (with approved amendments) and analysed the efficacy data accordingly. RIAT 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.

Our 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 Clinical Study Report 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 Adverse Events, 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 Case Report Forms to summary data sheets in the Clinical Study Report, and the analysis and reporting of these data sheets in Keller et al. Keller et al reported 265 adverse events with paroxetine, whereas we identified 479 from our analysis of the Clinical Study Report, and found a further 23 that had been missed from the 93 Case Report Forms that we reviewed. For all Adverse Events combined, Keller et al. reported a paroxetine burden of Adverse Events 1.25 times that of the placebo burden, compared with 1.5 times in the Clinical Study Report figures.

One reason why Keller et al.'s figures are lower than ours is because Keller et al. only presented data for Adverse Events reported for 5% of patients or more. The Clinical Study Report and Case Report Form figures also differ substantially from other figures quoted in Keller et al, because Keller et al did not report a category of psychiatric Adverse Events, 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 Adverse Events. The effect of this change was to unmask a clinically important difference in psychiatric Adverse Event profiles between paroxetine and placebo.

Keller et al. (Table 3) tabulated 51 psychiatric Adverse Events for paroxetine and 34 for placebo (5 vs 1 for Emotional lability, 7 vs 0 for Hostility, 14 vs 4 for Insomnia, 8 vs 5 for Nervousness, and 16 vs 3 for Somnolence). We found 101 psychiatric Adverse Events 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 Clinical Study Report. Our Case Report Form review added even more cases.

Table 11. Comparison of suicidal and self injurious behaviours using different safety methodologies

| | Keller et al. | | RIAT | | | |
|---|---|---|---|---|---|---|
| | Paroxetine (N=93) | Placebo (N=87) | Paroxetine | | Placebo | |
| | | | CSRs (N=93) | Additional events found in CRFs (N=31) | CSRs (N=87) | Additional events found in CRFs (N=22) |
| 'emotional liability (e.g., suicidal ideation/gestures)' | 5 | 2 | - | - | - | - |
| **Suicidal ideation (events)** | - | - | 4 | 2 | 1 | 1 |
| **Suicide attempt/self-harm (events)** | - | - | 8* | 1 | 0 | 0 |
| **suicidal and self injurious behaviours (unique individuals)** | ≤5 | ≤2 | 10 | | 2 | |

* 7 individuals; 1 made 2 attempts

Our coding process for suicidal and self injurious behaviours is fully detailed in RIAT Appendix 3.

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, which has not yet been subject to RIAT analysis.

*Comparison with other studies*

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.

*Reporting of adverse events*

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

Box 2. Potential 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 Adverse Events from the clinical record to the Adverse Event database

Our review of Case Report Forms disclosed significant under-recording of Adverse Events.

3. Filtering data on Adverse Events 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 RIAT 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 Adverse Events that occurred in more than 5% of patients obscured the harms burden. In contrast, we report all Adverse Events that have been recorded. These are available in Table v in RIAT Appendix 2 that accompanies this paper.

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

The effect of reporting only Adverse Events 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 RIAT Appendix 2, table v, the Adverse Events coded here under 'Other' are broken down under the additional MedDRA SOC headings including general, nervous system, metabolic, and pregnancy.

6. Grouping of Adverse Events

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 Adverse Events such as dizziness and headaches are grouped with psychiatric Adverse Events in the 'nervous system' SOC heading. Since these Adverse Events 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 followed MedDRA in reporting dizziness under 'cardiovascular' events and headache under 'nervous system'. There may be better categorisations; our grouping is provisional rather than strategic. In RIAT 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 Adverse Events.

7. Rating Severity

In addition to coding Adverse Events, 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 Adverse Event 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 Adverse Events. Another method is to select those Adverse Events 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 Adverse Event 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 Clinical Study Report (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 Adverse Events 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 Adverse Events.

9. Masking effects of concomitant medication

In almost all trials, patients will be on concomitant medications. The Adverse Events 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 Adverse Events 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 RIAT Appendix 2 and worksheets lodged at www.xxx, and in Appendix B from the Clinical Study Report. 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 Adverse Event profiles as the spreadsheets submitted offer the day of onset of Adverse Events and the dates of starting or stopping any concomitant medication. Another option to explore is the possibility of any prescribing cascades triggered by Adverse Events 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.

*RIAT Process*

This RIAT exercise proved to be demanding of resources. We have logged (www.xxx [TBA]) over 200,000 words of email correspondence amongst the team over 20 months. 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 Case Report Forms required extensive correspondence with GSK.[11] Although GSK ultimately provided Case Report Forms, 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 Case Report Forms. 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 Adverse Event reports. Our experience highlights that hard copies are crucial for an enterprise like this.

Our analysis indicates that although Clinical Study Reports 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 Case Report Forms.

Because we have been breaking new ground, we have not had precedents to call on in analysis and reporting. We await with interest other efforts to do something similar.

**Strengths and limitations of this study**

Study 329 was a randomised controlled trial with a reasonable sample size. However there was evidence of protocol violations, including some cases of blind-breaking. The coding of Adverse Events by the original investigators raised the possibility that some other data might be unreliable.

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.

The RIAT analysis broke new ground but was limited in that only 34% (92/275) of Case Report Forms could be checked. 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 analysis generated a useful taxonomy of potential barriers to accurate reporting of Adverse Events, and even allowing for the above limitations, demonstrated the value of permitting access to data.

**Conclusion and implications for research and policy**

Contrary to the original report by Keller et al., 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 Adverse Events in the paroxetine and imipramine arms, including serious, severe, and suicide related Adverse Events. This only became apparent when the data were made available for reanalysis. Researchers and clinicians should recognise the potential biases in published research, including the potential barriers to accurate reporting of harms that we have identified. Regulatory authorities should mandate accessibility of data.

As with most scientific papers, Keller et al. conveys an impression that 'the data have 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.

SUMMARY BOX

**Section 1: "What is already known on this topic"**

- There is a lack of access to data from most clinical randomised controlled trials, making it difficult to detect biased reporting.
- In the absence of access to primary data, misleading conclusions in publications of those trials can appear definitive.
- GlaxoSmithKline's Study 329, an influential trial that reported that paroxetine was safe and effective for adolescents, is one such study.

**Section 2: "What this study adds"**

- On the basis of access to the original Study 329 data, we report a reanalysis that concludes that paroxetine, a blockbuster antidepressant, was ineffective and unsafe in this study.

- Access to primary data makes clear the many ways in which data can be analysed and represented, demonstrating the importance of access to data and the value of reanalysis of trials.
- There are important implications for clinical practice, research, regulation of trials, licensing of drugs, and the sociology and philosophy of science.
- Our reanalysis has developed a methodology that may be adapted for future reanalyses of randomised controlled trials.

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.

Ethical approval: "The protocol and statement of informed consent were approved by an Institutional Review Board (IRB) prior to each center's initiation, in compliance with 21 United States Code of Federal Regulations (CFR) Part 56. Written informed consent was obtained from each patient prior to entry into the study, in compliance with 21 CFR Part 50. Case report forms were provided for each patient's data to be recorded" (Final Clinical Report page 000030). The sample informed consent is provided in Appendix to the Protocol, Appendix C, page 000590 to page 000594. No further information is available regarding the particular IRB that approved the 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.

Authorship

All authors meet ICMJE authorship criteria.
Conception/design of the work: Healy, Jureidini, Nardo
Acquisition of data: Jureidini (negotiation with GSK); Tufanaru and Abi-Jaoude (RIATAR); Nardo (efficacy data using GSK online remote system); Le Noury (harms data using GSK online remote system)
Data analysis: Nardo (efficacy); Le Noury and Healy (harms)
Data interpretation: all authors
Drafting the work and revising it critically for important intellectual content, final approval of the version to be published: all authors
Agreement to be accountable for all aspects of the work: all authors (guarantor Jureidini)
The first four authors made equal contribution to the paper.

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RIAT Appendices

1. RIATAR audit record, showing sources of data
2. Adverse event appendices
3. Study 329 – Suicidal & Self Injurious Behaviour

Supplementary material

Detailed data tables are available at http://study329.org/ [or on BMJ website if you prefer]

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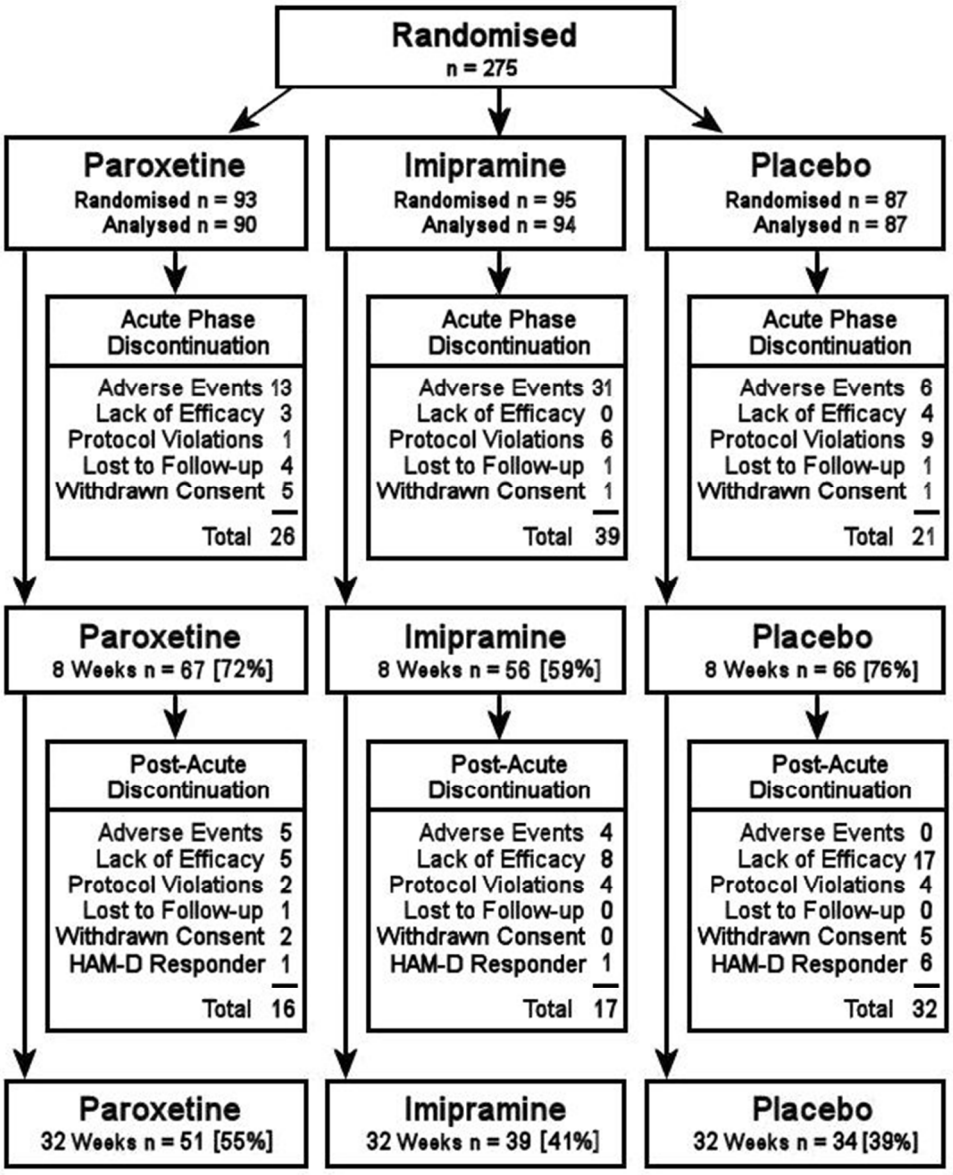
Table 3. Datasets for primary and secondary outcomes: Observed case, Last Observation Carried Forward, and Multiple Imputation

**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 | -12.2 [ -13.9 to -10.5 ] | 0.88 | 67 | -10.6 [ -12.5 to -8.7 ] | 0.97 | 56 | -10.5 [ -12.3 to -8.8 ] | 0.88 | 66 | 0.26 |
| | LOCF | -10.7 [ -12.3 to -9.1 ] | 0.81 | 90 | -9.0 [ -10.5 to -7.4 ] | 0.81 | 94 | -9.1 [ -10.7 to -7.5 ] | 0.83 | 87 | 0.20 |
| | MI | -12.5 [ -14.2 to -10.9 ] | 0.83 | 90 | -11.1 [ -12.9 to -9.4 ] | 0.89 | 94 | -10.7 [ -12.4 to -9.1 ] | 0.83 | 87 | 0.24 |
| | | 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 | | 0.13 |
| | LOCF | 66.7% | 60/30 | | 58.5% | 55/39 | | 55.2% | 48/39 | | 0.27 |
| | MI | 73.3% | 66/24 | | 70.2% | 66/28 | | 70.1% | 61/26 | | 0.24 |

**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 | -12.1 [ -13.8 to -10.3 ] | 0.91 | 67 | -10.7 [ -12.7 to -8.7 ] | 0.82 | 56 | -10.7 [ -12.5 to -8.9 ] | 0.92 | 65 | 0.46 |
| | LOCF | -11.4 [ -13.1 to -9.8 ] | 0.84 | 83 | -9.5 [ -11.1 to -7.9 ] | 0.82 | 88 | -9.4 [ -11.0 to -7.8 ] | 0.83 | 85 | 0.13 |
| | MI | -12.3 [ -13.9 to -10.6 ] | 0.84 | 83 | -11.5 [ -13.3 to -9.7 ] | 0.91 | 88 | -10.9 [ -12.6 to -9.2 ] | 0.86 | 85 | 0.54 |
| CGI Mean Score | OC | 1.9 [ 1.6 to 2.2 ] | 0.15 | 68 | 2.2 [ 1.8 to 2.5 ] | 0.17 | 56 | 2.4 [ 2.1 to 2.7 ] | 0.16 | 66 | 0.09 |
| | LOCF | 2.5 [ 2.1 to 2.7 ] | 0.16 | 90 | 2.7 [ 2.4 to 3.0 ] | 0.15 | 94 | 2.7 [ 2.4 to 3.0 ] | 0.16 | 87 | 0.16 |
| | MI | 1.9 [ 1.6 to 2.2 ] | 0.14 | 90 | 2.2 [ 1.9 to 2.5 ] | 0.15 | 94 | 2.4 [ 2.1 to 2.6 ] | 0.14 | 87 | 0.07 |
| Autonomous Function Check List Change | OC | 14.4 [ 8.8 to 19.9 ] | 2.83 | 58 | 13.3 [ 7.3 to 19.4 ] | 3.04 | 52 | 9.3 [ 3.8 to 14.8 ] | 2.81 | 60 | 0.32 |
| | LOCF | 14.7 [ 9.2 to 20.2 ] | 2.80 | 60 | 11.6 [ 5.8 to 17.3 ] | 2.92 | 57 | 9.3 [ 8.1 to 17.2 ] | 2.76 | 62 | 0.39 |
| | MI | 14.0 [ 8.7 to 19.3 ] | 2.65 | 60 | 14.5 [ 9.4 to 19.6 ] | 2.60 | 57 | 9.1 [ 4.2 to 14.1 ] | 2.52 | 62 | 0.24 |
| Self Perception Profile Change | OC | 12.9 [ 8.3 to 17.5 ] | 2.31 | 60 | 13.2 [ 8.4 to 18.1 ] | 2.46 | 55 | 12.7 [ 6.9 to 15.9 ] | 2.30 | 60 | 0.88 |
| | LOCF | 13.2 [ 8.6 to 17.8 ] | 2.33 | 61 | 13.1 [ 8.3 to 17.8 ] | 2.41 | 60 | 11.4 [ 6.9 to 15.9 ] | 2.27 | 63 | 0.88 |
| | MI | 15.4 [ 10.7 to 20.0 ] | 2.35 | 61 | 14 [ 8.9 to 19.2 ] | 2.60 | 60 | 14.7 [ 10.0 to 19.4 ] | 2.39 | 63 | 0.92 |
| Sickness Impact Profile Change | OC | -11.2 [ -14.3 to -8.1 ] | 1.57 | 62 | -13.5 [ -16.9 to -10.2 ] | 1.70 | 55 | -10.6 [ -13.7 to -7.5 ] | 1.57 | 62 | 0.24 |
| | LOCF | -11.4 [ -14.4 to -8.3 ] | 1.55 | 63 | -13 [ -16.2 to -9.8 ] | 1.62 | 60 | -9.9 [ -12.9 to -6.9 ] | 1.51 | 65 | 0.23 |
| | MI | -11.5 [ -14.2 to -8.7 ] | 1.39 | 63 | -13.9 [ -16.8 to -10.9 ] | 1.50 | 60 | -10.1 [ -13.0 to -7.1 ] | 1.48 | 65 | 0.19 |

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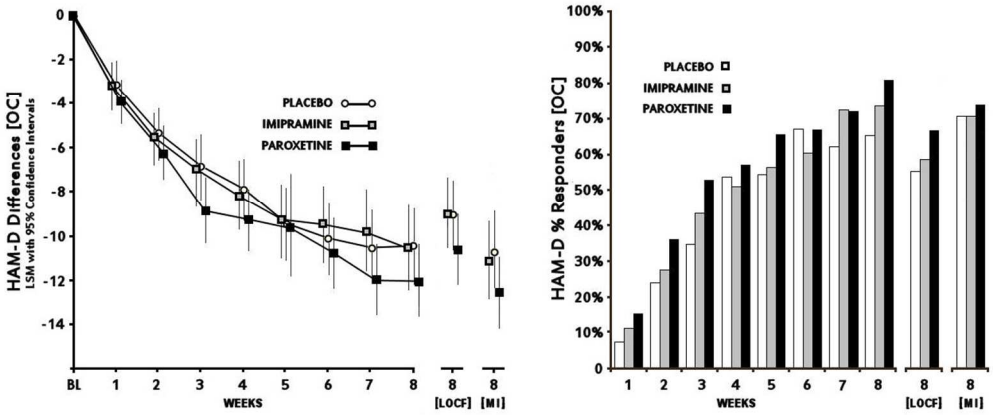


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# RIAT Audit Record (RIATAR)

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

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| **Title and abstract** | | | | | | |
| | 1a | Identification as a randomised trial in the title | p.1 | | | |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | p.1 | CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9. | CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9. | |
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| | 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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| | | 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; | |
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| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | p.4; p. 6-7; p. 8, Box 1; p.22-23; p.23-25, Box 2; p. 25; p.25-26, Box 3; | | | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | p.23-25, Box 2; p.25-26, Box 3; | Final Clinical Report, Acute Phase, Report Synopsis, Conclusions, page 21; 8 Conclusions, page 124; Continuation Study, Final Clinical Report, Report Synopsis, Conclusions, page 9; 8 Conclusions, page 64; | Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase; | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other | p.22-23; p. 25; | Final Clinical Report, Acute Phase, Report Synopsis, Conclusions page 21 paragraph 2; 7 Discussion, page 121-123;8 Conclusions, page 124; Continuation Study, Final Clinical Report, Report Synopsis, Conclusions, page 9; 7 Discussion, pages 61-63; 8 Conclusions, | Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase; | |

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

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

| Section/Topic | Item No | Checklist item | Reported on page No of RIAT manuscript | Source section(s) of the Clinical Study Report (CSR): page No. and paragraph** | PDF page No (for PDF files)*** | Notes |
|---|---|---|---|---|---|---|
| | | | | A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, IV. CASE REPORT FORM INSTRUCTIONS, page 586 to page 587 paragraph 1-2; Final Clinical Report Acute Phase, Appendix A, Protocol, APPENDIX B, ADMINISTRATIVE MATTERS, V. MONITORING BY SMITHKLINE BEECHAM (i.e. the Sponsor), page 587 paragraph 3-4; VI. ARCHIVING OF DATA, page 587 paragraph 6-7; VII. AUDITS, page 587 paragraph 8 to page 588 paragraph 1-4; VIII. CONFIDENTIALITY AND PUBLICATION, page 588 paragraph 5-6 to page 589 paragraph 1-3; Certificates of Analysis, page 1435-1446; Audited Investigator Sites, page 1480-1482;SmithKline Beecham study 29060/329, Final Clinical Report, Addendum to Study Report Continuation Phase, page 1; 3.3 Study Medication and Administration, page 20; 3.5 Method of Randomization, page 22; | | |

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

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

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

# Appendix 2

## List of Tables

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

## Primary Efficacy Variables [8 Weeks]

| | | Omnibus | Paroxetine v. Placebo | Imipramine v. Placebo | Paroxetine v. Imipramine |
|---|---|---|---|---|---|
| | | **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]

| | | Omnibus | Paroxetine v. Placebo | Imipramine v. Placebo | Paroxetine v. Imipramine |
|---|---|---|---|---|---|
| | | **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 multiple 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 |
| | BodyBP shakes | 0 | 1 | 0 |
| | Fever | 0 | 0 | 1 |
| | **Total** | **4** | **4** | **1** |
| **Nervous systems disorders** | Headache | 0 | 2 | 0 |
| | **Total** | **0** | **2** | **0** |
| **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 and 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 ('depression worsening' & 'increased irritability') were found during the continuation phase.

## 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** | 100 | 113 | 77 |
| **Respiratory, thoracic and mediastinal disorders** | 42 | 22 | 39 |
| **General disorders and administration site conditions** | 15 | 10 | 17 |
| **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, including those classed as 'Severe' by investigator - events from CSR Appendix D check 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 disorders** | Abnormal dreams | 3 | 0 | 5 | 0 | 2 | 0 |
| | Aggravated depression | 5 | 3 | 3 | 0 | 2 | 1 |
| | Aggression/ increased anger | 7 | 3 | 3 | 2 | 0 | - |
| | Agitation | 0 | - | 1 | 0 | 0 | - |
| | Akathisia | 18 | 1 | 12 | 1 | 8 | 0 |
| | Anorgasmia | 1 | 1 | 0 | - | 0 | - |
| | Anxiety | 2 | 1 | 0 | - | 1 | 1 |
| | Concentration low | 2 | 0 | 1 | 0 | 0 | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 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 | 8 | 4 | 3 | 0 | 0 | - |
| | **TOTAL** | **100** | **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 |
| | Headache | 59 | 3 | 59 | 9 | 56 | 4 |
| | 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** | **100** | **7** | **113** | **13** | **77** | **7** |
| | | | | | | | |
| **Respiratory, thoracic and mediastinal disorders** | Chest cold/ congestion | 11 | 1 | 6 | 0 | 14 | 1 |
| | Coughing | 6 | 0 | 4 | 0 | 6 | 0 |
| | Dyspnea | 3 | 1 | 5 | 1 | 2 | 0 |
| | Epistaxis | 1 | 0 | 1 | 0 | 0 | - |
| | Nasopharyngitis | 3 | 0 | 0 | - | 1 | 0 |
| | Respiratory disorder | 0 | | 0 | - | 2 | 0 |
| | Rhinitis | 10 | 0 | 3 | 0 | 5 | 1 |
| | Sinusitis | 8 | 0 | 3 | 0 | 8 | 2 |
| | Sneezing | 0 | - | 0 | - | 1 | 0 |
| | **TOTAL** | **42** | **2** | **22** | **1** | **39** | **4** |
| | | | | | | | |
| **General disorders and administration site conditions** | Body Shakes | 0 | - | 0 | - | 0 | - |
| | Fatigue | 15 | 2 | 8 | 1 | 11 | 1 |
| | Fever | 0 | - | 2 | 0 | 4 | 0 |
| | Pain | 0 | - | 0 | - | 2 | 0 |
| | **TOTAL** | **15** | **2** | **10** | **1** | **17** | **1** |
| | | | | | | | |
| **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 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 |
| | Headache | 4 | 1 | 7 | 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** | **7** | **1** | **9** | **2** | **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** | Fatigue | 1 | 0 | 1 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **disorders and administration site conditions** | **TOTAL** | **2** | **0** | **1** | **0** | **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 | 7 | 1 | 9 | 2 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 3 | 0 | 1 | 0 | 0 | 0 |
| General disorders and administration site conditions | 1 | 0 | 1 | 0 | 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 – 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** | 100 | 7 (7.0%) | 113 | 13 (11.5%) | 77 | 7 (9.1%) |
| **Respiratory, thoracic and mediastinal disorders** | 42 | 2 (4.8%) | 22 | 1 (4.5%) | 39 | 4 (10.3%) |
| **General disorders and administration site conditions** | 15 | 2 (13.3%) | 10 | 1 (10.0%) | 17 | 1 (5.9%) |
| **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** | **478** | **70 (14.6%)** | **552** | **50 (9.1%)** | **330** | **25 (7.6%)** |

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

CRF REVIEW: Out of 31 reviewed CRFs, 9 changes to reasons for withdrawal were proposed:

| | Patient ID | SKB/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 | SKB/GSK reason for withdrawal (as per Appendix 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 | SKB/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 reviewed CRFs, 3 changes to reasons for withdrawal were proposed:

| | Patient ID | SKB/GSK Reason for withdrawal (as per Appendix 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:

| | Patient ID | SKB/GSK reason for withdrawal (as per Appendix G) | RIAT reason for withdrawal |
|---|---|---|---|
| **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 | SKB/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 | |

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

| | **Patient ID** | **SKB/GSK reason for withdrawal (as per Appendix 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 x - 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 & HAM-D). Patient showed 'worsening depression' during the study, was admitted to hospital during week 4 and given Zoloft. SKB/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 xi – Suicidality at screening (Kiddie-SADS)**

From the sample of reviewed CRFs, 27% of patients on placebo were reported as having severe (or extreme) suicidal ideation at screening, compared with 13% in the paroxetine group and 3% in imipramine (see part b of table xi).

**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 Two Weeks' at Screening (-1 week)**

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

**Table xii - Types of medication taken during month prior to enrolment**

| ATC Level 2 drug type grouping | Drug | Paroxetine (n=24) | Imipramine (n=31) | Placebo (n=26) |
|---|---|---|---|---|
| **Analgesics** | Acetylsalicylic acid (aspirin) | 1 | 1 | 0 |
| | cinnamedrine hydrochloride (Midol) | 1 | 0 | 0 |
| | paracetamol | 10 | 9 | 4 |
| | Paracetamol plus (Tylenol/Benadryl cold/flu) | 2 | 1 | 1 |
| | Codeine phosphate | 0 | 1 | 0 |
| | Diphenhydramine citrate (Exedrin PM) | 0 | 1 | 0 |
| | Mepyramine maleate (Pamprin) | 0 | 0 | 1 |
| | Analgesic unknown | 0 | 1 | 1 |
| | Unknown Chinese medicine | 0 | 1 | 0 |
| | **Total** | **14** | **15** | **7** |
| | | | | |
| **Antibiotics** | amoxicillin | 1 | 2 | 4 |
| | tetracycline | 1 | 0 | 0 |
| | erythromycin | 0 | 1 | 2 |
| | azithromycin | 0 | 0 | 1 |
| | **Total** | **2** | **3** | **7** |
| | | | | |
| **Psychoanaleptics** | Fluoxetine (Prozac) | 1 | 0 | 0 |
| | Sertraline | 1 | 0 | 0 |
| | Amitriptyline | 0 | 0 | 1 |
| | **Total** | **2** | **0** | **1** |
| | | | | |
| **Psycholeptics** | diazepam | 0 | 0 | 1 |
| | **Total** | **0** | **0** | **1** |
| | | | | |
| **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** | Phenobarbital, 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 (Tavist-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 xiii - AEs occurring in patients taking other medication during month prior to enrolment vs. those taking no other medication:**

**a) Paroxetine group**

| | | 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 | 7 |
| | Cramps | 3 | 11 |
| | Diarrhea | 1 | 11 |
| | Dry Mouth | 5 | 15 |
| | Dyspepsia | 1 | 7 |
| | Food poisoning | 1 | 0 |
| | Gastroenteritis | 0 | 0 |
| | Nausea | 8 | 29 |
| | Reflux | 1 | 0 |
| | Retching | 0 | 0 |
| | Sores | 0 | 0 |
| | Stomatitis | 0 | 0 |
| | Ulcer | 0 | 2 |
| | Vomiting | 2 | 9 |
| | **TOTAL** | **22** | **90** |
| | | | |
| **Vascular disorders** | Hypertension | 0 | 0 |
| | Migraine | 0 | 1 |
| | **TOTAL** | **0** | **1** |
| | | | |
| **Nervous system disorders** | Bad taste | 0 | 0 |
| | Convulsion | 0 | 0 |
| | Dystonia | 4 | 1 |
| | Headache | 25 | 34 |
| | Laryngitis dystonia | 0 | 1 |
| | Memory loss | 0 | 0 |
| | Myoclonus | 3 | 1 |
| | Paresthesia | 0 | 1 |
| | Sore throat-dystonia | 7 | 3 |
| | Tics | 0 | 1 |
| | Tinnitus | 0 | 0 |
| | Toothache dystonia | 4 | 2 |
| | Tremor | 4 | 7 |
| | Vision blurred | 0 | 2 |
| | **TOTAL** | **47** | **53** |
| | | | |
| **General disorders and administration site conditions** | Fatigue | 6 | 9 |
| | Fever | 0 | 0 |
| | Pain | 0 | 0 |
| | **TOTAL** | **6** | **9** |
| | | | |
| **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 | 4 | 12 |
| | Paranoia | 1 | 0 |
| | Psychosis | 0 | 1 |
| | Somnolence | 9 | 15 |
| | Substance abuse | 0 | 1 |
| | Suicidal ideation/gesture | 0 | 4 |
| | Suicide attempt | 2 | 6 |
| | **TOTAL** | **30** | **70** |
| | | | |
| **Respiratory, thoracic and mediastinal disorders** | Coughing | 4 | 2 |
| | Chest cold | 2 | 9 |
| | Epistaxis | 0 | 1 |
| | Dyspnea | 0 | 3 |
| | Nasopharyngitis | 2 | 1 |
| | Respiratory disorder | 0 | 0 |
| | Rhinitis | 4 | 6 |
| | Sinusitis | 3 | 5 |
| | Sneezing | 0 | 0 |
| | **TOTAL** | **15** | **27** |
| | | | |
| **Cardiac disorders** | Atrial ectopic | 0 | 0 |
| | AV block | 0 | 1 |
| | Bradycardia | 0 | 0 |
| | Bundle branch block | 0 | 0 |
| | Dizziness | 14 | 21 |
| | Chest pain | 0 | 2 |
| | ECG/ T-ECG abnormal | 0 | 0 |
| | Hot flush | 0 | 0 |
| | Postural hypotension | 1 | 2 |
| | QT interval prolonged | 0 | 0 |
| | Tachycardia | 1 | 2 |
| | **TOTAL** | **16** | **28** |
| | | | |
| **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 | 1 |
| | **TOTAL** | **2** | **2** |
| | | | |
| **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 | 4 |
| | Thirst | 0 | 0 |
| | Weight gain | 1 | 1 |
| | Weight loss | 0 | 2 |
| | **TOTAL** | **4** | **13** |
| | | | |
| **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 conditions** | Pregnancy | 0 | 0 |
| | **TOTAL** | **0** | **0** |
| | | | |
| **Surgical and medical procedures** | Tooth extraction | 0 | 1 |
| | **TOTAL** | **0** | **1** |
| | | | |
| **Total number of AEs** | | **158** | **320** |

**b) Imipramine group**

| | | **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 | 2 |
| | Dry Mouth | 15 | 33 |
| | Dyspepsia | 4 | 8 |
| | Food poisoning | 0 | 0 |
| | Gastroenteritis | 0 | 1 |
| | Nausea | 14 | 29 |
| | Reflux | 0 | 0 |
| | Retching | 0 | 1 |
| | Sores | 0 | 0 |
| | Stomatitis | 0 | 2 |
| | Vomiting | 6 | 5 |
| | **TOTAL** | **48** | **99** |
| | | | |
| **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 |
| | Headache | 32 | 27 |
| | 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 | 14 | 6 |
| | Vision blurred | 1 | 4 |
| | **TOTAL** | **58** | **55** |
| | | | |
| **General** | Fatigue | 5 | 3 |

| | | | |
|---|---|---|---|
| **disorders and administration site conditions** | Fever | 0 | 2 |
| | Pain | 0 | 0 |
| | **TOTAL** | **5** | **5** |
| | | | |
| **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 | 2 | 1 |
| | Sneezing | 0 | 0 |
| | **TOTAL** | **8** | **13** |
| | | | |
| **Cardiac disorders** | Atrial ectopic | 0 | 0 |
| | Arrythmia | 0 | 1 |
| | AV block | 1 | 1 |
| | Bradycardia | 0 | 1 |
| | Bundle branch block | 0 | 1 |
| | Dizziness | 19 | 38 |
| | Chest pain | 4 | 1 |
| | ECG/ T-ECG abnormal | 3 | 4 |
| | Hot flush | 3 | 3 |
| | Postural hypotension | 7 | 10 |
| | QT interval prolonged | 2 | 1 |
| | Tachycardia | 12 | 16 |
| | **TOTAL** | **51** | **77** |
| | | | |
| **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 disorders** | Albuminuria | 0 | 0 |
| | Cystitis | 0 | 0 |
| | 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 | 1 |
| | Eosinophilia | 1 | 0 |
| | Leukopenia | 2 | 0 |
| | Lymphadenopathy | 0 | 0 |
| | Thrombocythemia | 0 | 0 |
| | **TOTAL** | **3** | **1** |
| | | | |
| **Musculoskeletal and connective tissue disorders** | Arthralgia | 1 | 0 |
| | Back pain | 0 | 2 |
| | Chills | 0 | 3 |
| | Myalgia | 1 | 0 |
| | **TOTAL** | **2** | **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 procedural complications** | Head injury | 0 | 1 |
| | Overdose | 0 | 1 |
| | Trauma | 0 | 1 |
| | **TOTAL** | **0** | **3** |
| | | | |
| **Pregnancy, puerperium and perinatal conditions** | Pregnancy | 0 | 2 |
| | **TOTAL** | **0** | **2** |
| | | | |
| **Surgical and medical Procedures** | Tooth extraction | 0 | 2 |
| | **TOTAL** | **0** | **2** |
| | | | |
| **Total number of AEs** | | **220** | **332** |

**c) Placebo group**

| | | **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 | 13 |
| | Reflux | 0 | 0 |
| | Retching | 0 | 0 |
| | Sores | 0 | 1 |
| | Stomatitis | 0 | 0 |
| | Vomiting | 2 | 3 |
| | **TOTAL** | **32** | **47** |
| | | | |
| **Vascular disorders** | Hypertension | 0 | 0 |
| | Migraine | 0 | 0 |
| | **TOTAL** | **0** | **0** |
| | | | |
| **Nervous system disorders** | Bad taste | 0 | 0 |
| | Convulsion | 0 | 0 |
| | Dystonia | 2 | 1 |
| | Headache | 29 | 27 |
| | 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** | **38** | **39** |
| | | | |
| **General disorders and administration site conditions** | Fatigue | 3 | 8 |
| | Fever | 1 | 3 |
| | Pain | 1 | 1 |
| | **TOTAL** | **5** | **12** |
| | | | |
| **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 |
| | Arrhythmia | 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 | 4 |
| | 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** | **4** |
| | | | |
| **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** | **193** |

**Table xiv - Attrition of patients by week**

| Treatment group | Efficacy [randomised] | 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 randomised patients had no post-treatment visits [1 Imipramine, 3 Paroxetine].
“total” is the number of patients in the study for each week.
“data” is the number with data for each week.

**RIAT Appendix 3: Study 329 – Suicidal & Self Injurious Behaviour**

| Patient ID | CSR Appendix D Patient Data Listings of Adverse Events | | | Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G | MedDRA based on CSR | Additional information from CRF | MedDRA based on CRF |
|---|---|---|---|---|---|---|---|
| | Verbatim terms | SKB/GSK ADECS preferred term | Day AE occurred | | | | |
| **Paroxetine** | | | | | | | |
| Case 1: 329.002.00058 | Intentional overdose (Tylenol overdose took 80 pills) | Emotional lability | 122 (during taper) | - Appendix G: Reason for withdrawal = Adverse Event (AE) intercurrent illness (intentional overdose).<br>- SAE narrative: *The patient was hospitalized on 19-Jan-95 after taking 80 Tylenol tablets…. The investigator considered the event to be moderately severe. The patient was withdrawn from the study due to the overdose.* | Suicide attempt/ self harm | - | Suicide attempt/ self harm |
| Case 2: 329.002.00245 | Tylenol overdose (intentional) | Emotional lability | 14 | - Appendix G: AE classed as severe.<br>- Patient withdrawn: AE intercurrent illness | Suicide attempt/ self harm | - p141 Adverse Event Report *Overdose on 27-28 Tylenol pills. Tylenol overdose. {intentional}*<br>- p175 Adverse experience *Tylenol overdose - Intentional* | Suicide attempt/ self harm |
| Case 3: 329.003.00250 | 3.1. Overdose intentional | Emotional lability | 37 | - Appendix G: SAE rated as moderate intensity. Patient continued in study.<br>- SAE narrative: *The patient exceeded compliance from 19APR96 through 09May96. The overdose was rated by the investigator as serious, moderate in intensity and unrelated to the patient's use of the study drug.* | Suicide attempt/ self harm | - | Suicide attempt/ self harm |
| | 3.2. Overdose | Emotional | 75 (during | - Patient's 2nd overdose during study. | Suicide | - p267 - Extra note written on | Suicide |

| | | | | | | | |
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| | intentional | lability | taper) | - Appendix G: Severe AE. Patient withdrawn for Adverse Event, including intercurrent illness - *Pt took overdose and was hospitalized.*<br>- SAE narrative: *The patient took a 20-tablet overdose of study medication. She was taken to the emergency room by her sister….the patient was discharged from the general hospital and admitted to psychiatric unit as she remained suicidal.* | attempt/ self harm | Adverse Experience log: *Hospitalisation resulting from suicide attempt* and *Pt took overdose 'intentional'.*<br>- Series of query log* entries whether to include suicidal ideation as another AE reason for hospitalisation.<br>- 'Hospitalisation' removed as an AE; suicidal ideation not included.<br>- p335 Query log states: *We asked the site to clarify if pt was hosp. for 'Suicidal ideation'. They answered that hosp. should show possibly related to study med.*<br>- Appendix D - AE is logged as 'UNRELATED'. | attempt/ self harm |
| Case 4: 329.003. 00313 | 4.1. Superficial cuts - risk to self | Emotional lability | 12 | - Appendix G: classed as SAE, severe.<br>- Reason for withdrawal= AE intercurrent illness - *Patient was dropped due to hospitalization i.e. adverse experience.*<br>- Patient also auditory hallucinations on Day 12 (severe).<br>- SAE narrative: *Patient hospitalised for psychosis [no previous history of psychosis] with auditory hallucinations and superficial cuts. A voice commanded him to hurt himself.* | Suicide attempt/ self harm (and psychosis – missing from Appendix D) | Week 2 visit a *serious attempt at suicide* was reported on the Hamilton rating scale and it was noted that the patient reported cutting himself 3 times over a period of 6 days.<br><br>p.182: *X experiencing auditory hallucinations. A voice commands him to hurt himself. He has cut himself in response to the voice on three occasions in the past six days. On the back of his hand he has carved a cross with small adorning cuts. On his forearm he has made 10-15 cuts, each about six inches long. On his upper arm are three additional cuts.* | Suicide attempt/ self harm |

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| | | | | | | p120 week 2 HAM-D item 3 suicide: *Attempts at suicide (any serious attempt rates 4)* - patient rated 4. | |
| | 4.2. missing | - | 12 | - SAE narrative: *The voice also commanded the patient to jump off the roof. Although the patient went to the roof he did not jump. It was determined that the patient was a risk to himself.* | Suicidal ideation | - | Suicidal ideation |
| Case 5: 329.004. 00015 | 5.1. Self Mutilation | Emotional lability | 31 | - An increase in suicidal ideation reported on HAM-D *suicide ideas or gesture* around week 5, during which time the patient is also noted to be self harming *'self mutilation'.* | Suicide attempt/ self harm | - | Suicide attempt/ self harm |
| | 5.2. Suicidal ideation | Emotional lability | 31 | - See above.<br>No SAE narrative | - | - p502 & 512 query log *'Spends most of day in bed without eating'*.<br>- Query log entries: 'Loss of appetite' (p.502) and 'weight loss' (p511) noted. These additional AEs were noted. | Suicidal ideation |
| Case 6: 329.006. 00038 | Attempted suicide (intentional) | Emotional lability | 57 | - Appendix G: AE Severe, patient withdrawn: *Several personal crisis led patient to overdose on several medications including study medications on 12APR95 - move to withdraw.*<br>- SAE narrative: *Following a disagreement with her mother, the patient intentionally overdosed.* | Suicide attempt/ self harm | p193 Week 8 paperwork not completed. Note on file: *Pt attempted suicide this day - in emergency room facilities.*<br>- 'GI complaints' & 'Nausea' - coded as part of suicide attempt by SKB/GSK.<br>'Weight loss' and 'fatigue' also added during our CRF check. | Suicide attempt/ self harm |
| Case 7: 329.006. 00039 | 7.1. Superficial scratches | Trauma | 18 | - Appendix G: reason for withdrawal: Lack of Efficacy Day 92.<br>- AE coded as Trauma – duration of 12 days; Number of episodes reported as CONTINUOUS.<br>- Other adverse events recorded in Appendix D: Day 43 = asthenia, more | Suicide attempt/ self harm | - Within 2 weeks of starting the acute phase the patient was reported as *more tired* and *more sick* in CRF.<br><br>- There was also a hand written note under 'obvious retardation at | Suicide attempt/ self harm |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | depressed, irritable/ nervousness, myoclonus (grimacing face with blinking eyes).<br><br>No SAE narrative | | interview': *softness of speech*. All these AEs were missing from Appendix D.<br><br>-At the week 6 visit a number of additional adverse events were noted – fatigue, more angry (missing from Appendix D), more depressed, irritable mood, grimacing face and blinky eyes (which were classed as myoclonus in Appendix D but recorded separately under MedDRA coding).<br>- Kiddie SADS scores:<br>Week 4: 'Non-suicidal acts of self harm in last 2 weeks' = 4 (moderate). | |
| | 7.2. missing | - | | See above | - | HAM-D weeks 5 & 6 – score '3' - 'suicidal ideas or gesture'<br>The final visit notes described the patient as having 'headaches- more severe than usual' – these were recorded in Appendix D; *worse general/overall feeling depressed with a HAM-D score of 24*. Adverse event of worsening depression – missing from Appendix D. | Suicidal ideation |
| Case 8: 329.001. 0065 | 8.1. Needed 6 stitches to hand after breaking pictures (due to anger) resulted in hospitalisation to prevent aggression against self | Hostility | 14 | -Other adverse event included on day 14: Worsening of depression, hospitalised (Severe, possibly related, stopped from study).<br>- From SAE narrative: '*the patient became very angry....His anger subsided, but he expressed hopelessness and possible suicidal thoughts. The patient was hospitalized due to his severe anger* | Suicidal ideation<br><br>(& Aggression) | - | Suicidal ideation<br><br>(& Aggression) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | *outburst and a worsening of his depression... In the opinion of the investigator, the worsening of depression was possibly related to study medication.'* | | | |
| | 8.2 missing | - | 14 | - Appendix G: reason for withdrawal: Adverse Event, including intercurrent *Needed psychiatric hospitalisation for increased aggression against self.* | - | -CRF study conclusion form reports hospitalisation for *increased aggression against self*.<br><br>-p108 Adverse experience: *needed 6 stitches to hand. Aggression to self.*<br>-p.136 Query log reports: *Telephone report also indicates a symptom of increased self harm.*<br>- Adverse events of 'self harm' 'hopelessness' 'inc anger' suicidal ideation' combined as HOSTILITY, but coded separately under MedDRA coding.<br>- Discussion in the CRF query log of the patient needing stitches to their hand following a *severe angry outburst* and *increased self `harm*. | Suicide attempt/ Self Harm |
| Case 9: 329.005. 00333 | Suicidal ideation | Emotional lability | 37 | - Appendix G: Reason for withdrawal 'Lack of Efficacy' (day 33). Severe SAE.<br>- Other adverse events included: abnormal dreams (day 19) for 11 days.<br>- SAE narrative: '*patient did not sleep well all night, cried and experienced suicidal intentions. She was subsequently hospitalized for severe suicidal ideation.'* | Suicidal ideation | -p198 & 224: *Suicidal ideation. The pt had Prozac 5mg x1 pd given for MDD.*<br>- 'Depression worsening' added as additional AE.<br>-p174 Adverse Experience log: *Suicidal Ideation.* | Suicidal ideation |
| Case 10: 329.002. 00106 | Oppositional Defiant Disorder | Hostility | 51 | - Appendix G records this as a severe SAE.<br>- SAE narrative: *patient was hospitalised after an argument. She had become combative with her mother and had* | Suicidal ideation/ gesture (& Aggressi | -p178: *no week 8 visit due to psychiatric hospitalization.*<br>-p 185 *Zoloft added for 'depression' following hospitalization for ODD.* | Suicidal ideation/ gesture (& Aggressio |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | *threatened suicide...several days before her hospitalisation she had not taken her study medication.* | on) | | n) & Depressio n |
| **Imipramine** | | | | | | | |
| Case 1: 329.005. 00295 | Suicidal threat with scissors | Emotional lability | 23 | - Appendix G: Adverse Event entered 'suicidal threat' = moderate and 'probably related'.<br>- Patient withdrawn on Day 53. Reason for withdrawal: AE intercurrent illness - *investigators decision to discontinue study because pt threatened to kill parents.* This event coded as 'hostility' severe; probably related. | Suicide attempt/ self harm | Kiddie-SADS Week 4: suicidal ideation increased to 3. | Suicide attempt/ self harm |
| Case 2: 329.012. 00223 | 2.1. Suicidal ideation | Emotional lability | 26 | Appendix G: suicidal ideation coded as moderate lasting 10 days. | Suicide attempt/ self harm | -p193 *SAE: Patient admitted to hospital for 3 days by precaution b/c she was more depressed with self mutilation and suicidal ideation.* Approx wk 4-5 | Suicidal ideation |
| | 2.2. Self mutilation | | 31 | - Appendix G: self mutilation coded as moderate, continuous, and classed as a SAE.<br>- SAE narrative: '*the patient experienced depression and self mutilation for which she was hospitalized*'. | Suicide attempt/ self harm | See above. | Suicide attempt/ self harm |
| Case 3: 329.005. 00113 | 3.1. Suicidal ideation | Emotional lability | 32 | Appendix G: Patient withdrawn on day 32. Reason: Adverse Event including intercurrent illness. | Suicidal ideation | See below. | Suicidal ideation |
| | 3.2. missing | - | 32 | - SAE narrative: '*Study medication was stopped on day 32 because of suicidal ideation with gesture considered to be of moderate severity.*' | Suicidal gesture | - Week 4 note on p191 of CRF: *Pt suicidal and went to ER.*<br>- p190 - *SAE for suicidal ideation and gesture started on 02Mar95.* | Suicidal gesture |
| Case 4: 329.010. 00279 | "Strange thoughts" | Thinking abnormal | 33 | No SAE narrative | Suicidal ideation | No clarification given re: strange thoughts in query log *'pt and mother can't remember'* | Suicidal ideation |
| **Placebo** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Case 1: 329.001.00123 | Suicidal thoughts | Emotional lability | 46 | Appendix G: adverse event classed as severe, related, a SAE. Study drug was stopped and patient was withdrawn. Other adverse events noted = Worsening of depression day 46 (severe, related, SAE, stopped)<br>- Patient withdrawn DAY 49 'Lack of Efficacy'.<br>- SAE narrative: '*Approximately 6 weeks after commencing study 329, the patient experienced severe worsening of depression with severe suicidal thoughts'.* | Suicidal ideation | - | Suicidal ideation |
| Case 2: 329.009.00129 | missing | - | | - | - | Acute phase conclusion: *Patient doing some what worse. Mother worried about increase in death wishes.* | Suicidal ideation |

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

**Coding Challenges**

Paroxetine case 7 (329.006.00039), who had a severe (but not serious) Adverse Event, was our most ambiguous case. As with all of our coding, the coder was blind to the treatment allocation.

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 Adverse Events in Clinical Study Report Appendix D.

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

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

The patient discontinued treatment during the continuation phase. Had she been deemed to have discontinued because of an Adverse Event, 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 Adverse Events 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/GSK but were recoded separately by us).

In spite of the self-harm being recorded as 'superficial scratches', we opted for 'suicide attempt' as the correct coding for what SKB/GSK had coded as trauma at week 2 (see above). This was because the patient had 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, along with being more angry, depressed and irritable. There are arguments for having coded the event differently; choosing the more severe of the alternatives brings to the fore any possible adverse effects from medication or placebo.

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 Adverse Event 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/GSK coded this way, the patient would have required a patient narrative.