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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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.

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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 SmithKline Beecham'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. Adverse experiences were to be compared primarily by using descriptive statistics. No coding dictionary was pre-specified.

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 were observed, including suicidal ideation and behaviour and other serious adverse events 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). 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, with Dr Martin Keller as the primary author (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'.[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. 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, publically 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 approximately 77,000 pages of 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, RIAT Audit Record (RIATAR).

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 RIAT Appendix 1. In cases where the methodology used and published by Keller et al. diverged from the protocol, we followed the original 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 BMJ peer-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; Child Global Assessment Scale severity score < 60; Hamilton Depression Scale (17-item) score ≥ 12; Medically healthy; IQ ≥ 80 (based on Peabody Picture Vocabulary Test).	Current or past *DSM-III-R* diagnosis of: bipolar disorder, schizoaffective disorder, anorexia nervosa, bulimia, alcohol or drug abuse/dependence, obsessive-compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder; Current (within 12 months) *DSM-III-R* diagnosis of post-traumatic stress disorder; Adequate antidepressant trial within 6-months; Suicidal ideation with a definite plan, suicide attempt during current depressive episode, or history of suicide attempt by medication overdose; Medical illness which contraindicates the use of

	heterocyclic antidepressants; Current use of psychotropic medications (including anxiolytics, antipsychotics, mood stabilizers), or illicit drugs; Organic brain disease, epilepsy or mental retardation; Patients who are pregnant or lactating; Sexually active females not using reliable contraception; Use of an investigational drug within 30 days or within five half-lives of the investigation drug.

An unkown number of patients (not disclosed in the available documents) 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]
- 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 for any outcome variable, 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 chose to adhere to the protocol and use the last observation carried forward method, including Multiple Imputation for comparison only.

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 in Appendix D of the Clinical Study Report report the Verbatim Terms used by the blinded investigators along with Preferred Terms as coded by SKB using the Adverse Drug Events Coding System (ADECS) dictionary. Appendix D also includes ratings of severity and ratings of relatedness. We used the Medical Dictionary for Regulatory Activities (MedDRA®) to code the verbatim terms provided in Clinical Study Report Appendix D. 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]

Several limitations of the ADECS coded preferred terms provided in Clinical Study Report Appendix D became clear when we examined the ADECS preferred terms assigned to the verbatim terms: First, a number of verbatim terms had been left uncoded into ADECS. Second, a number of adverse events found in the patient narratives of serious Adverse Events that led to discontinuation from the trial were not transcribed into Appendix D.

Therefore we approached GSK for access to Case Report Forms (Appendix H of the Clinical Study Report, which are not publically available). GSK made available all 275 Case Report Forms for patients entered into Study 329. However, the Case Report Forms, which totalled approximately 77,000 pages, 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

[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

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 MedDRA. 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 identified additional Adverse Events that had not been recorded as verbatim terms in Clinical Study Report Appendix D. 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

Choice of coding dictionary for harms

The protocol (p.25) indicates that adverse events were to be coded and compared by preferred term and body system using descriptive statistics, but does not pre-specify a choice of coding dictionary for generating preferred terms from verbatim terms. The Clinical Study Report (written after the study concluded) 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 and is no longer available.

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. For coding purposes, we have taken the original terms used by the clinical investigators as transcribed into the Clinical Study Report Appendix D, and applied MedDRA codes to these descriptions. 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, but took no part in the actual coding. All coding was carried out by JLN, and checked by DH, or vice versa.

All of our coding from the verbatim terms in the Clinical Study Report Appendix D was done blind, as was coding from the Case Report Forms.

We present results as SKB presented them in the Clinical Study Report using the ADECS dictionary (table 14.2.1), and as coded by us using MedDRA.

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

Classifying a problem as a 'respiratory system disorder' (inflammation) rather than as a 'dystonia' (a central nervous system disorder) can make a significant difference to the apparent 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 coding 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 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. There were few challenging coding decisions. Our coding of cases where suicidal and self-injurious behaviours were considered is set out in RIAT Appendix 3.

Analysis of harms data

In analysing the harms data for the safety population, we have done the following: First we explored the discrepancies in the number of events between Case Report Forms and the Clinical Study Report. Second we present all Adverse Events rather than only those happening at a particular rate (as Keller et al. did). Third we have grouped events into broader system-organ-class (SOC) groups – psychiatric, cardiovascular, gastrointestinal, respiratory and other; Table iv in RIAT Appendix 2 summarises all adverse events by all MedDRA SOC groupings. Fourth, 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. Fifth, 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. Sixth, 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]'; '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 made changes in a proportion of cases.

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 to be 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, table i 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.

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

Insert Table 3 here

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 Case Report Forms

We reviewed Case Report Forms in Appendix H for 93 (34%) of 275 patients. This review discovered adverse events recorded onto case report forms but not transcribed into the patient level listings of adverse events in CSR Appendix D. We present these discrepancies 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]

The 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.

Coding and Representation of Adverse Event Data

Table 5 presents the number of Adverse Events found in this study summarised by System-Organ-Class (SOC), firstly as coded by SKB using ADECS, secondly as reported by Keller et al (who only reported adverse events that occurred at frequency of more than 5%), and thirdly as coded by us using MedDRA. A full listing of Adverse Events can be found in Table iv in RIAT Appendix 2.

Table 5. Adverse events in the Clinical Study Report (ADECS and MedDRA coded) and in Keller et al

	Paroxetine (N = 93)			Imipramine (N = 95)			Placebo (N = 87)		
Adverse Event SOC**	**CSR ADECS coded***	**Reported in Keller et al**	**CSR RIAT MedDRA coded**	**CSR ADECS Coded***	**Reported in Keller et al**	**CSR RIAT MedDRA coded**	**CSR ADECS Coded***	**Reported in Keller et al**	**CSR RIA MedDR coded**
Cardiovascular	7	5	44	60	42	130	12	6	32
Gastro-intestinal/Digestive	80	84	112	108	106	147	59	61	79
Psychiatric	-	-	103	-	-	63	-	-	24
Respiratory	39	33	42	32	27	22	43	37	39
Neurological/Nervous system	106	115	101	117	135	114	42	65	77
Other	121	28	79	51	30	76	30	38	79
Body as a Whole	106	-	-	125	-	-	121	-	-
Total	338	265	481	493	340	552	277	207	330

* source = CSR, table 14.2.1. It is not clear whether this includes the taper phase.

**While in the CSR, headaches were included in 'Body as a Whole', in the Keller et al paper, the Adverse Events 'headache' along with 'dizziness' were grouped with psychiatric Adverse Events under the heading 'Nervous System'. The MedDRA dictionary allows dizziness to be coded under 'Cardiovascular or Neurological SOCs' and headaches under 'Neurological SOC'. See also RIAT Appendix 2, tables iv & v.

We included events occurring during the taper phase that SKB allocated to the continuation phase as acute phase adverse events. 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. SKB do not appear to have done this, leading to some differences in numbers.

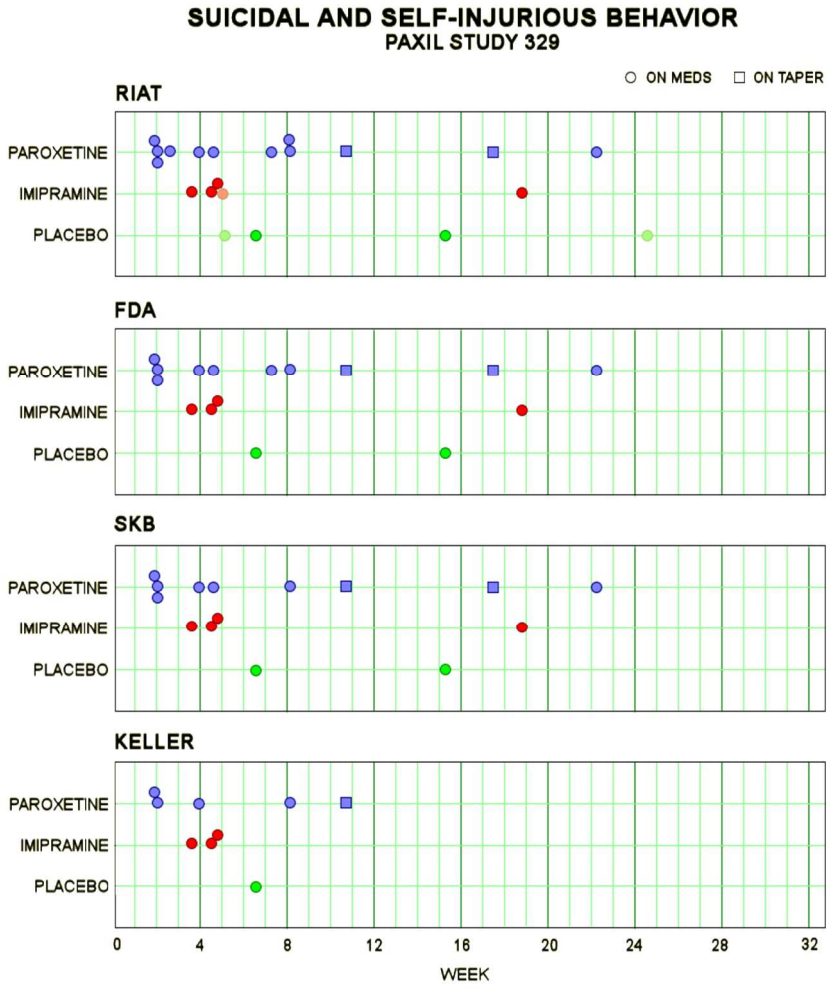
Table 6: Comparison of suicidal and self-injurious behaviours using different safety methodologies*

	Paroxetine (N = 93)	Imipramine (N = 95)	Placebo (N = 87)
	Patients (events)	Patients (events)	Patients (events)
Keller et al	5	3	1
SKB Acute from Clinical Study Report	7	3	1
RIAT Acute & Taper from Clinical Study Report	11 (14)	4 (6) 3 definite 1 possible	2 1 definite 1 possible

* In Keller et al, and in the Clinical Study Reports, suicide related events were primarily coded under Emotional Lability.

Figure 3 shows when suicidal and self-injurious events occurred. It depicts those events identified by SKB, the FDA and our RIAT analysis.

Figure 3: Timing of suicidal and self-injurious events using different safety methodologies and as analysed by the FDA.



The full details for patients included in this table can be found in Appendix 3, along with working notes and directions to where in the CSR the key details can be found. It is possible to take different approaches to moving taper phase events into the continuation phase and reviewing the coding for all cases, especially 039, 089 and 106 that were designated suicidal and self-injurious behaviours in the RIAT recoding, thereby arriving at different figures.

There were no noteworthy changes in physiological data, which are detailed in the Clinical Study Report Appendix F Patient Data Listings of Laboratory Tests.

Severity Ratings

The Clinical Study Report reported serious Adverse Events (defined as events that 'resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious') as 11 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 7; note the high number and proportion of severe psychiatric events in the paroxetine group. In contrast, few of the many cardiovascular events in the imipramine group were rated as severe).

Table 7. Adverse events deemed serious by investigator

Adverse Event SOC	Paroxetine (N = 93)	Imipramine (N = 95)	Placebo (N = 87)
Cardiovascular	1	3	0
Gastro-intestinal	25	20	4
Psychiatric	32	4	6
Respiratory	2	1	4
Neurological	7	14	7
Other	3	8	5
Total	70	50	26

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 8 presents reasons for withdrawal during the acute phase and taper due to Adverse Events and other causes. Note that we examined all discontinuations reported in Appendix G: CRF Tabulations by Patient and compared our findings with Case Report Forms from Appendix H.

Table 8. 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 Event	**Aggression**	1	0	0	1	0	0
	Mania	1	2	0	0	0	0

	Overdose	1	1	0	0	0	0
	Depression worsening	0	1	0	0	0	1
	Agitation	0	1	0	0	0	0
	Suicidality	0	5*	0	2	0	1
	Hallucinations	0	0	0	1	0	0
	Conduct disorder	1	1	0	0	0	0
	Hospitalisation/surgery	1	0	1	0	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 viii).

Taking the displaced taper into account 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 9.

Table 9. 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 coded, **App G**	**RIAT proposed***	SKB coded, **App G**	**RIAT proposed***	SKB coded, **App G**	**RIAT proposed***
Adverse	Aggression/paranoia	1	1	0	0	0	0

event							
	Overdose	1	0	0	0	0	0
	Depression worsening	0	1	0	0	0	0
	Homicidality	0	0	1	1	0	0
	Suicidality	0	2	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 10.

Table 10. 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	9	0	0	0
Gastrointestinal disorders	9	4	18	4	4	0
Psychiatric disorders	15	8	2	0	1	1
Respiratory & thoracic disorders	3	0	1	0	0	0
All other SOCs	16	1	20	5	5	0
Total Adverse Events	**47**	**13**	**50**	**9**	**10**	**1**

SKB did not present an ADECS analysis for the taper phase in the CSR.

Effects of Other Medications

In Table 11 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 11. 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	42	12	21	6	11
Total Adverse Events (acute + taper)	158	323	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 journal publication

Our RIAT analysis of Study 329 revealed that neither paroxetine nor high-dose imipramine demonstrated efficacy for major depression in adolescents, and there was a clinically significant increase in harms with both drugs. This analysis contrasts with both Keller et al.'s published conclusions 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). 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 not been mentioned 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, those summarised in the Clinical Study Report using the ADECS methodology, and those reported in Keller et al. These differences arise from inadequate and incomplete entry of data from Case Report Forms to summary data sheets in the Clinical Study Report, the ADECS coding system used by SKB, and the reporting of these data sheets in Keller et al. SKB reported 338 adverse events with paroxetine, Keller et al reported 265, 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 RIAT MedDRA coded 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 the SOC 'Nervous System'.

MedDRA distinguishes between Neurological and Psychiatric SOCs. We have placed headaches in the Neurological rather than the Psychiatric SOC. MedDRA allows dizziness to be coded under Cardiovascular or Neurological SOCs. In most cases of dizziness, given the dose of imipramine being used, dizziness seems likely to be cardiovascular, with Keller et al also reporting a high rate of postural hypotension on imipramine. We have thus filed all dizziness under Cardiovascular rather than Neurological. There is scope for others accessing the data to parse out whether there is sufficient information to file certain instances of dizziness, such as dizziness during paroxetine taper, as neurological, but we have stepped back from this finer grain analysis.

Dizziness and headache comprise 54 of 115 events on paroxetine (47%), 83 of 135 events on imipramine (62%), and 50 of 65 events on placebo (77%).The effect of disentangling these two symptoms from psychiatric adverse events unmasks a clinically important difference in psychiatric Adverse Event profiles between paroxetine and placebo.

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 (Table 6).

talWith regard to dropouts, Keller et al. stated that 69% of patients completed the acute phase. However, only 45% went on to the continuation phase, which has not yet been subject to RIAT analysis.

Comparison with other studies

Our findings are consistent with those of other studies, including a recent examination of 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%) reported 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 differences 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, at odds with the SKB protocol that called for primary comparisons to be made using descriptive statistics. 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, since study power is based on these. 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 As such, 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 , Tables xi and xii, 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. Our analyses 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 two years. 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 we could 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. The extent of the clinically significant increases in Adverse Events in the paroxetine and imipramine arms, including serious, severe, and suicide related Adverse Events 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 occassioned development of 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 (RIATAR)
2. Adverse event tables
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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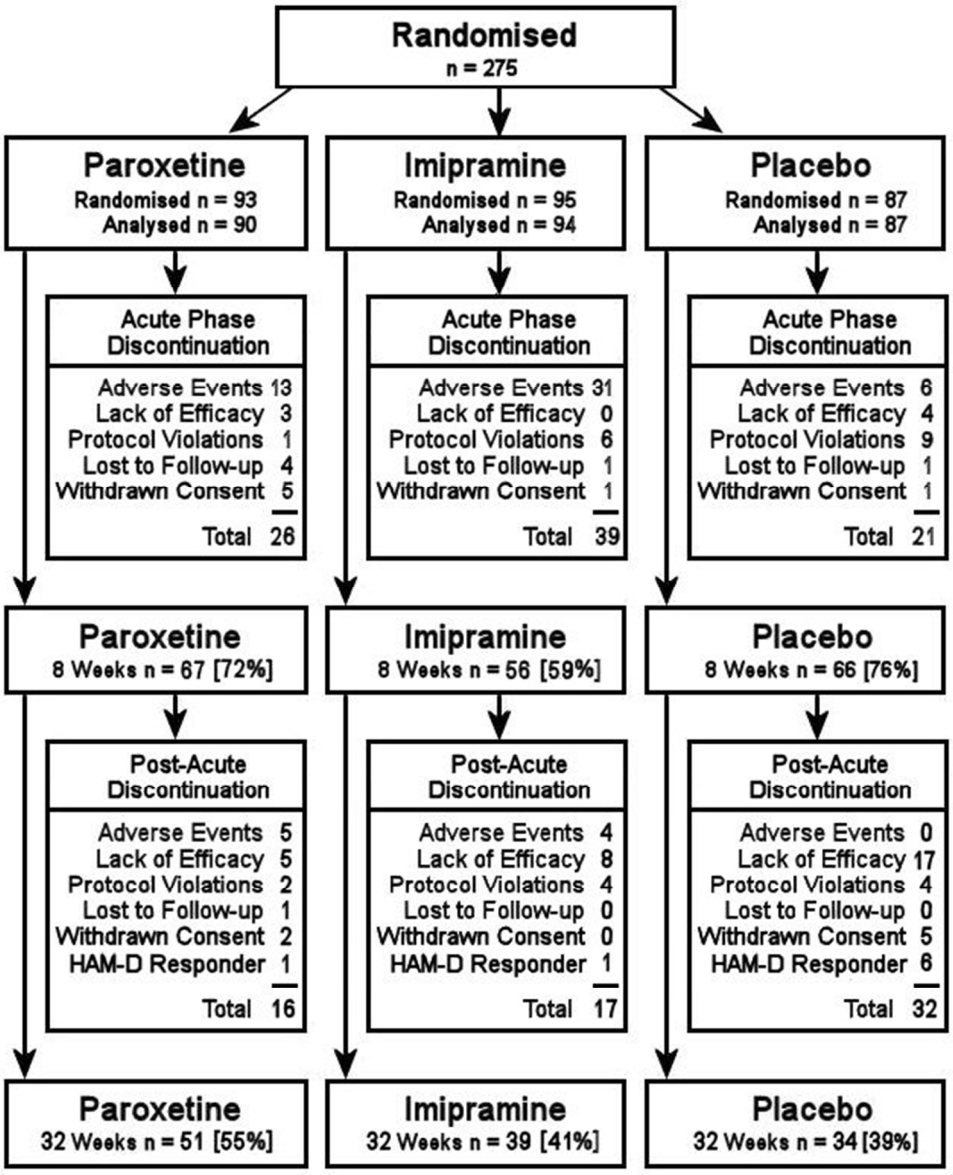
Table 3. Datasets for primary and secondary outcomes: Observed case, Last Observation Carried Forward, and Multiple Imputation

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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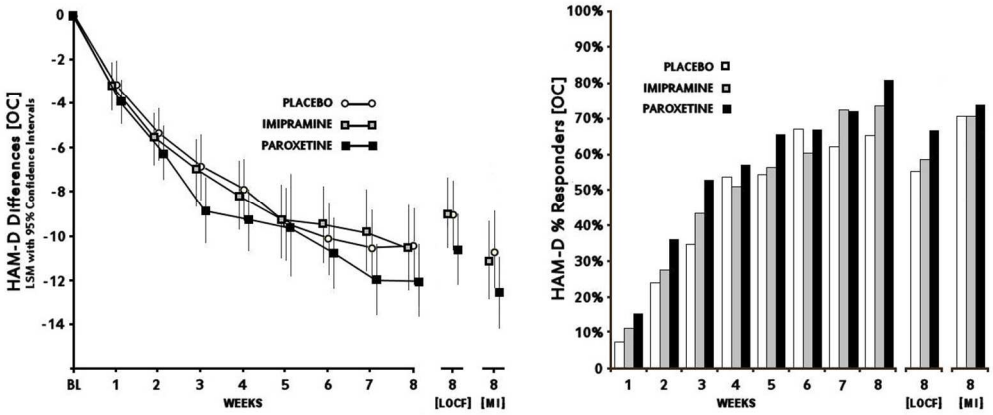

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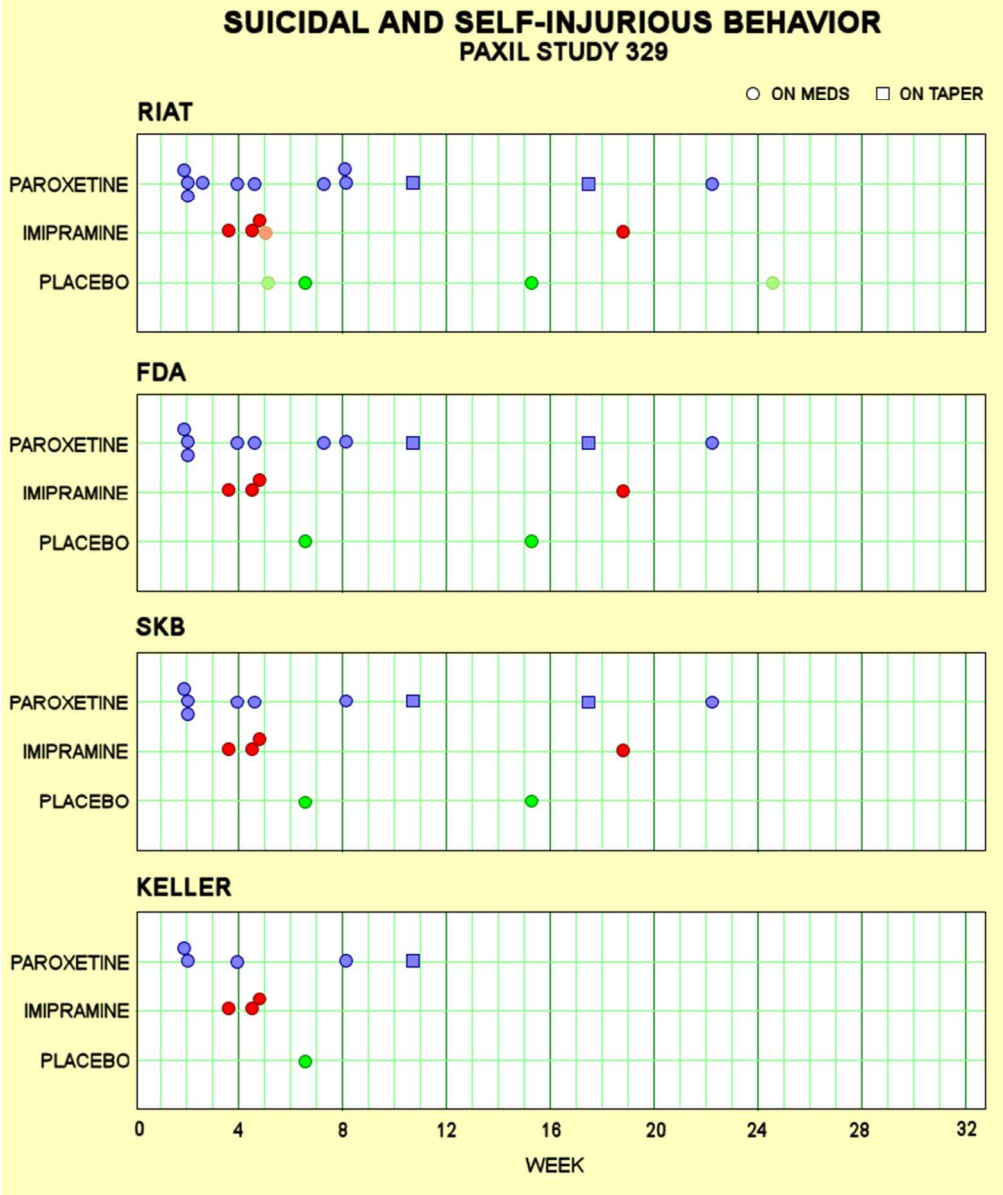

Figure 3: Timing of suicidal and self-injurious events using different safety methodologies and as analysed by the FDA.
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Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes

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*

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
Title and abstract						
	1a	Identification as a randomised trial in the title	p.1			
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.1	CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9.	CSR Final Clinical Report Acute Phase; Report Synopsis, pages 13-21; Continuation Study, Final Clinical Report, Report Synopsis, pages 4 to 9.	
Introduction				CSR Final Clinical Report Acute Phase; 1 Introduction, pages 22-23; Appendix A, Protocol, 1.0 INTRODUCTION, page 545-546; Continuation Study, Final Clinical Report,Introduction, page 17.	CSR Final Clinical Report Acute Phase, Same pages; Appendix A, Protocol, PDF pages 15-16;Continuation Study, Final Clinical Report,Introduction, page 17.	
Background and objectives	2a	Scientific background and explanation of rationale	p.2-3;	CSR Final Clinical Report Acute Phase; 1 Introduction, page 22, paragraphs 1-2; Appendix A, Protocol, 1.0 INTRODUCTION, page 545, paragraphs 1-2;	CSR Final Clinical Report Acute Phase; 1 Introduction, page 22, paragraph 1-2; Appendix A, Protocol, 1.0 INTRODUCTION, page 15, paragraph 1-2;	
	2b	Specific objectives or hypotheses	p.2-3	CSR Final Clinical Report Acute Phase; Report Synopsis, Objectives, page 14, paragraphs 1 to 3;2 Objectives, 2.1 Primary, page 24, paragraph 1; Objectives, 2.2 Secondary, page 24, paragraphs 2-4; Appendix A, Protocol, SYNOPSIS, OBJECTIVES OF STUDY,	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, SYNOPSIS, OBJECTIVES OF STUDY, page 10; 2.0 OBJECTIVES, Primary,	

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

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
		reasons		Amendment 2 (approved 28 October 1996), pages 27-28; Amendment #1, page 536-537; Amendment #2, page 538-539;	1994), pages 26-27; Amendment 2 (approved 28 October 1996), pages 27-28; Appendix A, Protocol, PDF page 6-7; page 8-9;	
Participants	4a	Eligibility criteria for participants	p.3-4; Table 1;	CSR Final Clinical Report Acute Phase; Report Synopsis, Study Population, page 14, paragraph 5; 3 Methodology, 3.1 Study Design, page 25, paragraph 1,; page 26, Figure 1; 3.4 Eligibility Criteria, 3.4.1 Inclusion Criteria, page 30, paragraph 2; 3.4.2 Exclusion Criteria, pages 30, paragraph 3 to page 31; Appendix A, Protocol, 4.0 STUDY POPULATION, 4.2 Inclusion criteria, page 549 paragraph 2; 4.3 Exclusion Criteria, page 549 paragraph 2 to page 550; Continuation Study, Report Synopsis, Study Population, PDF page 2; Continuation Phase Final Clinical Report, 3.2 Inclusion Criteria: Continuation Phase, page 20 paragraph 1;4 Study Population, 4.1 Entry into the Continuation Phase, page 24; 4.2 Reasons for Not Entering the Continuation Phase, page 25 to page 26 paragraph 1;	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 19-20;	
	4b	Settings and locations where the data were collected	p.4	CSR Final Clinical Report Acute Phase; Report Synopsis, Investigators and Centers, page 13, paragraph 2; 3.2 Investigators, page 28, paragraph 3 to page 29;	Clinical Report Acute Phase,Same pages;	
Interventions	5	The interventions	p.4	CSR Final Clinical Report Acute Phase;	CSR Final Clinical Report	

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
		for each group with sufficient details to allow replication, including how and when they were actually administered		Report Synopsis, Treatment and Administration, page 15, paragraphs 1 to 3; 3.5 Treatments and Administration, 3.5.1 Study Medication, page 32; 3.5.2 Dosage and Administration, page 33 to page 35 paragraph 1; 3.5.4 Other Protocol-specified Therapy, page 35, paragraph 4; 3.6 Compliance with Study Medication, page 36; 3.7 Prior and Concomitant Medication, 3.7.1 Prior Medication, page 36, paragraph 2; 3.7.2 Concomitant Medication, page 36, paragraph 3-5; Appendix A, Protocol, 6.0 DRUG SUPPLIES AND PACKAGING, 6.1 Formulations, page 559; 6.2 Study Drug Administration, page 559; 6.4 Concomitant Medication, page 560 paragraph 1-2; 6.5 Packaging, page 560; 6.6 Labeling and Preparation, page 560; 6.7 Storage, page 560; 6.8 Drug Accountability, page 560; 6.9 Assessment of Compliance, page 561; Appendix A, Protocol Appendices, APPENDIX G, CLINICAL MANAGEMENT FOR ADOLESCENT DEPRESSION, pages 599 to 623; Continuation Study, Report Synopsis, Treatment and Administration, PDF page2; Continuation Phase Final Clinical Report, 3.3 Study Medication and Administration, page 20 paragraph 2 to page 21 paragraphs 1-2;	Acute Phase,Same pages; Appendix A, Protocol, PDF page 29, 30-31; page 69-93; Continuation Study, Report Synopsis, Treatment and Administration, PDF page2; Continuation Phase Final Clinical Report, 3.3 Study Medication and Administration, page 20 paragraph 2 to page 21 paragraphs 1-2;	
Outcomes	6a	Completely defined pre-specified primary	p.4-9	CSR Final Clinical Report Acute Phase; Report Synopsis, Evaluation Criteria, Efficacy Parameters, Safety Parameters,	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol,	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
		and secondary outcome measures, including how and when they were assessed		Other Parameters, page 15, paragraphs 4-5, page 16, paragraphs 1-2; 3.9 Efficacy Assessments, pages 41-44; 3.9.1 Primary Efficacy Parameters, pages 43 paragraph 4 to page 44 paragraph 1; 3.9.2 Secondary Efficacy Parameters, page 44 paragraph 2;3.10 Safety Assessments, 3.10.1 Adverse Experiences, page 44 paragraph 4 to page 45 paragraphs 1-2; 3.13.4 Planned Efficacy Evaluations, page 49, paragraph 5, Primary Efficacy Variables, page 49 paragraph 6 to page 50 paragraphs 1-6; Appendix A, Protocol, 9.0 DATA EVALUATION, 9.1 Criteria for Efficacy, 9.1.1 Primary efficacy variables, page 571 paragraph 1; 9.1.2 Secondary efficacy variables, page 571 paragraph 2; Appendix A, APPENDIX F, INSTRUMENTS, pages 597-598. Continuation Study, Report Synopsis, Evaluation Criteria, PDF page 2; Continuation Phase Final Clinical Report, 3.6 Planned Efficacy Evaluations, page 22 paragraphs 2-4;	PDF page 41, 67-68; Continuation Study, Report Synopsis, Evaluation Criteria, PDF page 2; Continuation Phase Final Clinical Report, 3.6 Planned Efficacy Evaluations, page 22 paragraphs 2-4;	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	p.5	CSR Final Clinical Report Acute Phase; Report Synopsis, Evaluation Criteria, Efficacy Parameters, page 15, paragraph 5;	Clinical Report Acute Phase,Same pages;	
Sample size	7a	How sample size was determined	p.4,9	CSR Final Clinical Report Acute Phase; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 2 (approved 28 October 1996), pages 27-28; 3.13.2 Target Sample Size, page 49	Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF pages 3, 8-9. 42;	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
				paragraph 3; Appendix A, Protocol, Amendment #2 page 533, last line; Amendment #2, page 538-539; 9.2.2 Sample size determination, page 572 paragraphs 1-2;		
	7b	When applicable, explanation of any interim analyses and stopping guidelines	4	CSR Final Clinical Report Acute Phase; 3 Methodology, 3.1 Study Design,3.1.1 Protocol Amendments, Amendment 2 (approved 28 October 1996), pages 27-28; 3.13.2 Target Sample Size, page 49 paragraph 3; 3.13.4 Planned Efficacy Evaluations, page 49; Appendix A, Protocol, Amendment #2, page 538-539;	Clinical Report Acute Phase,Same pages; Appendix A Protocol, PDF pages 8-9;	
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49 paragraph 4; Appendix A, Protocol, 5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 555 paragraph 2;Appendix A, Randomisation Code, page 1431 to 1434; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 25; Appendix A, Protocol PDF pages 901-904; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	Clinical Report Acute Phase,Same pages; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; 3.5.3 Methods of	Clinical Report Acute Phase,Same pages; Appendix A, Protocol,	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
		sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		Blinding, page 35, paragraph 2-3; Appendix A, Protocol, 5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 555 paragraph 2; Blank Case Report Form (CRF), QUALIFICATION FOR ENTRY TO DOUBLE-BLIND PHASE, page 734; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	5.2.2 Randomization, Randomized Assignment of Subjects to Treatment, page 25 paragraph 2; Blank Case Report Form (CRF), QUALIFICATION FOR ENTRY TO DOUBLE-BLIND PHASE, page 204; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p.9	CSR Final Clinical Report Acute Phase; 3.13.3 Method of Randomization, page 49, paragraph 4; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	Clinical Report Acute Phase,Same pages; Continuation Study, Final Clinical Report, 3.5 Method of Randomization, page 22.	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	p.9	CSR Final Clinical Report Acute Phase; 3.1.1 Protocol Amendments, Amendment 1, page 27, paragraph 3; Amendment 2, page 28, paragraph 2; 3.5.3 Methods of Blinding, page 35, paragraph 2-3; Final Clinical Report, Treatment and Administration, page 15, paragraph 3; Appendix A, Protocol, 5.2.3 Treatment Phase, Termination at end of acute study for non-responders, page 557, paragraph 5; 6.3 Blinding, page 559 paragraph 3;	Clinical Report Acute Phase,Same pages; PDF page Appendix A, pages 27, 29;	
	11b	If relevant, description of the	p.9	CSR Final Clinical Report Acute Phase; Report Synopsis, Treatment and	CSR Final Clinical Report Acute Phase,Same pages;	

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
		similarity of interventions		Administration, page 15, paragraphs 1 to 3; 3.5 Treatments and Administration, 3.5.1 Study Medication, page 32; 3.5.2 Dosage and Administration, page 33 to page 35 paragraph 1; 3.5.4 Other Protocol-specified Therapy, page 35, paragraph 4; 3.7 Prior and Concomitant Medication, 3.7.1 Prior Medication, page 36, paragraph 2; 3.7.2 Concomitant Medication, page 36, paragraph 3-5; Appendix A, Protocol, 6.4 Concomitant Medication, page 560 paragraph 1-2; Protocol Appendices, APPENDIX G, CLINICAL MANAGEMENT FOR ADOLESCENT DEPRESSION, pages 599 to 623;	Appendix A, Protocol, PDF page 30; page 69-93;	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.10	CSR Final Clinical Report Acute Phase; Report Synopsis, Statistical Methods, page 16, paragraph 3; 3.13 Statistical Evaluation, page 48, paragraphs 6-7; 3.13.1 Comparison of Interest, page 49; 3.13.5 Methods of Analysis, page 50 paragraph 7-8 to page 51 paragraph 1-6; 3.13.6 Populations/Data Sets to be Evaluated, page 51 paragraph 7 to page 54 paragraph 1-3; 5.1 Efficacy Evaluation, 5.1.1 Data Sets Analyzed, page 71 paragraph 1-2; 5.2.4 Sustained Response, page 78 paragraph 1; Appendix A, Protocol, 9.2 Statistical Methods, 9.2.1 Comparisons of interest, page 571 paragraph 3; Protocol, 9.3 Efficacy Analysis, 9.3.1 Intent to Treat Analysis, 9.3.2 Patients Valid For The EfficacyAnalysis, page 572 paragraph 2	CSR Final Clinical Report Acute Phase,Same pages; Appendix A, Protocol, PDF page 41; pages 42-43; page 43; pages 43-44; Statistical Report PDF pages 922-927; pages 928-949;	

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
				to page 573 paragraph 1; Protocol, 9.3.3 Statistical Methodology, page 573 paragraph 2-5; Protocol, 9.3.4 Test of Significance, page 573 paragraph 6 -7; Statistical Report, pages 1452-1453; Statistical Report, 2 Statistical Methodology, page 1454 to 1457; Details of statistical methods presented also in Statistical Report, 3 Summary of Statistical Results, page 1458-1479; Continuation Phase Final Clinical Report, 3.6.3 Statistical Analysis, page 23 paragraphs 2-3; 3.7 Planned Safety Evaluations, page 23 paragraph 3;		
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p.6-9 (methods for additional harms analysis);	CSR Final Clinical Report Acute Phase; page 15, paragraph 5; 3.1.1 Amendments, Amendment 2, page 27 paragraph 6 to page 28 paragraph 1; page 44, paragraph 3; 3.13.5 Methods of Analysis, page 50 paragraph 3; 5.1.1 Data Sets Analyzed, page 71 paragraph 1; 5.4 Efficacy Subgroup Analysis, page 89 paragraph 1 to page 90 paragraph 1-2; Appendix A, Statistical Report, 2.5 Covariate Analyses, page 1456 paragraph 6;	Clinical Report Acute Phase,Same pages; Appendix A, PDF page 926;	
Results						
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for	p.11 , Figure 1;	Final Clinical Report, Acute Phase, Report Synopsis, Patient Disposition and Key Demographic Data page 16 paragraph 4; Table Demographic and Clinical Characteristics at Entry page 17; Table Patient Disposition page 17; 4 Study Populations, 4.2 Patient Disposition, 4.2.1 Number and	Same page numbersin the PDF of Final Clinical Report, Acute Phase, Final Clinical Report, Continuation Phase, and Appendix B;	

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
		the primary outcome		Distribution of Patients page 56 paragraph 2; Table 7, Number of Patients Who Were Randomized (R) to Each Treatment Groupand Who Completed* (C) Acute Phase of Treatment at Each Center, page 57; 4.2.2 Number of Patients Present at Each Visit, page 57; Table 8, Number of Patients Remaining in the Study by Visit and Treatment Group, page 58; 4.7 Treatment Compliance and Titration, 4.7.1 Treatment Compliance, Table 18, Summary of Patient Compliance with Study Medication over the 8 Week Treatment Period (number (%) of patients), page 69; 4.7.2 Titration of Dose Table 19 Number of Patients at Dose Level by Treatment Group and Study Week, page 70; 5 Efficacy Results, 5.2 Efficacy Results, 5.2.1 Change from Baseline in Total HAM-D Score, Table 20 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in TotalHAM-D Score for OC Dataset at Each Treatment Week and the LOCF Dataset atWeek 8, page 72; 5.2.2 Change from Baseline in HAM-D Subscales, Table 22 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Mood Item andFactors* of the HAMD for the Week 8 LOCF and OC Week 8 Datasets, page 74; 5.2.3 Responders and Remission Analysis, Table 23 Number (%) of Patients Who Responded* to Treatment for OC Dataset atEach Treatment Week and the		

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
				LOCF Dataset at Week 8, page 76;Table 25 Number (%) of Patients in Remission* for OC Dataset at Each TreatmentWeek and the LOCF Dataset at Week 8, page 76; 5.2.5 CGI Improvement Scale, Table 28 Mean Improvement Score (+/- SE) on the CGI Scale for OC Dataset atEach Treatment Week and the LOCF Dataset at Week 8, page 80; Table 30 Number and Percent of Patients Having a CGI Score of "Very MuchImproved" or "Much Improved" for OC Dataset at Each Treatment Week and theLOCF Dataset at Week 8, page 82; 5.2.6 K-SADS-L - Depression 9-Item Scale - Change from Baseline, Table 32 Baseline Mean (+/- SE) and Change from Baseline (+/- SE) in KSADS-L - Depression 9-Item Scale for OC Dataset at Each Treatment Weekand the LOCF Dataset at Week 8, page 84; 5.2.7 Change from Baseline in K-SADS-L Depressed Mood Item, Table 34 Baseline Mean (+/- SE) andMean Change from Baseline (+/- SE) inDepressed Mood Item of the K-SADS-L Depression Scale for the Week 8 OC andWeek 8 LOCF Datasets, page 86; 5.3 Functional, Self Perceptive and Behavioral Scales5.3.1 Autonomous Functioning Checklist, Table 36 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) inTotal Score and Subscores on the Autonomous Functioning Checklist at Endpoint, page 87; 5.3.2 Self Perception Profile, Table 37 Baseline Mean (+/- SE) and Mean		

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

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
				Baseline at Each Visit–HAM-D Scale (ITT Population), page 58;6.4 Clinical Global Impression of Improvement, Table 21 Distribution of Patients in Each Class of CGI Global Improvement atWeek 32 LOCF Endpoint (Intent to Treat Population), page 59; Table 22 Mean (±SE) CGI Global Improvement at Each Visit (ITT Population), page 59; 9 Data Source Tables: Study Population, Table 12.2 Summary of Patients Remaining in the Study at Weekly Intervals(Intent to Treat Population), pages 66-67; 10 Data Source Tables: Efficacy, pages 88-112;		
	13b	For each group, losses and exclusions after randomisation,together with reasons	p.11; Figure 1;	Final Clinical Report, Acute Phase, Report Synopsis, Patient Disposition and Key Demographic Data page 16 paragraph 4; Table Patient Disposition,page 17; 4 Study Populations, 4.2 Patient Disposition, 4.2.1 Number and Distribution of Patients, page 56 paragraph 2; Table 7, page 57; Table 8, page 58; 4.2.3 Withdrawal Reasons, page 58; Table 9, Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal, page 59; page 59; Table 10, Number and Cumulative Percentage of Patients Withdrawn from the Study by Reason and by Week, page 60; 4.3 Protocol Violations, pages 60-62; 6.7 Withdrawals for Adverse Experiences, page 110; Table 49,Treatment-emergent Adverse Experiences, Regardless of Attribution,	Same page numbersin the PDF of Final Clinical Report, Acute Phase, Final Clinical Report, Continuation Phase, and Appendix B;	

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
				page 111-112; Table 50, Adverse Experiences Leading to WithdrawalLeading to Withdrawal (number (%) of patients), page 113-114; 10 Data Source Tables: Study Population, Table 12.3 Summary of Patient Withdrawals (Intent-to-Treat Population), pages 133-134;Table 12.4 Distribution of Patient Withdrawals by Reason and Week (Intent-to-Treat Population), pages 135-140; 12 Data Source Tables: Safety Results,Table 14.9.1 Summary of Adverse Experiences Leading to Withdrawal during Acute Phase by ADECS Body System and Preferred Term Non-gender Specific Adverse Experiences (Intent-to-Treat Population), pages 308-309;Table 14.9.1a, Adverse Experiences Leading to Withdrawal Patient Narratives, pages 310-366;Table 14.9.3 Summary of Adverse Experiences Leading to Withdrawalduring Acute Phase by ADECS Body System and Preferred Term Female Specific Adverse Experiences (Intent-to-Treat Population), page 367; Appendix B: Patient Data Listings of Demographic, Appendix B.1 Listing of Patient Terminations by Treatment Group and Patient Intent-to-Treat Population, pages 2-21; Continuation Study, Final Clinical Report, Report Synopsis, Patient Disposition and Key Demographic Data, page 6; 4 Study Population 4.1 Entry into the Continuation Phase, Figure 2 Disposition		

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
				of Patients, page 25; 4.3 Disposition of Patients in the Continuation Phase, page 26; Table 4 Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal (ITT Population), page 27; 5 Safety Results, 5.5 Withdrawals for Adverse Events, pages 41-45; 9 Data Source Tables: Study Population, Table 12.3 Summary of Patient Withdrawals (Intent to Treat Population), pages 68-69; 12.4 Distribution of Patient Withdrawals by Reason and Week (Intent toTreat Population), pages 70-75; 10 Data Source Tables: Efficacy, Table 15.1 Number (%) of Patients Withdrawing for Lack of Efficacy (Continuation Phase) (Intent to Treat Population), page 87; 11 Data Source Tables: Safety, Table 16.9.1 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Non-gender Specific Adverse Experiences (Intent to Treat Population), page 192; Table 16.9.2 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Male Specific Adverse Experiences (Intent to Treat Population), page 193; Table 16.9.3 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Female Specific Adverse Experiences (Intent to		

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
				Treat Population), page 194; Table 16.9.4 Narratives for Patients with Non-Serious Adverse Events Leading to Withdrawal, pages 195-210;		
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p.3	Final Clinical Report, Acute Phase, Report Synopsis, Study Dates, page 13, paragraph 5; 3.2 Investigators, page 28 paragraph 4; 4 Study Populations, 4.1 Study Dates, page 56 paragraph 1; Continuation Study, Final Clinical Report, Report Synopsis, Study Dates, page 4, paragraph 2; 4 Study Population 4.1 Entry into the Continuation Phase, page 24, paragraph 2;	Same page numbersin the PDF of Final Clinical Report, Acute Phase and Final Clinical Report, Continuation Phase;	
	14b	Why the trial ended or was stopped				
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Page 10-11; Table 2;	Final Clinical Report, Acute Phase, Report Synopsis, Table Demographic and Clinical Characteristics at Entry, page 17; 4 Study Populations, 4.4 Demographic and Baseline Characteristics, 4.4.1 Demographic Characteristics, Table 13 Demographic Characteristics of Randomized Patients, page 63; 4.4.2 Baseline Characteristics, Table 14 Baseline Characteristics Regarding Major Depressive Disorder of All Randomized Patients, page 65; Table 15 Medical or Surgical Conditions Occurring in 3 or More of Patients in Any Treatment Group at Baseline (number (%) of patients), page 66; Table 16 Presenting Conditions Occurring in 3 or	Same page numbersin the PDF of Final Clinical Report, Acute Phase and Final 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
				More of Patients in Any Treatment Group at Baseline (number (%) of patients), page 67; 4.6 Prior and Concomitant Medications, Table 17 Concomitant Medications Received by 5% or More of Patients in Any Treatment Group (number (%) of patients), page 68; 10 Data Source Tables: Study Population; Table 12.5.1 Summary of Demographic Data Intent-to-Treat Population, page 141-142; Table 12.5.2 Summary of Height and Weight at Screening/Baseline Intent-to-Treat Population, page 143; Table 12.6Summary of Child Global Assessment Scale (Scores at Screening)Intent to Treat Population, page 144; Table 12.7Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at ScreeningIntent to Treat Population, page 145-150; Table 12.8Summary of Personal HistoryIntent-to-Treat Population, page 151-152; Table 12.9Summary of Medical/Surgical HistoryIntent-to-Treat Population, page 153-156; Table 12.10Summary of Presenting ConditionsIntent-to-Treat Population, page 157-160; Table 12.11Summary of Prior Medications by WHO ATC ClassificationIntent-to-Treat Population, page 161-165; Table 12.14Summary of Concomitant Medications by WHO ATC ClassificationAcute PhaseIntent-to-Treat Population, page 167-172; Table 12.20 Summary of Duration of Current Episode (mo) Intent to Treat Population, page		

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
				176; Table 12.21Summary of Number of Depressive Episodes Intent to Treat Population, page 177; Table 12.21 Summary of Number of Depressive Episodes Intent to Treat Population, page 178; Table 12.22 Summary of Age at Onset of First Episode (yr) Intent to Treat Population, page 179;Table 12.23 Summary of Melancholic/Endogenous Depression Intent to Treat Population,page 180; Table 12.24 Summary of Atypical Depression Intent to Treat Population, page 181; Table 12.25 Summary of Family History of Major Depression Intent to Treat Population, page 182; Table 12.26 Summary of Any Concomitant Diagnosis Intent to Treat Population, page 183; Table 12.27 Summary of Anxiety DisorderIntent to Treat Population, page 184; Table 12.28 Summary of Externalizing Disorder Intent to Treat Population, page 185; Continuation Study, Final Clinical Report, 5.6 Vital Signs and Body Weight, 5.6.1 Mean Values and Changes in Value, Table 13 Vital Signs and Body Weight at Baseline and Endpoint (mean ± SD) (ITT Population), page 46; 6 Efficacy Results, 6.3 Hamilton Depression Scale, Table 20 Baseline Mean (±SE) and Mean Change from Baseline at Each Visit– HAM-D Scale (ITT Population), page 58; 9 Data Source Tables: Study Population, Table 12.15 Summary of Concomitant Medications by WHO ATC Classification		

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
				Continuation Phase Intent-to-Treat Population, page 76-79; 10 Data Source Tables: Efficacy, Table 15.3 Baseline Mean and Mean Change from Baseline at Monthly Intervals-HAMD Scale (Continuation Phase) (Intent to TreatPopulation), page 89; Table 15.4 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-K-SADS-L Depression 9-Item Scale (Continuation Phase)(Intent to Treat Population), page 90; Table 15.7 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-HAMD Anxiety Somatization Scale (Continuation Phase)(Intent to Treat Population), page 93; Table 15.8 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-HAMD Sleep Scale (Continuation Phase) (Intent to TreatPopulation), page 94; Table 15.9 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-HAMD Cognitive Disturbance Scale (Continuation Phase)(Intent to Treat Population), page 95; Table 15.10 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-HAMD Retardation Scale (Continuation Phase) (Intent toTreat Population), page 96; Table 15.11 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Self Perception Profile Scale (Continuation Phase) (Intent toTreat Population), page 97; Table 15.12 Baseline Mean and Mean Change		

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
				from Baseline at MonthlyIntervals-Autonomous Functioning Scale (Continuation Phase) (Intentto Treat Population), page 98; Table 15.13 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Autonomous Functioning Scale: Self/Family Care Subscore(Continuation Phase) (Intent to Treat Population), page 99; Table 15.14 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Autonomous Functioning Scale: Management Subscore(Continuation Phase) (Intent to Treat Population), page 100; Table 15.15 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Autonomous Functioning Scale: Recreational ActivitySubscore (Continuation Phase) (Intent to Treat Population), page 101; Table 15.16 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Autonomous Functioning Scale: Social/VocationalActivities Subscore (Continuation Phase) (Intent to Treat Population), page 102; Table 15.17 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-Sickness Impact Profile Scale (Continuation Phase) (Intent toTreat Population), page 103; Table 15.18 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-SIP Scale: Present Health Subscore (Continuation Phase)(Intent to Treat Population), page		

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
				104; Table 15.19 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-SIP Scale: Present Quality of Life Subscore (ContinuationPhase) (Intent to Treat Population), page 105; Table 15.20 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-SIP Scale: Sleep/Rest Subscore (Continuation Phase) (Intentto Treat Population), page 106; Table 15.21 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-SIP Scale: Home Maintenance Subscore (Continuation Phase) (Intent to Treat Population), page 107; Table 15.22 Baseline Mean and Mean Change from Baseline at Monthly Intervals-SIP Scale: Social Interaction Subscore (Continuation Phase) (Intent to Treat Population), page 108; Table 15.23 Baseline Mean and Mean Change from Baseline at MonthlyIntervals-SIP Scale: Alertness Behavior Subscore (Continuation Phase) (Intent to Treat Population), page 109; Table 15.24 Baseline Mean and Mean Change from Baseline at Monthly Intervals-SIP Scale: Communication Subscore (Continuation Phase) (Intent to Treat Population), page 110; Table 15.25 Baseline Mean and Mean Change from Baseline at Monthly Intervals-SIP Scale: Recreational Pastimes Subscore (Continuation Phase) (Intent to Treat Population), page 111; Table 15.26 Baseline Mean and Mean Change from Baseline at Monthly		

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
				Intervals-HAMD Depressed Mood Item (Continuation Phase) (Intent to Treat Population), page 112;		
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 11, Figure 1; page 12, table 3; page 13, Table 4; page 13, Table 5; page 14, Table 6; page 15 , Table 7; page 16-17, Table 9; page 17-19, Table 10; page 19-21, Table 11; page 21, Table 12; page 21-22, Table 13;	Final Clinical Report, Acute Phase, Report Synopsis, Table Demographic and Clinical Characteristics at Entry page 17;Table Patient Disposition page 17; Table Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definitionof Responder or Remission, page 19; 4.3 Protocol Violations, 4.3.1 Protocol Violations Excluded from the Per-Protocol Population, page 60; Table 11 Numbers of Patients With Protocol Violations Leading to Exclusion From the Per-Protocol Analysis, page 61; 4.3.2 Protocol Deviations Included in the Per-Protocol Population, page 61-62; Table 12 Numbers of Patients With Protocol Deviations Included in the Per- Protocol Analysis, page 62; 5 Efficacy Results, 5.2 Efficacy Results, 5.2.3 Responders and Remission Analysis, Figure 4 Percent of Patients in LOCF and OC Datasets Achieving Responder and Remission Status, page 78; 10 Data Source Tables: Study Population, pages 130-185; Table 12.1 Summary of Patient Distribution by Investigator by Treatment Intent-to-Treat Population, page 130; Table 12.2 Summary of Patients Remaining in the Study at Weekly IntervalsIntent-to-Treat	Same page numbersin the PDF of Final Clinical Report, Acute Phase and Final 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
				Population, page 131-132; Table 12.5.1 Summary of Demographic Data Intent-to-Treat Population, page 141; Table 12.8 Summary of Personal History Intent-to-Treat Population, page 151; Table 12.9 Summary of Medical/Surgical History Intent-to-Treat Population, page 153; Table 12.10 Summary of Presenting Conditions Intent-to-Treat Population, page 157; Table 12.11 Summary of Prior Medications by WHO ATC Classification Intent-to-Treat Population, page 161; Table 12.14 Summary of Concomitant Medications by WHO ATC ClassificationAcute Phase Intent-to-Treat Population, page 167; Table 12.16 Summary of Patient ComplianceAcute Phase Intent-to-Treat Population, page 173; Table 12.21 Summary of Number of Depressive Episodes Intent to Treat Population, page 177; Table 12.23 Summary of Melancholic/Endogenous DepressionIntent to Treat Population, page 180; Table 12.24 Summary of Atypical Depression Intent to Treat Population, page 181; Table 12.25 Summary of Family History of Major Depression Intent to Treat Population, page 182; Table 12.27 Summary of Anxiety Disorder Intent to Treat Population, page 184; 11 Data Source Tables: Efficacy Results, pages 186-221; 12 Data Source Tables: Safety Results, pages 222-489. Continuation Study, Final Clinical Report, Report Synopsis, Patient Disposition and Key		

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
				Demographic Data, Patient Disposition table, page 6; Safety Results, Adverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo table, page 7; 4 Study Population, 4.3 Disposition of Patients in the Continuation Phase, Table 4 Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal (ITT Population), page 27; 4.4 Concomitant Medications, Table 5 Concomitant Medications by ATC Classification Received by 10% or Moreof Patients in Any Treatment Group (number (%) of patients) (ITT Population), page 28; 5 Safety Results, 5.1 Extent of Exposure, Table 6 Exposure of Patients to Each Daily Dose of Study Medication and Duration of Exposure (number (%) of patients) (Continuation Phase) (ITT Population), page 31; 5.2 Adverse Events,Table 7 Number (%) of Patients with Treatment-emergent Adverse Events Most Frequently Reported (≥5% in Any Treatment Group), by Body System and Preferred Term (ITT Population), page 33; Table 8 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo (ITT Population), page 34; Table 11 Treatment-emergent Adverse Events, Regardless of Attribution, Leading to Withdrawal (number (%) of patients (ITT Population), page 42; 5.6 Vital Signs and Body Weight, 5.6.1 Mean Values and		

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
				Changes in Value, Table 13 Vital Signs and Body Weight at Baseline and Endpoint (mean ± SD) (ITT Population), page 46; Table 14 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During the Continuation Phase (ITT Population), page 47; Table 15 Number of Patients with Laboratory Values Considered to Be of Clinical Concern (ITT Population), page 49; 5.8 Safety Results in the Continuation Phase Compared to the Acute Phase, Table 16 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo in Either Phase of the Study or Both Phases Combined (ITT Population), page 52; Table 17 Number (%) of Patients with Serious Adverse Events in Each Phase of the Study and Both Phases Combined (ITT Population), page 54; 6 Efficacy Results, 6.1 Withdrawals Due to Lack of Efficacy, Table 18 Number (%) of Patients Withdrawing for Lack of Efficacy (Intent to Treat Population), page 55; Table 19 Summary of Relapse During the Continuation Phase for Patients Who Had a HAM-D ≤8 at End of Acute Phase (ITT Population), page 56; 6.4 Clinical Global Impression of Improvement, Table 21 Distribution of Patients in Each Class of CGI Global Improvement at Week 32 LOCF Endpoint (Intent to Treat Population), page 59; 9 Data Source Tables: Study Population, pages 65-84;		

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
				10 Data Source Tables: Efficacy, pages 85-112; 11 Data Source Tables: Safety, pages 116-260.		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p.11-12; Figure 2; page 12; Table 3; page 13, Tables 4 and 5; page 14, table 6; page 15, table 7; page 16, Table 8; page 16-17, table 9; page 17-19, table 10;	Final Clinical Report, Acute Phase, Report Synopsis, Efficacy Results, page 17 paragraph 2 to page 18 paragraph 1, paragraph 2; TableMean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission, page 19; 5 Efficacy Results, 5.2 Efficacy Results, 5.2.1 Change from Baseline in Total HAM-D Score, page 71, Table 20 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total HAM-D Score for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 72; Table 21 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in Total HAM-D Score, page 72; Figure 3 Mean Change from Baseline (SE) in Total HAM-D Score for the Week 8 LOCF and Week 8 OC Datasets, page 73; 5.2.2 Change from Baseline in HAM-D Subscales, page 73 paragraph 3 to page 74 paragraph 1, Table 22 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Mood Item and Factors* of the HAMD for the Week 8 LOCF and OC Week 8 Datasets, page 74; 5.2.3 Responders and Remission Analysis, page 75, paragraphs 2-3, Table	Same page numbersin the PDF of Final Clinical Report, Acute Phase and Final Clinical Report, Continuation Phase; Pages 929-938, 949 PDF, Appendix A, Statistical Report;	

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
				23 Number (%) of Patients Who Responded* to Treatment for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 76; Table 24 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) ofPatients who Responded, page 76; Table 25 Number (%) of Patients in Remission* for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 76; Table 26 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) of Patients in Remission, page 77; Figure 4 Percent of Patients in LOCF and OC Datasets Achieving Responder and Remission Status, page 78; 5.2.4 Sustained Response, page 78 paragraph 2, Table 27 Survival Analysis of Sustained Response During the Acute Phase, page 79; Figure 5 Kaplan Meier Survival Curves for Time to Sustained Response During Acute Phase, page 79; 5.2.5 CGI Improvement Scale, page 80 paragraph 2, Table 28 Mean Improvement Score (+/- SE) on the CGI Scale for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 80; Table 29 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) on the CGI Scale, page 80; page 81 paragraph 2, Figure 6 Mean CGI Score (SE) for Week 8 LOCF and Week 8 OC Datasets, page 81,Table 30 Number and Percent of Patients Having a CGI Score of "Very Much Improved" or "Much Improved" for OC		

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
				Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 82; Table 31 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) of Patients Having a CGI Score of "Very Much Improved" or "Much Improved", page 82; Figure 7 Percent of Patients Very Much Improved and Much Improved in CGI Global Improvement at Endpoint, page 83; 5.2.6 K-SADS-L - Depression 9-Item Scale - Change from Baseline, page 83,Table 32 Baseline Mean (+/- SE) and Change from Baseline (+/- SE) in KSADS- L - Depression 9-Item Scale for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 84; Table 33 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in KSADS- L Depression 9-Item Scale, page 84, Figure 8 Mean Change From Baseline (SE) in K-SADS-L - Depression 9-Item ScaleFor Week 8 LOCF and Week 8 OC Datasets, page 85; 5.2.7 Change from Baseline in K-SADS-L Depressed Mood Item, page 85 paragraph 2 to page 86 paragraph 1, Table 34 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Depressed Mood Item of the K-SADS-L Depression Scale for the Week 8 OC and Week 8 LOCF Datasets, page 86; Table 35 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in Depressed Mood Item, page 86; 5.3 Functional, Self Perceptive and Behavioral Scales 5.3.1 Autonomous		

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
				Functioning Checklist,page 87 paragraph 2, Table 36 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score and Subscores on the Autonomous Functioning Checklist at Endpoint, page 87; 5.3.2 Self Perception Profile, page 88 paragraph 1, Table 37 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in TotalScore on the Self Perception Profile for the Week 8 OC and Week 8 LOCF Datasets, page 88; 5.3.3 Sickness Impact Profile, page 88 paragraph 2, Table 38 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score and Subscores on the Sickness Impact Profile for the Week 8 OC and Week 8 LOCF Datasets, page 89; 11 Data Source Tables: Efficacy Results, page 186-221; Final Clinical Report, Acute Phase, Appendix A, Statistical Report, 3 Summary of Statistical Results, page 1459-1468; Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission, page 1479; Continuation Study, Final Clinical Report, Report Synopsis, Safety Results, page 7 paragraph 1 to page 8 paragraph 4, Adverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo, page 7; Efficacy Results, page 8; 5 Safety Results, 5.2 Adverse Events, page 32		

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
				paragraph 1, Table 7 Number (%) of Patients with Treatment-emergent Adverse Events Most Frequently Reported (≥5% in Any Treatment Group), by Body System and Preferred Term (ITT Population), page 33;Table 8 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo (ITT Population) page 34;Table 9 Number (%) of Patients with the Five Most Frequently Reported Treatment-emergent Adverse Events by the Time of First Occurrence During the Continuation Phase (ITT Population) page 36; page 37 paragraphs 1-2; 5.3 Deaths page 37; 5.4 Serious Non-Fatal Adverse Events, page 38 paragraph 1 to page 39 paragraph 4;Table 10 Serious Non-Fatal Adverse Events (ITT Population), page 40; 5.5 Withdrawals for Adverse Events, page 41;Table 11 Treatment-emergent Adverse Events, Regardless of Attribution, Leading to Withdrawal (number (%) of patients (ITT Population), page 42;Table 12 Adverse Events Leading to Withdrawal in Continuation Phase (ITT Population), page 43; 5.6 Vital Signs and Body Weight 5.6.1 Mean Values and Changes in Value, page 45 paragraph 5, Table 13 Vital Signs and Body Weight at Baseline and Endpoint (mean ± SD) (ITT Population), page 46; 5.6.2 Patients with Vital Signs of Potential Clinical Concern, page 46 paragraph 1 to page 47 paragraph 1; Table 14 Number (%) of		

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
				Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During the Continuation Phase (ITT Population), page 47; 5.7 Laboratory Tests, Table 15 Number of Patients with Laboratory Values Considered to Be of Clinical Concern (ITT Population), page 49; 5.8 Safety Results in the Continuation Phase Compared to the Acute Phase, page 50 paragraph 5 to page 51 paragraph 2, Table 16 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo in Either Phase of the Study or Both Phases Combined (ITT Population), page 52; 5.8.1 Serious Adverse Events in Both Phases Combined, page 53, Table 17 Number (%) of Patients with Serious Adverse Events in Each Phase of the Study and Both Phases Combined (ITT Population), page 54; 6 Efficacy Results, 6.1 Withdrawals Due to Lack of Efficacy, Table 18 Number (%) of Patients Withdrawing for Lack of Efficacy (Intent to Treat Population), page 55; 6.2 Analysis of Relapse, page 56 paragraph 2, Table 19 Summary of Relapse During the Continuation Phase for Patients Who Had a HAM-D ≤8 at End of Acute Phase (ITT Population) page 56;Figure 3 Kaplan Meier Survival Curves for Relapse During the Continuation Phase (ITT Population) page 57;page 57 paragraph 2; 6.3 Hamilton Depression Scale, page 58, Table 20 Baseline Mean		

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
				(±SE) and Mean Change from Baseline at Each Visit– HAM-D Scale (ITT Population) page 58; 6.4 Clinical Global Impression of Improvement, page 58 paragraph 3, Table 21 Distribution of Patients in Each Class of CGI Global Improvement at Week 32 LOCF Endpoint (Intent to Treat Population) page 59; page 59 paragraph 2, Table 22 Mean (±SE) CGI Global Improvement at Each Visit (ITT Population) page 59; 6.5 Other Secondary Scales, page 59 paragraph 3 to page 60 paragraph 1; 10 Data Source Tables: Efficacy, pages 85-112; 11 Data Source Tables: Safety, pages 113-260;		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Page 11-12, Figure 2, percent responding; page 12, table 3;	Final Clinical Report, Acute Phase, Report Synopsis, Efficacy Results, page 18 paragraph 1, paragraph 2; TableMean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission, page 19; 5 Efficacy Results, 5.2 Efficacy Results, 5.2.3 Responders and Remission Analysis, page 75, paragraphs 2-3;Table 23 Number (%) of Patients Who Responded* to Treatment for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 76; Table 24 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) of Patients who Responded, page 76; Table 25 Number (%) of Patients in Remission*	Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase; Appendix A, Statistical Report, PDF pages 934, 949;	

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
				for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 76; Table 26 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) of Patients in Remission, page 77; Figure 4 Percent of Patients in LOCF and OC Datasets Achieving Responder and Remission Status, page 78;5.2.4 Sustained Response, Table 27 Survival Analysis of Sustained Response During the Acute Phase, page 79; Figure 5 Kaplan Meier Survival Curves for Time to Sustained Response During Acute Phase, page 79; 5.2.5 CGI Improvement Scale, Table 30 Number and Percent of Patients Having a CGI Score of "Very Much Improved" or "Much Improved" for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8, page 82; Table 31 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) of Patients Having a CGI Score of "Very Much Improved" or "Much Improved", page 82; Figure 7 Percent of Patients Very Much Improved and Much Improved in CGI Global Improvement at Endpoint, page 83; 11 Data Source Tables: Efficacy Results, Table 13.3 Number (%) of Patients Responding to Treatment Acute Phase (Intent to Treat Population) page 193; Table 13.3.1 Number (%) of Patients Responding to Treatment Acute Phase (Per Protocol Population) page 194; Table 13.6 Number (%) of Patients Withdrawing for Lack of Efficacy Acute Phase (Intent to Treat Population) page		

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
				197; Table 13.11 Number (%) of Patients In Remission Acute Phase (Intent-to-Treat Population) page 203; Table 13.12 Number (%) of Patients With Sustained Response Acute Phase (Intent-to-Treat Population) page 204;Final Clinical Report, Acute Phase, Appendix A, Statistical Report, 3 Summary of Statistical Results, 3.4 Survival Analysis, Table 6 Survival Analysis of Sustained Response During the Acute Phase, page 1464; 3.7 Confidence Intervals for Efficacy Results at Week 8, Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission, Week 8, ITT Population, page 1479; Continuation Study, Final Clinical Report, Report Synopsis, Safety Results, page 7 paragraph 1 to page 8 paragraph 4; Table regardingAdverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo, page 7; Efficacy Results, page 8; 5 Safety Results, 5.2 Adverse Events, page 32 paragraph 1, Table 7 Number (%) of Patients with Treatment-emergent Adverse Events MostFrequently Reported (≥5% in Any Treatment Group), by Body System and Preferred Term (ITT Population), page 33; , Table 8 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X		

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
				Placebo (ITT Population) page 34; Table 9 Number (%) of Patients with the Five Most Frequently Reported Treatment-emergent Adverse Events by the Time of First Occurrence During the Continuation Phase (ITT Population) page 36;page 37 paragraphs 1-2; 5.3 Deaths,page 37; 5.4 Serious Non-Fatal Adverse Events, page 38 paragraph 1 to page 39 paragraph 4; Table 10 Serious Non-Fatal Adverse Events (ITT Population), page 40; 5.5 Withdrawals for Adverse Events, page 41;Table 11 Treatment-emergent Adverse Events, Regardless of Attribution, Leading to Withdrawal (number (%) of patients (ITT Population), page 42; 5.6.2 Patients with Vital Signs of Potential Clinical Concern, page 46 paragraph 1 to page 47 paragraph 1;Table 14 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During the Continuation Phase (ITT Population), page 47; 5.7 Laboratory Tests, Table 15 Number of Patients with Laboratory Values Considered to Be of Clinical Concern (ITT Population), page 49; 5.8 Safety Results in the Continuation Phase Compared to the Acute Phase, page 50 paragraph 5 to page 51 paragraph 2; Table 16,Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo in Either Phase of the Study or Both Phases Combined (ITT Population), page 52; 5.8.1 Serious		

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
				Adverse Events in Both Phases Combined, page 53;Table 17, Number (%) of Patients with Serious Adverse Events in Each Phase of the Study and Both Phases Combined (ITT population), page 54; 6 Efficacy Results, 6.1 Withdrawals Due to Lack of Efficacy, Table 18, Number (%) of Patients Withdrawing for Lack of Efficacy (Intent to Treat Population), page 55; 6.2 Analysis of Relapse, page 56 paragraph 2; Table 19,Summary of Relapse During the Continuation Phase for Patients Who Had a HAM-D ≤8 at End of Acute Phase (ITT Population) page 56;Figure 3, Kaplan Meier Survival Curves for Relapse During the Continuation Phase (ITT Population) page 57;page 57 paragraph 2; 6.4 Clinical Global Impression of Improvement, page 58 paragraph 3;Table 21, Distribution of Patients in Each Class of CGI Global Improvement at Week 32 LOCF Endpoint (Intent to Treat Population) page 59; , page 59 paragraph 2; Table 22 , Mean (±SE) CGI Global Improvement at Each Visit (ITT Population) page 59; 10 Data Source Tables: Efficacy, Table 15.1,Number (%) of Patients Withdrawing for Lack of Efficacy (Continuation Phase) (Intent to Treat Population)pages 87; Table 15.2 Summary of Relapse During Continuation Phase for Patients Who Had HAMD </=8 at the End of Acute Phase (Intent to Treat Population), page		

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
				88; Table 15.6 Distribution of Patients in Each Class of CGI Global Improvement at Endpoint (Continuation Phase) (Intent to Treat Population), page 92; 11 Data Source Tables: Safety, pages 113-260;		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Results of additional harms analysis, p.13, table 4, table 5; page 14, table 6; page 15, table 7; page 16, table 8; page 16-17, table 9; page 17-19, table 10; page 19-21, table 11; page 21, table 12; page 21-22, table 13;	Final Clinical Report, Acute Phase, Report Synopsis,Safety Results, pages 19-20; , Table regardingAdverse Events Occurring in ≥ 5% of Any Group and at Least 2X Placebo, page 20; Vital Signs:, page 20; ,Laboratory Tests, page 21; 5 Efficacy Results, 5.3 Functional, Self Perceptive and Behavioral Scales 5.3.1 Autonomous Functioning Checklist, page 87 paragraph 2;Table 36,Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) inTotal Score and Subscores on the Autonomous Functioning Checklist at Endpoint, page 87; 5.3.2 Self Perception Profile, page 88 paragraph 1, Table 37,Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score on the Self Perception Profile for the Week 8 OC and Week 8 LOCF Datasets page 88; 5.3.3 Sickness Impact Profile, page 88 paragraph 2, Table 38, Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score and Subscores on the Sickness Impact Profile for the Week 8 OC and Week 8 LOCF page 89; 5.4 Efficacy Subgroup Analysis, page 90 paragraphs 3-4; Table 39, Summary of Responders by Subgroup at Endpoint, page 90; Table 40	Same page numbersin the PDF of Final Clinical Report, Acute Phase andFinal Clinical Report, Continuation Phase; Clinical Report, Acute Phase,Appendix A, Statistical Report, PDF pages 928- 949.	

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
				Summary of Covariate Analysis for Responders at Endpoint, page 91; 6 Safety Results 6.1 Extent of Exposure, page 92 paragraphs 2-3;Table 41 , Exposure of Patients to Each Daily Dose of Study Drug (in mg) and Duration of Exposure, by Treatment Group (number (%) of patients) page93;6.2 Adverse Experiences, pages 94-95;Table 42,Treatment-emergent Adverse Experiences Most Frequently Reported (by= or > 5% in Any Treatment Regimen), by Body System and Preferred Term(number (%) of patients), page 96; Analysis of Adverse Experiences by Age, page 97 paragraphs 2-3; Table 43 , Number and Percent of Patients with Adverse Experiences by Age (by = or >5% in Any Group), by Body System, and Preferred Term (number (%) patients), pages 98-100;Male and Female - Specific Adverse Experiences, page 100; 6.2.1 Adverse Experiences by Severity , page 101 paragraphs 1-2; Table 44,Severe Treatment-emergent Adverse Experience and those Occurring in More Than One Patient in any Group (number (%) of patients), page 101; 6.2.2 Adverse Experiences by Time of First Occurrence, page 102 paragraph 2;Table 45 , Number (%) of Patients of the Four Most Frequently Reported Treatment-emergent Adverse Experiences by the Time of First Occurrence, page 103; 6.3 Dose Reductions for Adverse		

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
				Experiences, page 104;Table 46,Treatment-emergent Adverse Experiences That Led to Dose Reductions, page 105; 6.4 Adverse Experiences Requiring Corrective Treatment, page 105 paragraph 1 to page 106 paragraph 2,; Table 47,Adverse Experiences That Required Corrective Treatment (≥ 5%), Regardless of Attribution to Study Medication, page 106;6.5 Deaths, page 106; 6.6 Serious Non-fatal Adverse Experiences, page 107 paragraph 2 to page 108 paragraph 3; Table 48 Serious Non-fatal Adverse Experiences page 109; 6.7 Withdrawals for Adverse Experiences,page 110; Table 49, Treatment-emergent Adverse Experiences, Regardless of Attribution, Leading to Withdrawal (number (%) of patients), pages 111-112;Table 50 , Adverse Experiences Leading to Withdrawal, pages 113-114; 6.8 Vital Signs and Body Weight, page 114 paragraph 2 to page 115;Table 51,Vital Signs and Body Weight at Screening, Baseline and at Endpoint (mean +/- SD), page 116;Table 52 Number (%) of Patients with Vital Sign or Body Weight Values ofPotential Clinical Concern at Any Time During Treatment, page 117; 6.9 Other Safety Data Serum Concentrations of Imipramine and Desipramine, page 117; Serum Pregnancy Tests, page 118; 6.10 Laboratory Tests Change from Baseline in Laboratory Values at Endpoint, page		

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
				118; Laboratory Values of Potential Clinical Concern, pages 119-120;Table 53,Criteria for Flagging of Selected Laboratory Parameters, page 119;Table 54,Number of Patients with Laboratory Values Considered to Be of Clinical Concern, page 120; 10 Data Source Tables: Study Population, pages 128-185; 11 Data Source Tables: Efficacy Results, pages 186-221; Data Source Tables: Safety Results, pages 222-526;13 Data Source Figures Figure 1 Kaplan Meier Survival Curves for Time to Sustained Response During Acute Phase Paroxetine - Protocol 329 Intent to Treat Population, page 528; Final Clinical Report, Acute Phase, Appendix A, Statistical Report,3 Summary of Statistical Results, 3.1 Efficacy Variables at Baseline, page 1458; 3.2 Change from Baseline Model Verification, page 1458;Table 2,Treatment-by-Investigator ANOVA P-values for Efficacy Parameters page 1459;3.2.1 HAMD Total (17 items), page 1459;Table 3,ANOV A Table for HAMD Total Mean Change from Baseline at Endpoint,page 1460;Figure 1,Plot of Treatment-by-Investigator HAMD Total Mean Change from Baseline at Endpoint, page 1460; 3.2.2 K-SADS-L Depression Subscale page 1460;Table 4,ANOVA Table for K-SADS-L Depression Subscale Mean Change from Baseline at Endpoint, page 1461; Figure 2 , Plot of Treatment-by-Investigator K-SADS-L Depression		

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
				Subscale Mean Change from Baseline at Endpoint,page 1461; 3.2.3 HAMD Retardation Subfactor page 1462;Table 5,ANOV A Table for HAMD Retardation Subfactor Mean Change from Baseline at Endpoint page 1462; Figure 3,Plot of Treatment-by-Investigator HAMD Retardation Subfactor MeanChange from Baseline at Endpoint, page 1463; 3.3 Percent Response Model Verification page 1463 paragraph 2; 3.4 Survival Analysis page 1464,Table 6 Survival Analysis of Sustained Response During the Acute Phase page 1464;Figure 4,Kaplan Meier Survival Curves for Time to Sustained Response During Acute Phase page 1465; 3.5 Per Protocol Analyses, 3.5.1 HAMD Total (17 items) page 1465; Table 7,ANOVA Table for HAMD Total Mean Change from Baseline at Endpoint Per Protocol Population page 1466;Figure 5,Plot of Treatment-by-Investigator HAMD Total Mean Change from Baseline at Endpoint Per Protocol Population page 1466;3.5.2 K-SADS-L Depression Subscale pages 1466-1467;Table 8 , ANOVA Table for K-SADS-L Depression Subscale Mean Change from Baseline at Endpoint Per Protocol Population page 1467;Figure 6 Plot of Treatment-by-Investigator K-SADS-L Depression Subscale Mean Change from Baseline at Endpoint Per Protocol Population,page 1468; 3.6 Covariate Analyses,3.6.1 Percentage of Responders, pages 1468, 1469		

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Source section(s) of the Clinical Study Report (CSR): page No. and paragraph**	PDF page No (for PDF files)***	Notes
				paragraph 2;Table 13.28.1 Summary of Covariate Analysis for Percentage of Responders at Endpoint, page 1470;Table 13.28.2 Summary of Response at Endpoint by Covariate, page 1471;3.6.2 HAMD Total page 1472 paragraph 2;Table 13.29.1 Summary of Covariate Analysis for HAMD Total at Endpoint, page 1473; Table 13.29.2 Summary of HAMD Total at Endpoint by Covariate, page 1474;3.6.3 KSADS Total page 1475 paragraph 2;Table 13.30.1 Summary of Covariate Analysis for KSAD Total at Endpoint, page 1476;Table 13.30.2 Summary of KSAD Total at Endpoint by Covariate, page 1477; Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission, page 1479;		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p.13, table 4, table 5; page 14, table 6; page 15, table 7; page 16, table 8; page 16-17, table 9; page 17-19, table 10; page 19-21,	Final Clinical Report, Acute Phase, Report Synopsis, Safety Results, Adverse Experiences, page 19-20; Table Adverse Events Occurring in ≥ 5% of Any Group and at Least 2X Placebo, page 20, page 21 paragraph 1; 6.2 Adverse Experiences, page 94-95; Table 42 Treatment-emergent Adverse Experiences Most Frequently Reported (by = or > 5% in Any Treatment Regimen), by Body System and Preferred Term (number (%) of patients), page 96; Analysis of Adverse	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
			table 11; page 21, table 12; page 21-22, table 13; ;	Experiences by Age, page 97; Table 43, Number and Percent of Patients with Adverse Experiences by Age (by = or >5% in Any Group), by Body System, and Preferred Term (number (%) patients), page 98-100; Male and Female - Specific Adverse Experiences, page 100; 6.2.1 Adverse Experiences by Severity, page 101 paragraphs 1-2; Table 44 Severe Treatment-emergent Adverse Experience and those Occurring inMore Than One Patient in any Group (number (%) of patients), page 101; 6.2.2 Adverse Experiences by Time of First Occurrence, page 102 paragraph 2; Table 45 Number (%) of Patients of the Four Most Frequently Reported Treatment-emergent Adverse Experiences by the Time of First Occurrence, page 103; 6.3 Dose Reductions for Adverse Experiences, page 104; Table 46 Treatment-emergent Adverse Experiences That Led to Dose Reductions, page 105; 6.4 Adverse Experiences Requiring Corrective Treatment, page 105-106; Table 47 Adverse Experiences That Required Corrective Treatment (≥ 5%), Regardless of Attribution to Study Medication, page 106; 6.5 Deaths, page 106; 6.6 Serious Non-fatal Adverse Experiences, page 106-108; Table 48 Serious Non-fatal Adverse Experiences, page 109; 6.7 Withdrawals for Adverse Experiences, page 110; Table 49 Treatment-emergent Adverse Experiences, Regardless of		

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
				Attribution,Leading to Withdrawal (number (%) of patients), page 111-112; Table 50 Adverse Experiences Leading to Withdrawal, page 113-114; 6.8 Vital Signs and Body Weight, page 114 paragraph 2 to page 115; Table 51 Vital Signs and Body Weight at Screening, Baseline and at Endpoint (mean +/- SD), page 116;Table 52 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During Treatment, page 117; 6.10 Laboratory Tests, Laboratory Values of Potential Clinical Concern, pages 118-120,Table 54 Number of Patients with Laboratory Values Considered to Be of Clinical Concern, page 120; Data Source Tables: Safety Results, Table 14.2.1 Summary of Treatment-Emergent Adverse Experiences during Acute Phase by ADECS Body System and Preferred Term Non-gender Specific Adverse Experiences Intent-to-Treat Population, page 226-229; Table 14.2.3 Summary of Treatment-Emergent Adverse Experiences during Acute Phase by ADECS Body System and Preferred Term Female Specific Adverse Experiences Intent-to-Treat Population, page 230; Table 14.3.1 Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum IntensityAcute Phase - Non-gender Specific Adverse Experiences Intent-to-		

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
				Treat Population, page 231-239; Table 14.3.3 Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum IntensityAcute Phase - Female Specific Adverse Experiences Intent-to-Treat Population, page 240-242; Table 14.4.1, Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Acute Phase) Non-gender Specific Adverse Experiences Intent-to-Treat Population, page 243-260; Table 14.4.3, Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Acute Phase)Female Specific Adverse Experiences Intent-to-Treat Population, page 261-266; Table 14.5.1 Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution by ADECS Body System and Preferred Term (Acute Phase) - Non-gender Specific Adverse Experiences Intent-to-Treat Population, page 267; Table 14.5.3 Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution by ADECS Body System and Preferred Term (Acute Phase) - Female Specific Adverse Experiences Intent-to-Treat Population, page 268; Table 14.6.1 Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution by ADECS Body System and Preferred Term (Acute Phase) - Non-		

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
				gender Specific Adverse Experiences Intent-to-Treat Population, page 269-270; Table 14.6.3 Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution by ADECS Body System and Preferred Term (Acute Phase) - Female Specific Adverse Experiences Intent-to-Treat Population, page 271; Table 14.8 Listing of Serious Adverse Experiences by Treatment Group and PatientAcute PhaseIntent-to-Treat Population, page 272-275; Table 14.8a Serious Adverse Experiences Patient Narratives, page 276-307; Table 14.9.1 Summary of Adverse Experiences Leading to Withdrawal during Acute Phase by ADECS Body System and Preferred Term Non-gender Specific Adverse Experiences Intent-to-Treat Population, page 308-309; Table 14.9.1a Adverse Experiences Leading to Withdrawal Patient Narratives, page 310-366; Table 14.9.3, Summary of Adverse Experiences Leading to Withdrawal during Acute Phase by ADECS Body System and Preferred TermFemale Specific Adverse ExperiencesIntent-to-Treat Population, page 367; Table 14.10.1 Summary of Treatment-Emergent Adverse Experiences by Age Group (Acute Phase) Non-gender Specific Adverse ExperiencesIntent-to-Treat Population, page 368-376; Table 14.10.2 Summary of Treatment-Emergent Adverse Experiences by Age		

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
				Group (Acute Phase) Male Specific Adverse Experiences Intent-to-Treat Population, page 377-379; Table 14.10.3 Summary of Treatment-Emergent Adverse Experiences by Age Group (Acute Phase)Female Specific Adverse Experiences Intent-to-Treat Population, page 380-382; Table 14.12 Summary of Clinically Significant Abnormal Vital Signs by Treatment GroupAcute PhaseIntent-to-Treat Population, page 392; Table 14.12a PATIENTS WITH ABNORMAL VITAL SIGNS OR BODY WEIGHT OFPOTENTIAL CLINICAL CONCERN DURING THE ACUTE PHASE, page 393-475; Table 14.14 Summary of Clinically Significant Abnormal Laboratory ValuesAcute PhaseIntent-to-Treat Population, page 488-489; Table 14.14a Clinically Significant Abnormal Laboratory Values Patient Narratives, page 490-526; Continuation Study, Final Clinical Report, Report Synopsis, Safety Results, page 7 paragraph 1 to page 8 paragraph 4; Table, Adverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo, page 7; 5 Safety Results, 5.2 Adverse Events, page 32; Table 7 Number (%) of Patients with Treatment-emergent Adverse Events Most Frequently Reported (≥5% in Any Treatment Group), by Body System and Preferred Term (ITT Population), page 33; Table 8 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at		

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
				Least 2X Placebo (ITT Population) page 34; Table 9 Number (%) of Patients with the Five Most Frequently Reported Treatment-emergent Adverse Events by the Time of First Occurrence During the Continuation Phase (ITT Population) page 36;page 37 paragraphs 1-2; 5.3 Deaths page 37; 5.4 Serious Non-Fatal Adverse Events, page 38 paragraph 1 to page 39 paragraph 4; Table 10 Serious Non-Fatal Adverse Events (ITT Population), page 40; 5.5 Withdrawals for Adverse Events, page 41; Table 11 Treatment-emergent Adverse Events, Regardless of Attribution, Leading to Withdrawal (number (%) of patients (ITT Population), page 42; Table 12 Adverse Events Leading to Withdrawal in Continuation Phase (ITT Population), page 43; 5.6 Vital Signs and Body Weight 5.6.1 Mean Values and Changes in Value, page 45 paragraph 3-5;Table 13 Vital Signs and Body Weight at Baseline and Endpoint (mean ± SD) (ITT Population), page 46; 5.6.2 Patients with Vital Signs of Potential Clinical Concern, page 46 paragraph 1 to page 47 paragraph 1;Table 14 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During the Continuation Phase (ITT Population), page 47; 5.7 Laboratory Tests, Table 15 Number of Patients with Laboratory Values Considered to Be of Clinical Concern (ITT Population), page 49; 5.8 Safety Results in the		

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
				Continuation Phase Compared to the Acute Phase, page 50 paragraph 4to page 51 paragraph 2;Table 16 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo in Either Phase of the Study or Both Phases Combined (ITT Population), page 52; 5.8.1 Serious Adverse Events in Both Phases Combined, page 53, Table 17 Number (%) of Patients with Serious Adverse Events in Each Phase of the Study and Both Phases Combined (ITT Population), page 54; 11 Data Source Tables: Safety, 16.2.1 Summary of Treatment-Emergent Adverse Experiences duringthe Continuation Phase by ADECS Body System and Preferred Term-Non-gender Specific Adverse Experiences (Intent to Treat Population) pages 120-122; 16.2.2 Summary of Treatment-Emergent Adverse Experiences during the Continuation Phase by ADECS Body System and PreferredTerm-Male Specific Adverse Experiences (Intent to Treat Population) page 123;16.2.3 Summary of Treatment-Emergent Adverse Experiences during the Continuation Phase by ADECS Body System and PreferredTerm-Female Specific Adverse Experiences (Intent to Treat Population) page 124;16.2.4 Summary of Treatment-Emergent Adverse Experiences during Both Phases Combined by ADECS Body System and Preferred Term (Intent to Treat Population) page 125-132; 16.3.1		

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
				Summary of Treatment-Emergent Adverse Experiences byADECS Body System and Preferred Term and by Maximum Intensity-Non-gender Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 133-138; 16.3.2 Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity -Male Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 139;16.3.3 Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity -Female Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 140-142; 16.4.1 Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence-Non-gender Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 143-154; 16.4.2 Summary of Treatment-Emergent Adverse Experiences by Timeof First Occurrence-Male Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 155; 16.4.3 Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence-Female Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 156-161;16.5.1 Summary of Treatment-Emergent Adverse Experiences Leading		

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
				to Dose Reduction Regardless of Attribution by ADECS Body System and Preferred Term-Non-gender Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 162;16.5.2 Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution by ADECS Body System and Preferred Term-Male Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 163;16.5.3 Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution by ADECS Body Systemand Preferred Term-Female Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 164; 16.6.1 Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution by ADECS Body System and Preferred Term-Non-gender Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 165-166; 16.6.2 Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution by ADECS Body System and Preferred Term-Male Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 167; 16.6.3 Summary of Treatment-Emergent Adverse Experiences Requiring Corrective		

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
				Therapy Regardless of Attribution by ADECS Body System and Preferred Term-Female Specific Adverse Experiences (Continuation Phase) (Intent to Treat Population) page 168;16.7 Listing of Deaths by Treatment Group and Patient (ContinuationPhase) (Intent to Treat Population) page 169; 16.8 Listing of Serious Adverse Experiences (Continuation Phase) (Intent to Treat Population) pages 170-172; Table 16.8.1 Narratives for Patients with Serious Non-Fatal Adverse Events pages 173-191; Table 16.9.1 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Non-gender Specific Adverse Experiences (Intent to Treat Population) page 192; Table 16.9.2 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Male Specific Adverse Experiences (Intent to Treat Population) page 193; Table 16.9.3 Summary of Adverse Experiences Leading to Withdrawal during the Continuation Phase by ADECS Body System and Preferred Term-Female Specific Adverse Experiences (Intent to TreatPopulation) page 194; Table 16.9.4 Narratives for Patients with Non-Serious Adverse Events Leading to Withdrawal pages 195-210;Table 16.10.1 Summary of Treatment-Emergent Adverse		

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

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

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

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.

JULY 2015

Appendix 2

List of Tables

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

Table ii – Additional AEs found during review of 93 CRFs (acute phase plus taper)

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

Table iv – Summary of all adverse events within each SOC, including those classed as 'Severe' by investigator

Table v – Full breakdown of all adverse events within each SOC, including those classed as 'Severe' by investigator – events from CSR check only.

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

Table vii – Breakdown of adverse events during taper phase only

Table viii – Changes to 'reasons for discontinuation' during acute (plus taper) phase
- a) Paroxetine group
- b) Imipramine group
- c) Placebo group

Table vix – Baseline screening errors (found during safety review)

Table x – Suicidality at screening (Kiddie-SADS)
- a) Kiddie-SADs items 108-117 'SUICIDAL IDEATION' at screening visit (-1 week)
- b) Kiddie-SADs item 108 'SUICIDAL IDEATION' – 'Current Episode' at screening (-1 week)
- c) Kiddie-SADs item 109 'SUICIDAL IDEATION' – 'Last Two Weeks' at screening (-1 week)

Table xi – Types of medications taken 1 month prior to enrolment

Table xii – AEs occurring in patients taking other medication during month prior to enrolment vs. those taking no other medication
- a) Paroxetine group
- b) Imipramine group
- c) Placebo group

Table xiii - Attrition of patients by week

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
	Body 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 within each SOC, including those classed as 'Severe' by investigator

SOC	Paroxetine N=93		Imipramine N=95		Placebo N=87	
	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	44	1 (2.3%)	130	3 (2.3%)	32	0
Gastrointestinal disorders	112	25 (22.3%)	147	20 (13.6%)	79	4 (5.1%)
Psychiatric disorders	103	32 (31.1%)	63	4 (6.3%)	24	6 (25%)
Nervous system disorders	101	7 (6.9%)	114	14 (12.3%)	77	7 (9.1%)
Respiratory, thoracic and mediastinal disorders	42	2 (4.8%)	22	1 (4.5%)	39	4 (10.3%)
General disorders	15	2 (13.3%)	10	1 (10.0%)	17	1 (5.9%)
Skin and subcutaneous tissue disorders	10	0	17	1 (5.9%)	10	1 (10%)
Renal and urinary disorders	5	0	9	1 (11.1%)	4	0
Immune system disorders	2	0	2	0	3	0
Endocrine disorders	1	0	1	1 (100%)	1	0
Blood and lymphatic disorders	1	0	4	0	3	0
Musculoskeletal and connective tissue disorders	8	0	7	0	16	0
Reproductive system and breast disorder	4	0	4	1 (25%)	4	1 (25%)
Infections	6	1 (16.7%)	5	1 (20%)	4	1 (25%)
Eye disorders	5	0	4	0	1	0
Metabolism and 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	**481**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**26 (7.9%)**

Table v – Full breakdown of all adverse events within each SOC, including those classed as 'Severe' by investigator – events from CSR check only.

SOC	MedDra Term	Paroxetine N=93		Imipramine N=95		Placebo N=87	
		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	Arrhythmia	0	-	1	0	1	0
	Atrial ectopic	0	-	0	-	1	0
	AV block	1	0	2	0	2	0
	Bradycardia	0	-	1	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
	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	-
	TOTAL	**44**	**1**	**130**	**3**	**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	2
	Aggression/ increased anger	7	3	3	2	0	-
	Agitation	1	-	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	-
	Impulsive behaviour	1	-	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	5	4	3	0	1	1
	Suicide attempt	8	4	3	0	0	-
	TOTAL	**103**	**32**	**63**	**4**	**24**	**6**
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	-
	Migraine	1	0	1	1	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	**101**	**7**	**114**	**14**	**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	Acne	3	0	2	0	1	0

subcutaneous tissue disorders	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 disorders	Anaemia	1	0	1	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		**481**	**70 (14.6%)**	**552**	**50 (9.1%)**	**330**	**26 (7.9%)**

Table vi – 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	9	0	0	0
Gastrointestinal Disorders	9	4	18	4	4	0
Psychiatric Disorders	15	8	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 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	13	50	9	10	1

Table vii – 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	Arrythmia	0	0	1	0	0	0
	AV block	1	0	0	0	0	0
	Bradycardia	0	0	1	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**	**9**	**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	2	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**	**8**	**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 disorders and site administration conditions	Fatigue	1	0	1	0	0	0
	TOTAL	**1**	**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 lymph disorders	Anaemia	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**	**13**	**50**	**9**	**10**	**1**

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

a) **Paroxetine group**

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

Patient ID	GSK reason for discontinuation	Proposed reason for discontinuation	Notes
329.001.00068	Lack of Efficacy	Lack of Efficacy	Non-responder (Ham-D)
329.001.00206	Lack of Efficacy	Lack of Efficacy	Non-responder (Ham-D)
329.003.00081	Lack of Efficacy	OTHER (misc)	HAM-D scores indicate patient a 'Responder'
329.003.00089	Lack of Efficacy	AE (suicidal)	SAE narrative: "the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed at risk to herself and was brought to the crisis service. She was hospitalized... and the decision was made she would not enter the continuation phase.
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	GSK reason for withdrawal (as per Appendix G)	RIAT reason for withdrawal
Reason for withdrawal changes	329.001.00065	AE (aggression)	AE (suicidal)
	329.002.00058	AE (overdose)	AE (suicidal gesture/attempt) – OD (Tylenol x 80 pills) 3 days after discontinuing meds
	329.003.00313	AE (hospitalisation)	AE (suicidal)
	329.004.00015 *	Other (conflict with school and study)	Withdrawn consent
	329.004.00212	PV (non compliance)	AE (sedation)
	329.005.00333	Lack of Efficacy	AE (suicidal)
	329.009.00133	Lost to Follow Up	Lack of Efficacy
	329.011.00288	Lack of Efficacy	AE (agitation, possibly suicidal)
	329.012.00228	PV	Withdrawn consent

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

	Patient ID	GSK reason for withdrawal (as per 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	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	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	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	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	**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 vix - Baseline screening errors (found during safety review)

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

Patient ID number	Drug Group	Inclusion criteria error
329.012.00221	Imipramine	Patient reported as having 'severe' suicidal ideation at the initial screening/baseline visits on both Kiddie-SAD (5-severe) and Ham-D (3 – suicidal ideas/gestures).
329.002.00241	Placebo	Patient reported as having 'severe' suicidal ideation at the initial screening visit. Two suicidal acts were reported within the current depressive episode with one of these occurring within the last 2 weeks. The patient also found to have an abnormality (arrhythmia) during baseline EKG, however this was cleared following a referral to a cardiologist.
329.006.00037	Placebo	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	Placebo	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	Placebo	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	Placebo	Has been re-coded as 'PV by investigator'. Patient was 'extremely' suicidal at screening with no suicidal acts (see Kiddie-SADs & HAM-D). Patient showed 'worsening depression' during the study,

		was admitted to hospital during week 4 and given Zoloft. GSK reason for withdrawal was AE 'ambivalence towards meds'. Alternatively could argue was withdrawn for 'AE worsening depression'.

No similar Protocol violations 'by investigator' were found for patients in the paroxetine group during the audit.

Table x - Suicidality at screening (Kiddie-SADS)

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

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

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

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

b) Kiddie-SADS item 108 'Suicidal Ideation' - '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 1 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 xii – Adverse events occurring in patients taking other medication prior to enrolment vs. those taking no other medication:

a) Paroxetine

SOC	MedDra Term	Patients taking 'other Medications' during month pre-enrolment	Patients taking 'No Medication' during month pre-enrolment
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	1
	Vomiting	2	9
	TOTAL	**22**	**90**
Nervous system disorders	Bad taste	0	0
	Convulsion	0	0
	Dystonia	4	1
	Headache	25	34
	Laryngitis dystonia	0	1
	Memory loss	0	0
	Migraine	0	1
	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**	**54**
General disorders	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	1
	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
	Impulsive behaviour	0	1
	Insomnia	4	12
	Paranoia	1	0
	Psychosis	0	1
	Somnolence	9	15
	Substance abuse	0	1
	Suicidal ideation/gesture	0	5
	Suicide attempt	2	6
	TOTAL	**30**	**73**
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
	Hypertension	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	Albuminuria	0	0
	Cystitis	0	1

disorders	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	Anaemia	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 nutritional 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**	**323**

b) imipramine

SOC	**MedDra Term**	**Patients taking 'other Medications' during month pre-enrolment**	**Patients taking 'No Medication' during month pre-enrolment**
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**
Nervous system disorders	Bad taste	1	2
	Convulsion	1	0
	Dystonia	2	5
	Headache	32	27
	Laryngitis dystonia	0	0
	Memory loss	0	1
	Migraine	1	0
	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	**59**	**55**

General disorders	Fatigue	5	3
	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
	Hallucinations	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	**9**	**13**
Cardiac disorders	Atrial ectopic	0	0
	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
	Hypertension	0	2
	Arrythmia	0	1
	Postural hypotension	7	10
	QT interval prolonged	2	1
	Tachycardia	12	16
	TOTAL	**51**	**79**
Skin and subcutaneous	Acne	2	0
	Dermatitis	2	0

tissue disorders	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 system disorders	Anaemia	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 disorders	Breast enlargement	0	0
	Dysmenorrhea	2	2
	TOTAL	**2**	**2**
Infections	Herpes zoster	0	0
	Infection	2	1
	Otitis media	1	1
	TOTAL	**3**	**2**
Eye disorders	Conjunctivitis	0	0
	Itchy eyes	0	1
	Mydriasis	1	0
	Photosensitivity	1	0
	Photopsia	0	1
	TOTAL	**2**	**2**
Metabolism and	Decreased appetite	1	1

nutritional disorders	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		**2**
Surgical and medical procedures	Tooth extraction	0	2
	TOTAL	**0**	**2**
Total number of AEs		**220**	**332**

c) placebo

SOC	**MedDra Term**	**Patients taking 'other Medications' during month pre-enrolment**	**Patients taking 'No Medication' during month pre-enrolment**
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**
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	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	Anaemia	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 nutritional disorders	Decreased appetite	1	3
	Increased appetite	0	1
	Thirst	1	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 xiii - 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.

Appendix 3: Study 329 – Suicidal & Self-Injurious Behavior

Table i: Suicidal and Self-Injurious Behaviour in Study 329

Patient ID	CSR Appendix D Patient Data Listings of Adverse Events			Other CSR sources e.g. HAM-D suicide, Serious Adverse Event (SAE) narrative, Appendix G	MedDRA based on CSR	Additional information from CRF	MedDRA based on CRF
	Verbatim terms	SKB/ ADECS preferred term	Day AE occurred				
Paroxetine							
Case 1: 329.002. 00058	Intentional overdose (Tylenol 80 pills)	Emotional lability	122 (during taper)	Appendix G: Withdrawal for Adverse Event (AE) intercurrent illness SAE narrative: *The patient was hospitalized on 19-Jan-95 after taking 80 Tylenol tablets…. The investigator considered the event to be moderately severe. The patient was withdrawn from the study due to the overdose.*	Suicide attempt/ self harm	-	Suicide attempt/ self harm
Case 2: 329.002. 00245	Tylenol overdose (intentional)	Emotional lability	14	Appendix G: AE classed as severe. Withdrawn: AE intercurrent illness	Suicide attempt/ self harm		Suicide attempt/ self harm
Case 3: 329.003. 00250	3.1. Overdose intentional	Emotional lability	37	Appendix G: SAE narrative: *The patient exceeded compliance from 19APR96 through 09May96. The overdose was rated by the investigator as serious, moderate in intensity and unrelated to the patient's use of the study drug.*	Suicide attempt/ self harm	-	Suicide attempt/ self harm
	3.2. Overdose intentional	Emotional lability	75 (during taper)	Appendix G: Severe AE. Withdrawn for Adverse Event intercurrent illness - SAE narrative: *The patient took a 20-tablet overdose of study medication. She was taken to the emergency room by her*	Suicide attempt/ self harm	P 267 Adverse Experience log: *Hospitalisation resulting from suicide attempt* and *Pt took overdose 'intentional'.* - Series of query log entries whether to	Suicide attempt/ self harm

				sister….the patient was discharged from the general hospital and admitted to psychiatric unit as she remained suicidal. Appendix D - AE is logged as 'UNRELATED'.		include suicidal ideation as another AE reason for hospitalisation. - 'Hospitalisation' removed as an AE; suicidal ideation not included. 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.*	
Case 4: 329.003. 00313	4.1. Superficial cuts - risk to self	Emotional lability	12	Appendix G: classed as SAE, severe. Reason for withdrawal= AE intercurrent illness - *Patient was dropped due to hospitalization i.e. adverse experience.* Patient also auditory hallucinations on Day 12 (severe). SAE narrative: *Patient hospitalised for psychosis [no previous history of psychosis] with auditory hallucinations and superficial cuts. A voice commanded him to hurt himself.*	Suicide attempt/ self harm psychosis – missing from Appendix D	Week 2 visit a *serious attempt at suicide* reported on Hamilton scale p.182: *X experiencing auditory hallucinations. A voice commands him to hurt himself. He has cut himself in response to the voice on three occasions in the past six days. On the back of his hand he has carved a cross with small adorning cuts. On his forearm he has made 10-15 cuts, each about six inches long. On his upper arm are three additional cuts.* P. 120 week 2 HAM-D item 3 suicide: *Attempts at suicide (any serious attempt rates 4)* - patient rated 4.	Suicide attempt/ self harm
	4.2. missing	-	12	SAE narrative: *The voice commanded the patient to jump off the roof. Although the patient went to the roof he did not jump. It was determined that the patient was a risk to himself.*	Suicidal ideation	-	Suicidal ideation
Case 5: 329.004.	5.1. Self Mutilation	Emotional lability	31	Patient noted to have had an episode of self harming '*self mutilation'.*	Suicide attempt/	-	Suicide attempt/

00015					self harm		self harm
	5.2. Missing Possible Event	-	35	Increase in suicidal ideation on HAM-D *suicide ideas or gesture* at week 5, as well as both suicidal ideation and self mutilation episodes on Kiddie SADS	Suicidal ideation		Suicidal ideation
	5.3 Suicidal Ideation	Emotional Lability	73	Recorded as an adverse event but no SAE narrative. Patient dropped out 4 month later coded as Other.	Suicidal ideation		Suicidal ideation
Case 6: 329.006. 00038	6. Attempted suicide (intentional)	Emotional lability	57	Appendix G: AE Severe, patient withdrawn: *Several personal crisis led patient to overdose on several medications including study medications on 12APR95 - move to withdraw.* SAE narrative: *Following a disagreement with her mother, the patient intentionally overdosed.*	Suicide attempt/ self harm	p. 193 Week 8 paperwork not completed. Note on file: *Pt attempted suicide this day - in emergency room facilities.* - 'GI complaints' & 'Nausea' - coded as part of suicide attempt by GSK.	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. AE coded as Trauma – Episode reported as CONTINUOUS over 12 days. No SAE narrative	Suicide attempt/ self harm	Week 6 visit adverse events noted – fatigue, angry (not in Appendix D), more depressed, irritable mood. Kiddie SADS scores: Week 4: 'Non-suicidal acts of self harm in last 2 weeks' = 4 (moderate)	Suicide attempt/ self harm
	7.2. missing	-	43	HAM-D weeks 5 & 6 – score '3' - 'suicidal ideas or gesture' The final visit described patient as having 'headaches- more severe than usual' – Recorded in Appendix D; *worse general/overall feeling depressed with a HAM-D score of 24.*	Suicidal ideation	Adverse event worsening depression – missing from Appendix D.	Suicidal ideation
Case 8: 329.001. 0065	8.1. Needed 6 stitches to hand after breaking	Hostility	14	Other adverse event included on day 14: Worsening of depression, hospitalised (Severe, possibly related, stopped from	Suicidal ideation	-	Suicidal ideation

	pictures (due to anger) resulted in hospitalisation to prevent aggression against self			study). SAE narrative: '*the patient became very angry....His anger subsided, but he expressed hopelessness and possible suicidal thoughts. The patient was hospitalized due to his severe anger outburst and a worsening of his depression... In the opinion of the investigator, the worsening of depression was possibly related to study medication.'*			
	8.2 missing	-	14	Appendix G: reason for withdrawal: Adverse Event, including intercurrent *Needed psychiatric hospitalisation for increased aggression against self.* .	Suicide Event – Self Harm	Study conclusion form reports hospitalisation for *increased aggression against self*. p.108 Adverse experience: *needed 6 stitches to hand. Aggression to self.* p.136 Query log reports: *Telephone report also indicates a symptom of increased self harm.* - Adverse events of 'self harm' 'hopelessness' 'inc anger' suicidal ideation' combined as HOSTILITY, but coded separately under MedDRA coding. Discussion in the CRF query log of the patient needing stitches to their hand following a *severe angry outburst* and *increased self `harm*.	Suicide attempt/ Self Harm
Case 9: 329.005. 00333	Suicidal ideation	Emotional lability	37	Appendix G: Withdrawal 'Lack of Efficacy' (day 33). Severe SAE. Other adverse events included: abnormal dreams (day 19) for 11 days. SAE narrative: '*patient did not sleep well all night, cried and experienced suicidal intentions. She was subsequently hospitalized for severe suicidal ideation.'*	Suicidal ideation	p198 & 224: *Suicidal ideation. The pt had Prozac 5mg x1 pd given for MDD* - 'Depression worsening' added as additional AE. p174 Adverse Experience log: *Suicidal Ideation.*	Suicidal ideation

Case 10: 329.002. 00106	Oppositional Defiant Disorder	Hostility	51	Appendix G records as a severe SAE. - SAE narrative: *patient was hospitalised after an argument. She had become combative with her mother and had threatened suicide...several days before her hospitalisation she had not taken her study medication.*	Suicidal ideation/ gesture & Aggression	p178: *no week 8 visit due to psychiatric hospitalization.* p 185 *Zoloft added for 'depression' following hospitalization for ODD.*	Suicidal ideation/ gesture & Aggression & Depression
Case 11: 329.005. 00011	Overdose intentional	Emotional lability	156	SAE narrative:"the patient took an intentional overdose of Bayer aspirin.. the patient had recently experienced several stressors (taunted by classmates about being depressed and failing grades. On the day of the event, the patient disobeyed her mother and became angry and went into a tantrum. The patient told her mother she just wanted to die and then proceeded to take an overdose.	Suicidal ideation and act		Suicidal ideation and act
Case 12 329.003. 00089	Elated and Expansive Mood	Euphoria	56	SAE narrative: "the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed at risk to herself and was brought to the crisis service. She was hospitalized... and the decision was made she would not enter the continuation phase.	Suicidal ideation/ gesture		Suicidal ideation/ gesture
Imipramine							
Case 1: 329.005. 00295	Suicidal threat with scissors	Emotional lability	23	Appendix G: Adverse Event entered 'suicidal threat' = moderate and 'probably related'. Patient withdrawn on Day 53. Withdrawal: AE intercurrent illness - *investigators decision to discontinue study because pt threatened to kill parents.* This event coded	Suicide attempt/ self harm	Kiddie-SADS Week 4: suicidal ideation increased to 3.	Suicide attempt/ self harm

				as 'hostility' severe; probably related.			
Case 2: 329.012.00223	2.1. Suicidal ideation	Emotional lability	26	Appendix G: suicidal ideation coded as moderate lasting 10 days.	Suicidal Ideation	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. 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: *Pt suicidal and went to ER.* p190 - *SAE for suicidal ideation and gesture started on 02Mar95.*	Suicidal gesture
Case 4: 329.010.00279	4.1. Strange thoughts	Thinking abnormal	33	No SAE narrative	? Suicidal ideation	No clarification given re: strange thoughts in query log *'pt and mother can't remember'*	? Suicidal ideation
Case 5: 329.012.00221	5.1 Overdose intentional	Emotional Lability	132	Patient up-dosed to Imipramine 250mg at week 4 and appears to have a manic reaction – leads to down-titration. Also has dizziness, constipation and dry mouth. Patient overdoses on lorazepam 8mg Coding changed to serious and at the upper limit of severity. SAE – overdoses on father's lorazepam after argument with girlfriend. Patient indicated overdose was impulsive, that he did not intend to die and was not activity suicidal. Patient recorded as withdrawing consent to study – refused down-titration – because he might be on placebo.	Suicide Attempt	Initially coded in CRF as mild with patient seen in hospital and discharged that day. After dropped out of study, coding changed to serious and at the upper limit of severity.	Suicide Attempt

Placebo							
Case 1: 329.001. 00123	Suicidal thoughts	Emotional lability	46	Appendix G: adverse event classed as severe, related, a SAE. Study drug was stopped and patient was withdrawn. Other adverse events noted = Worsening of depression day 46 Patient withdrawn DAY 49 'Lack of Efficacy'. SAE narrative: '*Approximately 6 weeks after commencing study 329, the patient experienced severe worsening of depression with severe suicidal thoughts'.*	Suicidal ideation	-	Suicidal ideation
Case 2: 329.009. 00129	Missing	-	35	Patients Ham-D item 3 and Kiddie Sads suicide ideation run at low grade suicidal ideation through the study 1-2 every week; Appendix G: Discontinues week 5: *Patient doing some what worse. Mother worried about increase in death wishes.*- coded as Lack of Efficacy	? Suicidal Ideation	Nothing else in CRF	? Suicidal ideation
Case 3: 329.002. 00241	Homicidal Ideation	Emotional Lability	106	SAE: Seven weeks into continuation phase, mother took to physician for "anger and irritability. The patient was evaluated and admitted due to severe suicidal and homicidal ideation (towards his parents).	Suicidal Ideation	Patient had abnormal ECG before entry and two suicidal gestures during the episode, one in the week before entry to trial. Close to protocol violation.	Suicidal ideation
Case 4 329.009. 00197	Superficial laceration to scalp	Trauma	172	On entry patient scored 2 on Ham-D item 3 and on Kiddie-Sads suicidal ideation but thereafter through acute and continuation phase scores 0. Six months into the study has a top of scalp laceration – no mention of stitching. Coded as mild. Augmentin (antibiotic) given.	? Suicide Attempt	Nothing else in CRF.	? Suicide Attempt

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

Appendix 3 (ii): Coding Decisions for Suicidal and Self Injurious Behaviour

The suicidal cases in Study 329 were at the heart of the Department of Justice's case against GSK that led to a $3 Billion fine. There were differing views as to how many cases there were – FDA's, GSK's and now RIATs.

See
http://www.justice.gov/sites/default/files/opa/legacy/2012/07/02/us-complaint.pdf#page=11

> *43. Moreover, the FDA asked for additional information about patients in the studies who had experienced adverse events and who had withdrawn from the study prematurely, as well as why GSK used the term "emotional lability" to describe the five patients who attempted to commit suicide or exhibited other self-injurious behaviour. In May 2003, GSK, for the first time provided the FDA with additional safety data from the studies.*
>
> *44. Although GSK told the FDA there was no statistically significant difference in suicidality between placebo and Paxil in all the Paxil pediatric depression studies cumulatively, the difference between the potential suicide-related events among Paxil patients versus potential suicide-related events among placebo patients became statistically significant when the first 30 days after therapy were included in the analysis.*
>
> *45. Likewise, upon closer examination the number of possible suicide-related events among the Study 329 Paxil patients increased beyond the five patients that GSK described in the JACAAP article as having "emotional lability". While collecting safety information for the FDA, GSK admitted that there were four more possible suicide-related events among Paxil patients in Study 329. In addition, the FDA later identified yet another possibly suicide-related event in the Study 329 Paxil patients, which also was not among the 11 serious adverse events listed in the JAACAP article. thus, altogether 10 of the 93 Paxil patients in Study 329 experienced a possibly suicidal event, compared to one of the 87 patients on placebo. This is a fundamentally different picture of Paxil's pediatric safety profile than the one painted by the JAACAP article, which listed at most five possibly suicidal events among Paxil patients, brushed those off as unrelated to Paxil, and concluded that treating children with Paxil was safe.*

Appendix 3 (iii): INTERNET LINKS TO STUDY 329 DATA

- Study synopsis acute PDF (0.03Mb)
- Study synopsis continuation PDF (0.03Mb)
- Full study report acute PDF (0.97Mb)
- Full Study report continuation PDF (0.56Mb)
- Appendix A PDF (19Mb)
- Appendix B PDF (18Mb)
- Appendix C PDF (19Mb)
- Appendix D PDF (8Mb)
- Appendix E PDF (3.5Mb)
- Appendix F PDF (23.5Mb)
- Appendix G PDF (53Mb)
- Appendix H PDF (60Kb)

Appendix 3 (iv): ***Suicidal and Self Injurious Behaviour***

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

Appendix 3 (v): **PAROXETINE CASES WITH SUICIDAL & SELF-INJURIOUS BEHAVIOR**

329.002.00058 Case 1: GSK Y;FDA Y; RIAT Y

APPENDIX D PAGE 125
APPENDIX G PAGE 167
FULL STUDY REPORT CONTINUATION PAGE 173

329.002.00245 Case 2: KELLER Y; GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 127
APPENDIX G PAGE 341
FULL STUDY REPORT ACUTE PAGE 283

329.003.00250 Case 3: KELLER Y; GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 131
APPENDIX G PAGE 511
FULL STUDY REPORT ACUTE PAGE 288
FULL STUDY REPORT CONTINUATION PAGE 177

329.003.00313 Case 4: KELLER Y; GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 131
APPENDIX G PAGE 553
FULL STUDY REPORT ACUTE PAGE 289

329.004.00015 Case 5: GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 132
APPENDIX G PAGE 607

329.006.00038 CASE 6: KELLER Y; GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 143
APPENDIX G PAGE 1074
FULL STUDY REPORT ACUTE PAGE 294

329.006.00039 CASE 7: RIAT Y

APPENDIX D PAGE 11
APPENDIX D PAGE 144
APPENDIX G PAGE 1082

329.001.00065 CASE 8: GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 25
APPENDIX D PAGE 29
APPENDIX D PAGE 124
APPENDIX G PAGE 29
FULL STUDY REPORT ACUTE PAGE 107

FULL STUDY REPORT ACUTE PAGE 272
FULL STUDY REPORT ACUTE PAGE 277

329.005.00333 CASE 9: KELLER Y; GSK Y; FDA Y; RIAT Y

APPENDIX D PAGE 28
APPENDIX D PAGE 142
APPENDIX G PAGE 1042
FULL STUDY REPORT ACUTE PAGE 272
FULL STUDY REPORT ACUTE PAGE 292

329.002.00106 Case 10: FDA Y; RIAT Y

APPENDIX G PAGE 257
FULL STUDY REPORT ACUTE PAGE 281

329.005.00011 Case 11: GSK Y; FDA Y; RIAT Y

APPENDIX D PAGES 28, 137
APPENDIX G PAGES 782, 783
FULL STUDY REPORT PAGE 500

329.005.00089 Case 12: RIAT Y

APPENDIX D PAGE 28
APPENDIX G PAGE 442
FULL STUDY REPORT ACUTE PAGE 272
FULL STUDY REPORT ACUTE PAGE 285

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

Case 00039

This case had as verbatim term 'Superficial Scratches'. GSK coded this as trauma. There were two cases of superficial lacerations coded as trauma – 00039 (superficial scratches) and 00197 (superficial laceration to the scalp). Both were coded blind and both were coded as suicidal. The 00197 case is a placebo case from the continuation phase – See Appendix Table.

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

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

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

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

The adverse event sheet for 039 shows that the superficial scratches happened over 10 days and involved multiple events and was recorded as continuous. This is not consistent with trauma.

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

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

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

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

Case 089

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

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

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

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

All that is coded is euphoria and insomnia. Plus, Euphoria is listed in Appendix D Page 130 as starting on April 4th and that this was severe and this led to the drug being stopped. The

Euphoria is classed as Serious because it led to hospitalization. The Suicidality has evaporated.

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

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

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

Case 106

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

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

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

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

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

Taper Patients

Two other patients are of interest, 058 and 250, where the event happened during Taper according to us or Continuation according to GSK. This is a new area where there can be legitimate differences of opinion.

Case 058

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

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

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

On this basis we have put the case into taper.

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

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

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

There are other notable things about 058; most of pages where the adverse events section should be are missing – but fortunately the page with the intentional overdose is present.

Case 250

This case has suicide attempts in acute and what GSK call continuation phase. The company recognises both events and code both as Emotional Lability.

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

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

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

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

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

Case 015.

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

GSK have another event in the Continuation Phase – suicidal ideation. We agree.

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

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

The patient later drops out of the study.

When patients drop out of a study for serious adverse events, companies are obliged to write a narrative that often sheds more light on what has been happening. There are 17 patients in Study 329 on whom SKB write such narratives – 11 Paxil, 5 Imipramine and 1 Placebo patient in the acute phase and more in the continuation phase. Case 015 is not among them.

There are other cases in the acute and continuation phases with serious events but who don't drop out where a company is not obliged to write narratives but often does. Case 015 has events that many would call serious but these are coded as mild – no narratives were written.

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

Possible Events

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

We also note an extra imipramine patient (00279) and two extra placebo patients (00129 and 00197) that may be suicide cases. These are laid out in Appendix 3A.

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