March 8, 2006

GlaxoSmithKline

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Thomas P. Laughren, M.D., Director
Division of Psychiatry Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 20-031; PAXIL® (paroxetine hydrochloride) Tablets
NDA 20-936; PAXIL CR™ (paroxetine hydrochloride) Controlled-Release Tablets for Treatment of Depression
NDA 20-982; PAXIL CR™ (paroxetine hydrochloride) Controlled-Release Tablets for Treatment of Panic Disorder
NDA 20-885; PAXIL® (paroxetine hydrochloride) Capsules
NDA 20-710; PAXIL® (paroxetine hydrochloride) Oral Suspension
General Correspondence: Briefing Document, Clinical, Meeting Request, Statistical Results from Suicidality Analysis of Adult MDD Paroxetine Clinical Studies

Dear Dr. Laughren:

Reference is made to our approved New Drug Application for Paxil® (paroxetine hydrochloride) Tablets, NDA 20-031. Reference is also made to the Agency's letter dated December 24, 2004, requesting that GlaxoSmithKline (GSK) provide specified patient-level data from all acute, double-blind, randomized placebo-controlled studies in adult Major Depressive Disorder (MDD) patients treated with paroxetine to support a suicidality analysis of antidepressants in adults. Further reference is made to GSK's subsequent submissions of datasets for MDD trials on September 16, 2005, for non-MDD trials on December 23, 2005 as well as amended datasets for MDD trials on December 23, 2005. In the amended submission of December 23, 2005, we informed the Agency about our plans to perform analyses on the paroxetine adult suicidality datasets and included a copy of the statistical analysis plan for the Agency's information and requested Agency comments.

GSK has recently completed the first portion of a comprehensive meta-analysis to evaluate the risk of suicidality in adult patients treated with paroxetine in placebo-controlled clinical trials. In this submission, we are providing the results of the first portion of this meta-analysis, which is of trials of patients with MDD. The data are being

Defendant's Exhibit
DX 101

PAR004372122

submitted to NDA 20-031 and incorporated by reference into the other referenced NDAs for paroxetine.

SUMMARY OF RESULTS OF GSK ADULT MDD SUICIDALITY ANALYSIS AND INTERPRETATION

The results of this analysis and the GSK interpretation of the data are summarized as follows:

- On the primary endpoint of definitive suicidal behavior or ideation, there was no statistically significant difference between adults with MDD treated with paroxetine compared to placebo (31/3455 (0.90%) vs. 11/1978 (0.56%); odds ratio = 1.3 (95% CI 0.7, 2.8); p=0.493).
- The results provide evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo; however, as the absolute number and incidence of events are very small (11/3455 (0.32%) for paroxetine, vs. 1/1978 (0.05%) for placebo; odds ratio = 6.7 (95% CI 1.1, 149.4); p=0.058), these data should be interpreted with caution.
- The analysis provided substantial evidence for efficacy in this patient population.
- There were proportionally slightly more events (suicidal behavior with or without ideation) in young adults between 18-24 years of age with MDD treated with paroxetine (compared to placebo) than in older adults, and less robust evidence for efficacy; however these data are not conclusive due to the relatively small sample size of the 18-24 age group and the small number of events. These trends are consistent with findings from previous analyses in pediatrics and adolescents, and while it appears that the risk seen in pediatrics seems to extend beyond age 18, the extent to which this occurs is less clear.
- The overall risk:benefit of paroxetine remains positive.

CONCLUSIONS AND PROPOSED NEXT STEPS

Based on these most recent findings in the adult patient dataset, GSK concludes that some statements in the approved prescribing information will need to be amended to reflect the results from this analysis following completion of the entire analysis. The remaining portion of the meta-analysis, which is of the non-MDD trials, represents a larger patient population than the MDD data set. Target completion of this portion of the analysis is end-March. Results from the non-MDD analysis will be submitted to FDA upon completion.

GSK believes that labeling revisions and direct communication with Health Care Professionals (HCPs) should be undertaken only after completion of the entire analysis, but is willing to discuss earlier labeling changes or communications with HCPs if so desired by the Agency. GSK requests that a teleconference be scheduled now for the

second week in April to allow for discussion of the entire set of results and to agree appropriate actions including a labeling revision.

CONTENT OF SUBMISSION

Appended to this submission is a briefing document that provides a historical summary of key adult suicidality analyses previously conducted with paroxetine, an overview and comparison of methods and a clinical summary of the most recent GSK analysis of suicidality in adult MDD clinical studies. Also included as appendices to the briefing document are: Reporting and Analysis Plan, Data Tables for MDD Analysis, Figures for MDD Analysis, and Narratives for Patients with Definitive Suicidal Behavior Events.

MEETING REQUEST

We respectfully request a teleconference with the Agency be arranged ideally for the week of April 10'th to discuss the findings, the label change and the communication strategy. Results of the GSK adult non-MDD analyses will be supplied upon availability and in advance of the requested meeting with FDA. We suggest that this meeting can be handled by teleconference.

This submission is provided in electronic format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999.* Please see the attached Guide to FDA Reviewers for complete details on the electronic submission.

An additional five desk copies of this submission are being provided to Dr. Renmeet Gujral of the Division to facilitate review.

If the Agency would like to discuss the attached data analysis on MDD trials we are available for a teleconference at any time. Should you have any questions regarding this submission or require additional information please do not hesitate to contact me by phone at (919) 483-5119 or via secure email at James.E.Murray@gsk.com.

Sincerely,

James E. Murray
Vice President
Regulatory Affairs, Psychiatry and Neurology

CC: Renmeet Gujral , Division of Psychiatry Products, (Five desk copies)

BRIEFING DOCUMENT

Paroxetine Adult Suicidality Analysis: Major Depressive Disorder

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been effectively used in the treatment of depressive illness and anxiety disorders since the late 1980s. A possible link between the use of SSRIs and suicidal behavior was first described as a case series in the published literature in 1990 by Teicher et al, who reported that fluoxetine, the first SSRI introduced to the U.S. market, can induce or exacerbate suicidal tendencies. However, subsequent meta-analyses conducted shortly thereafter did not provide evidence supporting this claim, nor did an expert panel convened by FDA in 1991 find any compelling evidence for such an association.

This issue, i.e., whether there is an increased risk of suicidality (suicidal thinking or behavior) associated with SSRI treatment, has been revisited periodically by GlaxoSmithKline (GSK, or legacy company SmithKlineBeecham) with regard to its SSRI paroxetine (Paxil®, Seroxat®, Aropax®, Deroxat®). As was the case for the earlier analyses of fluoxetine and suicidality in adults, these prior investigations of paroxetine's potential association with treatment-emergent suicidality did not produce evidence suggestive of an association in adults. For example, an analysis conducted by GSK in 2002 examined the incidence of attempted suicide in all placebo-controlled paroxetine trials in patients with depression. The incidence of suicide attempts in the paroxetine group was 2.0% (64/3192) compared to 1.9% for placebo (38/2047). This difference was not statistically significant (p=0.76).

While lack of appropriate treatment is clearly the largest contributor to suicide risk in depressed patients, concerns about SSRI treatment and a possible link to suicidality in some patients have persisted since Teicher first raised this issue. These concerns were heightened further with the recent finding that treatment with SSRIs, including paroxetine, was associated with an increased risk of suicidality relative to placebo in pediatric patients enrolled in controlled clinical trials. Partly as a result of this finding in pediatric patients, a number of regulatory agencies (including the FDA, and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK) have revisited this issue in adults, particularly in young adults. In May of 2003, an Expert Working Group (EWG) of the Committee on Safety of Medicines was convened in the UK to investigate ongoing public safety concerns with SSRIs, in particular around suicidal behavior and withdrawal reactions/dependence. As part of this review, SSRI manufacturers (including GSK) provided clinical trial data to the EWG in order for this group to conduct its own assessment. The EWG also evaluated available epidemiologic data from the UK General Practice Research Database (GPRD), as well as data from other sources including published literature and spontaneous reports from healthcare professionals.

Upon completion of its analyses, with respect to SSRIs as a class the EWG concluded:

- from the available adult clinical trial data, a modest increase in the risk of suicidal thoughts and self-harm in those taking SSRIs compared with placebo could not be ruled out;
- there was no clear evidence of an increased risk of self-harm and suicidal thoughts in young adults; however, given that individuals mature at different rates and that young adults are at a higher background risk of suicidal behavior than older adults, as a precautionary measure young adults treated with SSRIs should be closely monitored;
- there was insufficient evidence from clinical trial data to conclude any marked difference between members of the SSRI class, or between SSRIs and active comparators, with respect to their influence on suicidal behavior; and,
- evidence from non-experimental GPRD studies indicated that in adults there was no increased risk of suicidal behaviour with SSRIs compared with TCAs.

As part of its review, the EWG also conducted a meta-analysis of the adult clinical trials of paroxetine and concluded:

- there was no strong evidence of an increased risk of suicidal events for adult patients with depression exposed to paroxetine compared to placebo, although the point estimates and confidence intervals were consistent with a possible increase in risk.

During the same time period, the MHRA referred paroxetine to European (EU) regulatory authorities for an EU-level review (known as the "Article 31 Referral"). As part of this process, GSK was asked to provide specific analyses of its clinical trial data to evaluate the risk of suicide, suicidal thoughts and self-harm, with particular attention to potential risk factors including age and gender. GSK submitted the 1st set of analyses to the initial Article 31 questions in September 2003 and submitted the 2nd set of analyses in January 2004. Overall, i.e., in all indications studied in placebo-controlled trials in adults, the incidence of possible suicide-related events (i.e., thoughts and behaviors) was similar in the paroxetine and placebo groups (0.8% vs. 0.9%, respectively; OR 0.8 [95% CI 0.6, 1.2]). The findings were similar in the studies conducted specifically in patients with depression (1.7 vs. 1.9%, respectively; OR 0.9 [95% CI 0.6, 1.3]). In the 18-29 years age group, for all indications, the incidence of possibly suicide-related events was greater in the paroxetine group (1.8%) than in the placebo group (1.4%), although this difference was not statistically significant (OR 1.3 [95% CI 0.7, 2.3; p=0.46]).

In April 2004, the EU scientific committee (CHMP) reached their conclusions with respect to paroxetine use in adults, which are summarized as follows:

- The benefit/risk balance for paroxetine remains favorable across all adult indications; and
- There is a possibility of an increased risk of suicidal behavior associated with paroxetine in young adults (18-29 years), although the increased risk was not statistically significant. In the older age groups no such increase was observed. Results from observational studies indicate no increased risk of suicidality in patients who were prescribed paroxetine and likewise, post-marketing reports indicate low rates of suicidal related behaviours. Clinical trials show similar low rates in placebo and paroxetine treated depressed

patients. Rates in patients with other disorders for which paroxetine is indicated are similarly low.

In December 2004 the CHMP reaffirmed these conclusions following consideration of three new epidemiology studies which utilized the UK General Practice Research Database. That same month (Dec 2004) FDA initiated steps to enable its own examination of the relationship between antidepressant use and suicidality in adult patients by requesting all antidepressant manufacturers to provide specified patient-level data from all acute (i.e., ≤ 17 week), double-blind, randomized, placebo-controlled adult studies in major depressive disorder. Potential cases of suicidality were identified via adverse event text string searches, review of serious adverse event (SAE) narratives (including all deaths), and review of the comment fields from the Case Report Forms (CRFs) for all relevant studies. As part of this process, GSK contracted with Columbia University to have independent experts selected by Columbia blindly review each potential case of suicidality and classify the events into suicidal or non-suicidal categories using the same approach used in the pediatric suicidality review conducted by FDA.[†] In May of 2005, FDA expanded its request to also include all acute non-MDD studies (e.g., studies in anxiety disorders such as OCD, Panic Disorder, Social Anxiety Disorder, etc.). At this time GSK has fully complied with these requests from FDA, i.e., GSK has essentially submitted all required data to FDA (the only exception being the data from one small study conducted in the UK for which the data were not readily available and are currently being retrieved [study #298]).

Recently, GSK decided to conduct its own analyses of the datasets provided to FDA. To date, GSK has completed its analysis of the MDD specific dataset, which is the subject of this document. Before conducting this analysis, GSK consulted with external experts to obtain their advice and thoughts as to how to undertake this analysis. In addition, GSK's final statistical analysis plan was submitted on an informational basis to FDA in late December 2005, and to the Dutch MEB (Reference Member State in the EU) in early February 2006.

2. Brief Overview of Methods

The analysis plan developed by GSK for the present analysis of the adult suicidality data (see Appendix I) is based, in part, on methods used previously by FDA during their analysis of pediatric suicidality data. The analysis plan also reflects advice received by external consultants with expertise in suicidality. Because GSK previously conducted a similar analysis of suicidality data for paroxetine as part of the Article 31 Referral process in 2003, it is important to consider key methodologic differences between the previous and current analysis (see Table 1, below).

[†] It should be noted that events were coded by Columbia University in accordance with numerical codes specified by FDA for this review of adult data. These codes differ slightly from those used for the previous FDA review of paediatric studies, owing to the fact that there were no completed suicides in any of the SSRI pediatric trials.

Table 1. Key Differences Between Previous Article 31 Analysis and Current Analysis

	Article 31 Analysis	Current Analysis
Events adjudicated by external experts (Columbia University)	No	Yes
Search algorithm for AEs	Algorithm-based search of AE fields	Algorithm-based search of AE fields plus review of CRF comment fields and SAE narratives
Statistical methods	Pooled analysis (crude odds ratios)	Exact method, adjusted by trial (primary method)
Definition of young adults	18-29 yrs	18-24 yrs
Included trials of any duration (ie, included long-term trials where available)	Yes	Yes
Depression analysis – trial groupings	Depressive illnesses together	By indication (eg, MDD, Intermittent Brief Depression, Dysthymia, etc.)
Depression analysis – number of trials	26 depression trials (Dec 1982 through Aug 2001)	19 MDD trials (Dec 1982 to date; ie, through May 2005)

2.1 Comparison of statistical methods

The current analysis of suicidality data has been conducted using two statistical methods for estimating the common odds ratio and its confidence interval, as well as testing the null hypothesis that the common odds ratio is equal to 1. The primary analysis used an exact approach (Mehta et al, 1985) implemented in the statistical software StatXact®. The second approach was to use the Mantel-Haenszel (MH) method, with 0.5 continuity correction (Sutton et al, 2002) applied at the level of the trial. GSK used this additional approach because it was the same one used by FDA in its analysis of the pediatric datasets.

In some cases the results from the two methods diverge substantially. Notably, the odds ratios for Definitive Suicidal Behaviour are 6.7 (by the exact method) and 1.6 (by the MH method). The lower odds ratio estimated by the MH method is explained by the addition (under the continuity correction) of 4.5 events to each of the treatment groups which, proportionately, yields a greater increase in the placebo group than in the paroxetine group.

For the endpoint of Rating Scale Emergent Behaviour there is one event on paroxetine (0.03%) and zero events on placebo (0%), but the MH method estimates the odds ratio to be 0.4 (indicating *lower* risk with paroxetine than placebo). This is a result of the imbalanced randomization in study 009, in which the one event occurred.

With this dataset, GSK believes the MH method with continuity correction substantially underestimates the odds ratio for Definitive Suicidal Behaviour compared with the exact method, because of the small and disproportionate number of events observed between the two treatment groups and because of the imbalanced randomization in some of the trials. The exact method is not affected by either of these problems, and is designed particularly for sparse datasets such as this. We believe the exact method is the most appropriate statistical method for the assessment of this dataset, and should be used in preference to the MH method with continuity correction.

3. Clinical Summary

GSK has recently completed its analysis of paroxetine placebo-controlled clinical trials in patients with Major Depressive Disorder (MDD); see Appendices II - IV. A brief summary of key findings follows:

- On the primary endpoint of **definitive suicidal behavior or ideation**, there was no statistically significant difference between adults with MDD treated with paroxetine compared to placebo (31/3455 (0.90%) vs. 11/1978 (0.56%); odds ratio = 1.3 (95% CI 0.7 , 2.8); p=0.493).

- The results provide evidence of increased **suicide attempts** in adults with MDD treated with paroxetine compared to placebo; however, as the absolute number and incidence of events are very small (11/3455 (0.32%) for paroxetine, vs. 1/1978 (0.05%) for placebo; odds ratio = 6.7 (95% CI 1.1, 149.4); p=0.058), these data should be interpreted with caution.

- The analysis provided substantial evidence for efficacy in this patient population.

- There were proportionally slightly more events (suicidal behavior with or without ideation) in **young adults** between 18-24 years of age with MDD treated with paroxetine (compared to placebo) than in older adults, and less robust evidence for efficacy; however these data are not conclusive due to the relatively small sample size of the 18-24 age group and the small number of events. These trends are consistent with findings from previous analyses in pediatrics and adolescents, and while it appears that the risk seen in pediatrics seems to extend beyond age 18, the extent to which this occurs is less clear.

- The overall risk:benefit of paroxetine in the treatment of adult patients with MDD remains positive.

The finding of evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo is new, and was not found in GSK's Article 31 analysis nor GSK's prior analyses of suicide attempts. In the Article 31 analysis of self-harm in patients with depressive illness, there were 45 events reported in 3421 patients treated with paroxetine (1.3%), and 33 events in 2117 patients treated with placebo (1.6%), for an odds ratio of 0.84 (95% CI 0.54, 1.32). In contrast, the current

analysis of definitive suicidal behavior[†] in patients with MDD revealed 11 events in 3455 patients treated with paroxetine (0.32%), and 1 event in 1978 patients treated with placebo (0.05%); odds ratio 6.7 (95% CI 1.1, 149.4). There are two likely explanations for the difference in results between the prior Article 31 analysis and the current analysis: the datasets included in the analyses, and the methodology used for identifying the relevant events. With respect to the datasets, the current analysis was restricted to a single indication, MDD, consistent with FDA's approach. In terms of the methodology used to identify events, the cases comprising the current analysis were individually reviewed by external experts who were blinded to treatment. As a consequence of the above two factors, 36 events in the paroxetine group and 33 events from the placebo group that were included in the Article 31 analysis of self-harm were not included in the present analysis. The majority of these events (33 paroxetine and 33 placebo) were from two trials investigating intermittent brief depression, and involved patients with a previous history of suicidality. The remaining 3 paroxetine cases were not classified as suicidal behavior by the expert raters. Additionally, there were an additional 2 events identified in the paroxetine group and 1 event in the placebo group that were not identified by the methods used in the Article 31 analysis.

4. Implications for Labeling

Based on these most recent findings in the adult patient dataset GSK concludes that some statements in the approved prescribing information will need to be amended to reflect the results from this analysis following completion of the entire analysis. The remaining portion of the meta-analysis, which is of the non-MDD trials, represents a larger patient population than the MDD data set. Target completion of this portion of the analysis is end-March. Results from the non-MDD analysis will be submitted to FDA upon completion.

GSK believes that labeling revisions and/or direct communication with Health Care Professionals (HCPs) should be undertaken only after completion of the entire analysis, but is willing to discuss earlier labeling changes or communications with HCPs if so desired by the Agency.

References:

Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990, 147(2):207-10.

Mehta CR, Patel NR, and Gray R. Computing an exact confidence interval for the common odds ratio in several 2x2 contingency tables. *Journal of the American Statistical Association* 1985, Vol 80, no 392.

[†] "Definitive suicidal behavior" included events classified as completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior. In the results of the current analysis, there were no completed suicides nor events classified as preparatory acts (ie, all events were classified as suicide attempt).

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, and Song F. Methods for meta-analysis in medical research. *John Wiley & Sons*, NY 2002 page 69.

APPENDIX I: Reporting and Analysis Plan

APPENDIX II: Data Tables: MDD Analysis

APPENDIX III: Figures: MDD Analysis

APPENDIX IV: Narratives: Definitive Suicidal Behavior Events

Paroxetine Adult Suicidality Data Reporting and Analysis Plan

John T Davies, MSc
Biomedical Data Sciences
GlaxoSmithKline

Final
14th December 2005

1. Introduction

This document describes the statistical analysis and reporting to be undertaken for paroxetine adult suicidality data. The data include trials submitted, or planned to be submitted, as part of the adult suicidality review for the Food and Drug Administration (FDA) in September and December 2005. The data also include trials which, because of their duration, fall outside the scope of the FDA review.

Adult, randomized, parallel group, placebo controlled trials in which the total number of patients treated with paroxetine and placebo was at least 30, comprised the full set of trials included in the analysis (Appendix 1). The subset of trials which were less than 17 weeks in duration formed the set of trials submitted to the FDA.

2. Objectives

2.1 Primary objective

The primary objective is to compare the incidence of definitive suicidal behaviour and ideation on paroxetine and placebo. The null hypothesis is that there is no difference between the two treatment groups. The alternative hypothesis is that a difference between the two treatment groups does exist.

2.2 Secondary objectives

The secondary objectives are:

- To compare the incidence of other measures of suicidal behaviour and ideation on paroxetine and placebo.
- To compare the incidence of suicidal behaviour and ideation on paroxetine and placebo in disease and demographic subgroups.
- To compare the efficacy of paroxetine and placebo.

3. Indications

3.1 Datasets to be analysed

The following datasets will be analysed, according to the indication being investigated:

1. All Indications
2. All Depression (i.e. 3-7 below)
3. Major Depressive Disorder (MDD)
4. Intermittent Brief Depression (IBD)
5. Dysthymia*
6. Bipolar Disorder*
7. Depression with Chronic Back Pain*
8. All Non-Depression (i.e. 9-16 below)
9. Panic Disorder
10. Obsessive Compulsive Disorder (OCD)
11. Social Anxiety Disorder (SAD)
12. Generalized Anxiety Disorder (GAD)

13. Post-traumatic Stress Disorder (PTSD)
14. Pre-menstrual Dysphoric Disorder (PMDD)
15. Detoxification in Alcoholics (EtOH)*
16. Fibromyalgia*

*indicates that the indication contains only one trial

The trials included in each indication are specified in Appendix 1.

3.2 Long term extension trials

Where data are included from long term extension trials, in which patients continue on medication to which they were randomized in an acute trial, the data from the long term phase will be displayed within the results of the original trial in which patients were randomized. The trials affected are specified in Appendix 1.

4. Definitions

4.1 Columbia University Suicidality Classifications of Adverse Events

As part of the FDA's adult suicidality data review, potential cases of suicidality were identified from searches of adverse event terms, a review of all deaths and serious adverse events (SAEs) and from a review of comments fields on Case Report Forms (CRFs). Cases were only included in the list of potential events if they occurred during the double-blind phase of treatment or within one day following the cessation of randomized treatment.

For all potential events a detailed narrative was prepared by Drug Safety Alliance, Inc (DSA) and these narratives were forwarded to Dr Kelly Posner at the Columbia University Medical Centre, who randomly assigned them to a group of independent suicide experts for review and classification. Each narrative was reviewed by three expert raters and assigned a code according to the following classifications specified by the FDA:

1. Completed suicide
2. Suicide attempt
3. Preparatory acts toward imminent suicidal behaviour
4. Suicidal ideation
5. Self-injurious behaviour, intent unknown
6. Not enough information (fatal)
7. Self-injurious behaviour, no suicidal intent
8. Other: accident; psychiatric, medical
9. Not enough information (non-fatal).

Categories 1-4 above will be referred to collectively as *Definitive Suicidal Behaviour and Ideation*. Categories 1-3 above will be referred to collectively as *Definitive Suicidal Behaviour*.

4.2 Rating Scale Emergent Ideation and Behaviour (Depression only)

Data from the suicidality questions on the Hamilton Depression Rating Scale (HAMD, item 3) and Montgomery Asberg Depression Rating Scale (MADRS, item 10) will also be used to assess the risk of suicidality in trials of depression. In other indications the HAMD and MADRS were generally administered only at baseline, and for this reason they will not be used to assess emergent suicidality in those indications.

Item 3 of the HAMD measures suicidal thoughts and behaviour on the following scale:

0 = Absent
1 = Feels life is not worth living
2 = Wishes he were dead or any thoughts of possible death to self
3 = Suicidal ideas or gesture
4 = Attempts at suicide.

Item 10 of the MADRS measures suicidal thoughts and behaviour on the following scale:

0 = Enjoys life or takes it as it comes
1
2 = Weary of life. Only fleeting suicidal thoughts
3
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 = Explicit plans for suicide when there is an opportunity. Active preparation for suicide.

Emergent suicidal behaviour and ideation on HAMD (item 3) or MADRS (item 10) will be defined as any case where a patient's pre-treatment baseline score was 0 or 1 and where this score increased to a score of ≥ 3 while on double-blind treatment (including one day after the cessation of the treatment).

Emergent suicidal behaviour on HAMD (item 3) or MADRS (item 10) will be defined as any case where a patient's pre-treatment baseline score was 0 or 1 and the patient had a post-baseline score of 4 (HAMD) or 6 (MADRS) while on double-blind treatment (including one day after the cessation of the treatment).

In any trial where both the HAMD and MADRS were used, data will be assessed independently on each scale, and a patient will be considered to have satisfied the definition of emergent ideation or behaviour if the criteria have been met for one or both of the scales.

4.3 Intent to Treat Population

All analyses will be based on the Intent-to-Treat population, which is defined as all patients who were randomized and received at least one dose of trial medication. This is the same definition that was used in populating datasets for submission to the FDA.

Additionally, analyses of change from baseline require that at least one post-baseline measurement was taken for the parameter of interest.

5. Assessment of Risk

5.1 Endpoints

The following endpoints will be analysed:

1. Definitive Suicidal Behaviour and Ideation
2. Rating Scale Emergent Suicidal Behaviour and Ideation
3. Composite Suicidal Behaviour and Ideation (i.e. 1 or 2 above)
4. Definitive Suicidal Behaviour
5. Rating Scale Emergent Suicidal Behaviour
6. Composite Suicidal Behaviour (i.e. 4 or 5 above)

Definitive Suicidal Behaviour and Ideation (endpoint 1) is the primary endpoint. Endpoints 2, 3, 5, and 6 pertain only to the Depression indications.

Endpoints 1 and 4 above are obtainable directly from datasets supplied to FDA as part of the adult suicidality submissions (short term trials less than 17 weeks duration only). Endpoints 2, 3, 5, and 6 require additional data not included as part of the FDA datasets.

5.2 Statistical methods

For each endpoint the incidence of events will be compared between treatment groups (paroxetine and placebo). The analysis will be adjusted for trial using the exact method of StatXact® (PROC STRATIFY, StatXact for SAS®). Together with the incidence of the event in each treatment group, an estimate of the common odds ratio will be presented, together with 95% "mid-p" confidence interval (CI). For the overall estimates of treatment effect, but not for each individual trial, a p-value will be presented. For the adjusted analysis the exact p-value will be calculated by the method of summing all probabilities less than or equal to the observed.

To assess the robustness of the method of adjusting for trial, an overall estimate of the odds ratio and its 95% CI will also be obtained by adjusting for trial using the Mantel Haenszel method (with 0.5 continuity correction).

The number needed to harm (NNH) will also be presented. The NNH is equal to the reciprocal of the probability difference and is interpreted as the number of patients who need to be treated to incur one additional adverse outcome over a fixed time period. Larger values of NNH correspond to a lower risk of an adverse outcome on paroxetine relative to placebo. If the value of the NNH is negative this indicates that

the adverse outcome is less likely on paroxetine than on placebo and it is referred to as the number needed to treat (NNT) i.e. the number of patients who need to be treated to prevent one additional adverse outcome across a fixed time period. For adjusted analyses the NNH and NNT will be calculated using a conversion from the adjusted odds ratio (Appendix 2).

The results will be presented in a table similar to Table 1.

Table 1: Incidence of Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group, and Trial
Indication = Major Depressive Disorder

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT/NNH
Overall (exact, adjusted)	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)	0.xxx	z.z
Overall (Mantel Haenszel)	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)	0.xxx	z.z
Trial 1	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Trial 2	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Trial 3	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z

The results will also be presented in a Forest plot, displaying the results for each trial and for the overall results. An additional Forest plot may also be produced in which small trials are combined into a single group; this is dependent on the results and the visual clarity of the initial Forest plot.

Heterogeneity of results across trials will be assessed using Zelen's exact test, or with the Breslow-Day test if Zelen's test cannot be computed.

For datasets 1, 2, and 8 (i.e. All Indications Combined, All Depression Combined, and All Non-Depression Combined) the analysis will be adjusted for trial, but the tables and figures will be presented by indication, not by trial.

5.3 Risk factors

In addition to the overall analysis, results will be presented according to the following risk factors:

1. Baseline suicidal ideation, defined as the presence of one or more of:
   HAMD item 3 score ≥ 3
   MADRS item 10 score ≥ 3
   Symptom Checklist 90 (SCL-90) Q15 score ≥ 1
   Beck Depression Inventory (BDI) Q7 score ≥ 2
   BDI Q9 score ≥ 1
   One or more previous suicide attempts (trials 057 and 106).
2. Age (continuous covariate)
3. Age group (18-24, 25-64, ≥ 65)
4. Gender

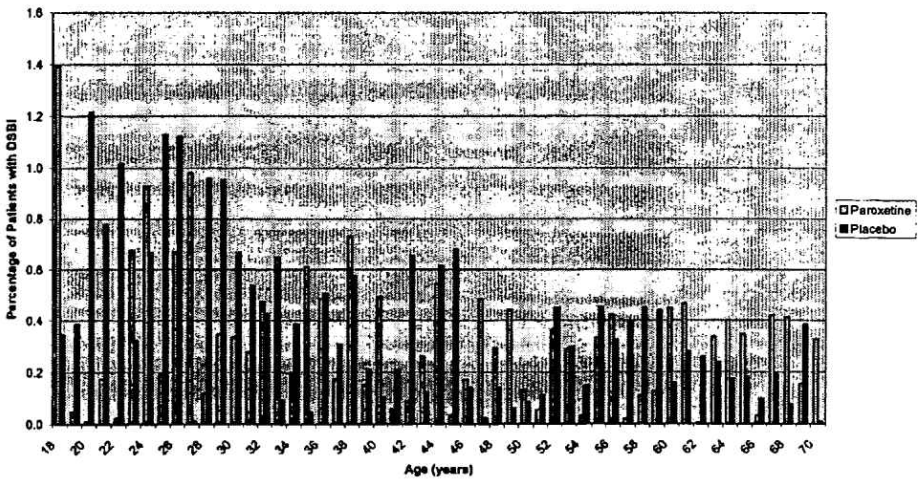
For categorical covariates (i.e. 1, 3 and 4 above) the data will be analysed and presented in the same way as the exact analysis described in section 5.2. A table similar to Table 2 will be produced to present the results according to each risk factor. A Forest plot will be presented showing the results for each risk factor.

Table 2: Incidence of Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group, and Risk Factors Indication = Major Depressive Disorder					
Trial	**Paroxetine**	**Placebo**	**OR (95% CI)**	**P-value**	**NNT/NNH**
Overall (exact, adjusted)	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)	0.xxx	z.z
Baseline suicidal ideation					
Absent	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Present	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Age Group					
18-24	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
25-64	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
≥65	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Gender					
Male	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z
Female	x / xxx (x.xx%)	y / yyy (y.yy%)	z.z (z.z, z.z)		z.z

For the analysis of age as a continuous covariate a generalized linear model will be fitted modelling the log-odds of an event as a linear function of age. In the event that the linear model does not provide a good fit, other models (e.g. quadratic) will be assessed. The results will be presented graphically showing the predicted odds ratio as a function of age. The incidence of an event for each individual age will be presented by treatment group in a histogram, similar to that in Figure 1 (Note: the data in Figure 1 are illustrative only, they are not data collected from paroxetine clinical trials). The number and percentage of patients with Definitive Suicidal Behaviour and Ideation will be tabulated by age.

In the initial stage, risk factor and subgroup analyses will be conducted only for the primary endpoint of Definitive Suicidal Behaviour and Ideation. Risk factor and subgroup analyses may be conducted subsequently for other endpoints if there are notable differences between the conclusions derived from the different endpoints.

Figure 1: Percentage of Patients with Definitive Suicidal Behaviour and Ideation by Treatment Group and Age



Note: in the figure that is produced the data will be clustered for each treatment group, not for each age group in the way shown in this illustration.

6. Assessment of Efficacy

6.1 Statistical methods

Continuous efficacy measures (i.e. "change from baseline") will be analysed using a general linear model, which will contain terms for baseline score, trial, and treatment group. If the model fails to converge then the smallest trials will be combined with each other until convergence is achieved. Categorical efficacy measures (i.e. "responder" analyses) will be analysed using the exact method described in section 5.2.

For efficacy measures the last time point eligible for inclusion as an endpoint measure will be the first day following the cessation of treatment.

For responder analyses the number needed to treat (NNT) will also be presented, and will be calculated using a conversion from the adjusted odds ratio (Appendix 2). The NNT is interpreted as the number of patients who need to be treated to achieve one additional positive outcome across a fixed time period. Smaller values of NNT correspond to a larger benefit of paroxetine relative to placebo. If the value of the NNT is negative this indicates that a positive outcome is more likely on placebo than on paroxetine and it is referred to as the number needed to harm (NNH) i.e. the number of patients who need to be treated to produce one additional adverse outcome across a fixed time period.

Trials with both an acute phase and an extension phase (see section 2.2) will be considered as a single trial, with the baseline measurement defined according to the point of randomization into the trial. For Last Observation Carried Forward (LOCF) analyses, the endpoint will always be measured for the acute phase of the trial.

6.2 Efficacy measures

6.2.1 All Depression Combined

Efficacy will be assessed using the following measures:

1. Change from baseline on the HAMD total score to LOCF endpoint.
2. Change from baseline on the MADRS total score to LOCF endpoint.
3. Change from baseline on the HAMD item 3 to LOCF endpoint.
4. Change from baseline on the MADRS item 10 to LOCF endpoint.
5. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on HAMD item 3 or MADRS item 10, reducing to a score of 0 or 1 at endpoint.
6. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on HAMD total score (or MADRS total score for trials where HAMD not recorded).

6.2.2 Major Depressive Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the HAMD total score to LOCF endpoint.
2. Change from baseline on the MADRS total score to LOCF endpoint.
3. Change from baseline on the HAMD item 3 to LOCF endpoint.
4. Change from baseline on the MADRS item 10 to LOCF endpoint.
5. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on HAMD item 3 or MADRS item 10, reducing to a score of 0 or 1 at endpoint.
6. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on HAMD total score (or MADRS total score for trials where HAMD not recorded).

6.2.3 Intermittent Brief Depression

Efficacy will be assessed using the following measures:

1. Change from baseline on the MADRS total score to LOCF endpoint.
2. Change from baseline on the MADRS item 10 to LOCF endpoint.
3. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on MADRS item 10, reducing to a score of 0 or 1 at endpoint.
4. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on MADRS total score.

6.2.4 Dysthymia

Efficacy will be assessed using the following measures:

1. Change from baseline on the HAMD total score to LOCF endpoint.
2. Change from baseline on the HAMD item 3 to LOCF endpoint.
3. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on HAMD item 3, reducing to a score of 0 or 1 at endpoint.
4. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on HAMD total score.

6.2.5 Bipolar Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the HAMD total score to LOCF endpoint.
2. Change from baseline on the HAMD item 3 to LOCF endpoint.
3. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on HAMD item 3, reducing to a score of 0 or 1 at endpoint.
4. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on HAMD total score.

6.2.6 Depression with Chronic Back Pain

Efficacy will be assessed using the following measures:

1. Change from baseline on the MADRS total score to LOCF endpoint.
2. Change from baseline on the MADRS item 10 to LOCF endpoint.
3. Declining suicidal ideation, i.e. a baseline score of ≥ 3 on MADRS item 10, reducing to a score of 0 or 1 at endpoint.
4. Responder analysis, i.e. reduction of 50% or more between baseline and endpoint on MADRS total score.

6.2.7 All Non-Depression Combined

Efficacy will be assessed using the following measure:

1. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.8 Panic Disorder

Efficacy will be assessed using the following measure:

1. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

The number of panic attacks is an endpoint common to all panic disorder trials, and being submitted as part of the FDA submission, but the time period in which the number of attacks is measured varies between trials. Consequently, this measure is not being used in this pooled analysis of data from panic disorder trials.

6.2.9 Obsessive Compulsive Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.10 Social Anxiety Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the Liebowitz Social Anxiety Scale (LSAS) total score to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.11 Generalized Anxiety Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the Hamilton Anxiety Scale (HAMA) total score to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.12 Post-traumatic Stress Disorder

Efficacy will be assessed using the following measures:

1. Change from baseline on the Clinician-Administered PTSD Scale (CAPS-2) total score to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.13 Pre-menstrual dysphoric disorder

Efficacy will be assessed using the following measures:

1. Change from baseline in Mean Luteal Phase Visual Analogue Scale (VAS) Mood Score to LOCF endpoint (trials 677, 688, 689 only).
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.14 Detoxification in Alcoholics

Efficacy will be assessed using the following measures:

1. Change from baseline on Total Daily Alcohol Consumption to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

6.2.15 Fibromyalgia

Efficacy will be assessed using the following measures:

1. Change from baseline on the VAS to LOCF endpoint.
2. Responder analysis, i.e. Clinical Global Impression (CGI) Improvement Score of 1 (Very Much Improved) or 2 (Much Improved) at LOCF endpoint.

7. Comparison of Adverse Event Reporting by Time

To assess whether there has been a change over time in adverse event reporting in general, or specifically for adverse events relating to suicidality, the incidence of Definitive Suicidal Behaviour and Ideation, and the incidence of any adverse event, will be plotted by trial and treatment group in a histogram. Trials will be ordered by start date. A corresponding summary table will also be produced.

8. List of Tables and Figures

The tables and figures to be produced are listed below.

Number	Title	Comments
Table 1.01	Demographic Characteristics by Indication, Treatment Group and Trial	
Table 2.01	Number and Percent of Patients with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial	Ordered by Start Date
Table 2.02	Number and Percent of Patients with Rating Scale Emergent Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial	Ordered by Start Date. Depression indications only
Table 2.03	Number and Percent of Patients with Composite Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial	Ordered by Start Date. Depression indications only
Table 2.04	Number and Percent of Patients with Definitive Suicidal Behaviour by Indication, Treatment Group and Trial	Ordered by Start Date
Table 2.05	Number and Percent of Patients with Rating Scale Emergent Suicidal Behaviour by Indication, Treatment Group and Trial	Ordered by Start Date. Depression indications only
Table 2.06	Number and Percent of Patients with Composite Suicidal Behaviour by Indication, Treatment Group and Trial	Ordered by Start Date. Depression indications only
Table 2.07	Number and Percent of Patients with Any Adverse Event by Indication, Treatment Group and Trial	Ordered by Start Date
Table 2.08	Number and Percent of Patients with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Risk Factors	
Table 3.01	Change from Baseline on HAMD Total Score to LOCF endpoint by Indication, Treatment Group and Risk Factors	Depression indications only
Table 3.02	Change from Baseline on MADRS Total Score to LOCF endpoint by Indication, Treatment Group and Risk Factors	Depression indications only
Table 3.03	Change from Baseline on HAMD Item 3 to LOCF endpoint by Indication, Treatment Group and Risk Factors	Depression indications only
Table 3.04	Change from Baseline on MADRS Item 10 to LOCF endpoint by Indication, Treatment Group and Risk Factors	Depression indications only
Table 3.05	Number and Percent of Patients with Declining Suicidal Ideation by Indication, Treatment Group and Risk Factors	Depression indications only

Table 3.06	Number and Percent of Patients with >= 50% Reduction in HAMD or MADRS Baseline Score by Indication, Treatment Group and Risk Factors	Depression indications only
Table 3.07	Number and Percent of CGI Responders (Very Much Improved or Much Improved) at LOCF endpoint by Indication, Treatment Group and Risk Factors	Non-Depression Indications only
Table 3.08	Change from Baseline on YBOCS Total Score to LOCF endpoint by Treatment Group and Risk Factors	OCD only
Table 3.09	Change from Baseline on LSAS Total Score to LOCF endpoint by Treatment Group and Risk Factors	SAD only
Table 3.10	Change from Baseline on HAMA Total Score to LOCF endpoint by Treatment Group and Risk Factors	GAD only
Table 3.11	Change from Baseline on CAPS-2 Total Score to LOCF endpoint by Treatment Group and Risk Factors	PTSD only
Table 3.12	Change from Baseline on Mean Luteal Phase VAS Mood Score to LOCF endpoint by Treatment Group and Risk Factors	PMDD only
Table 3.13	Change from Baseline on Total Daily Alcohol Consumption to LOCF endpoint by Treatment Group and Risk Factors	EtOH only
Table 3.14	Change from Baseline on VAS Score to LOCF endpoint by Treatment Group and Risk Factors	Fibromyalgia only
Figure 2.01	Definitive Suicidal Behaviour and Ideation by Indication and Trial	Forest plot
Figure 2.02	Rating Scale Emergent Suicidal Behaviour and Ideation by Indication and Trial	Forest plot. Depression indications only
Figure 2.03	Composite Suicidal Behaviour and Ideation by Indication and Trial	Forest plot. Depression indications only
Figure 2.04	Definitive Suicidal Behaviour by Indication and Trial	Forest plot
Figure 2.05	Rating Scale Emergent Suicidal Behaviour by Indication and Trial	Forest plot. Depression indications only
Figure 2.06	Composite Suicidal Behaviour by Indication and Trial	Forest plot. Depression indications only
Figure 2.07	Definitive Suicidal Behaviour and Ideation by Indication and Baseline Suicidal Ideation	Forest plot
Figure 2.08	Definitive Suicidal Behaviour and Ideation by Indication and Age	Model

Figure 2.09	Definitive Suicidal Behaviour and Ideation by Indication and Age Group	Forest plot
Figure 2.10	Definitive Suicidal Behaviour and Ideation by Indication and Gender	Forest plot
Figure 2.11	Percent of Patients with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial	Histogram
Figure 2.12	Percent of Patients with Any Adverse Event by Indication, Treatment Group and Trial	Histogram, Ordered by Start Date
Figure 2.13	Percent of Patients with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Age	Histogram

Appendix 1: List of trials

Trial	Indication	Trial	Indication
276 (MDUK09 Edwards)	MDD	118	OCD
279 (MDUK12 Trimble)	MDD	136	OCD
274 (MDUK06 Naylor)	MDD	241 (LTX of 136)	OCD
001	MDD	414	OCD
002	MDD	660	OCD
009	MDD	108	Panic
003	MDD	120	Panic
115	MDD	187	Panic
128	MDD	222 (LTX of 120)	Panic
251	MDD	223	Panic
448	MDD	228 (LTX of 187)	Panic
449	MDD	494	Panic
487	MDD	495	Panic
625	MDD	497	Panic
785	MDD	384	Panic
810	MDD	410	Panic
NKD20006*	MDD	400	PMDD
874	MDD	427 (LT)	PMDD
442	MDD	658	PMDD
057 (LT)	IBD	677	PMDD
106 (LT)	IBD	688	PMDD
327	Dysthymia	689	PMDD
352	Bipolar	711 (LTX of 677, 688, 689)	PMDD
298	Dep with back pain	627	PTSD
433	Fibromyalgia	648	PTSD
201	EtOH	651	PTSD
637	GAD	382	SAD
641	GAD	454	SAD
642	GAD	502	SAD
791	GAD	790	SAD
116	OCD	661	SAD

* paroxetine was the active comparator.

LTX = Long Term Extension, not included in FDA review

LT = Long Term, not included in FDA review

Appendix 2: Calculation of Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

NNT and NNH for Unadjusted Analyses

The NNT/NNH is calculated as the reciprocal of the probability difference for an event, i.e.

$NNT = 1/(Pt - Pc)$

where Pt is the probability of a beneficial outcome in the test group (paroxetine)
and Pc is the probability of a beneficial outcome in the control group (placebo).

If the NNT is negative then it is referred to as the NNH. If the outcome is a measure of harm (e.g. an adverse event) then the NNT and NNH are reversed.

NNT and NNH for Adjusted Analyses

Where an analysis is adjusted for trial or other covariates, the NNT/NNH can be calculated by converting the adjusted odds ratio:

$$NNT = \frac{Pc*(AOR - 1) + 1}{Pc*(AOR - 1)*(1 - Pc)}$$

where Pc is the probability of a beneficial outcome in the control group (placebo) and AOR is the adjusted odds ratio for a beneficial outcome (expressed as the odds of the outcome on paroxetine relative to placebo).

If the NNT is negative then it is referred to as the NNH. If the outcome is a measure of harm (e.g. an adverse event) then the NNT and NNH are reversed.

Paroxetine Adult Suicidality Analysis
Major Depressive Disorder, Short Term Trials
Table 1.01. Demographic Characteristics by Trial

			Age					Gender		Baseline Suicidal Ideation	
Trial	Treatment	N	Mean	Standard Deviation	Median	Minimum	Maximum	Males	Females	Present	Absent
Overall	PAROXETINE	3455	46.0	15.57	44.0	18	91	1424 (41.2%)	2031 (58.8%)	413 (12.0%)	3042 (88.0%)
	PLACEBO	1978	46.5	15.50	44.0	18	87	788 (39.8%)	1190 (60.2%)	240 (12.1%)	1736 (87.8%)
276	PAROXETINE	20	45.1	12.75	46.0	22	62	9 (45.0%)	11 (55.0%)	5 (25.0%)	15 (75.0%)
	PLACEBO	21	43.4	12.68	43.0	22	64	9 (42.9%)	12 (57.1%)	5 (23.8%)	16 (76.2%)
279	PAROXETINE	21	40.8	18.32	38.0	20	75	6 (28.6%)	15 (71.4%)	6 (28.6%)	15 (71.4%)
	PLACEBO	10	51.6	17.25	56.5	23	71	3 (30.0%)	7 (70.0%)	2 (20.0%)	8 (80.0%)
274	PAROXETINE	22	41.6	13.20	42.0	18	64	6 (27.3%)	16 (72.7%)	0 (0.0%)	22 (100.0%)
	PLACEBO	23	43.3	11.84	45.0	22	60	7 (30.4%)	16 (69.6%)	0 (0.0%)	23 (100.0%)
001	PAROXETINE	25	42.6	11.70	42.0	20	65	16 (64.0%)	9 (36.0%)	2 (8.0%)	23 (92.0%)
	PLACEBO	25	44.2	13.13	43.0	24	64	19 (76.0%)	6 (24.0%)	7 (28.0%)	18 (72.0%)
002	PAROXETINE	170	40.5	11.59	39.5	18	77	86 (50.6%)	84 (49.4%)	55 (32.4%)	115 (67.6%)
	PLACEBO	171	42.5	12.67	40.0	18	73	78 (45.6%)	93 (54.4%)	49 (28.7%)	122 (71.3%)
009	PAROXETINE	421	41.1	13.17	38.0	18	85	208 (49.4%)	213 (50.6%)	79 (18.8%)	342 (81.2%)
	PLACEBO	53	40.6	10.45	39.0	23	70	24 (45.3%)	29 (54.7%)	13 (24.5%)	40 (75.5%)
003	PAROXETINE	241	40.3	11.28	39.0	18	69	113 (46.9%)	128 (53.1%)	60 (24.9%)	181 (75.1%)
	PLACEBO	244	40.4	11.92	38.0	19	70	122 (50.0%)	122 (50.0%)	67 (27.5%)	177 (72.5%)
115	PAROXETINE	283	41.8	12.53	41.0	18	86	101 (35.7%)	182 (64.3%)	31 (11.0%)	252 (89.0%)
	PLACEBO	117	41.5	11.67	40.0	19	71	32 (27.4%)	85 (72.6%)	14 (12.0%)	103 (88.0%)
128	PAROXETINE	357	41.8	12.70	40.0	18	82	135 (37.8%)	222 (62.2%)	48 (13.4%)	309 (86.6%)
	PLACEBO	140	42.8	12.17	42.0	20	76	40 (28.6%)	100 (71.4%)	11 (7.9%)	129 (92.1%)
251	PAROXETINE	125	41.3	11.17	41.0	19	65	42 (33.6%)	83 (66.4%)	0 (0.0%)	125 (100.0%)
	PLACEBO	129	41.3	10.56	41.0	18	71	45 (34.9%)	84 (65.1%)	3 (2.3%)	126 (97.7%)
448	PAROXETINE	212	39.3	10.66	39.5	18	62	81 (38.2%)	131 (61.8%)	16 (7.5%)	196 (92.5%)
	PLACEBO	103	38.4	10.04	39.0	19	64	36 (35.0%)	67 (65.0%)	4 (3.9%)	99 (96.1%)
449	PAROXETINE	223	41.3	11.60	42.0	18	71	65 (29.1%)	158 (70.9%)	30 (13.5%)	193 (86.5%)
	PLACEBO	110	40.7	11.56	40.0	19	63	44 (40.0%)	66 (60.0%)	21 (19.1%)	89 (80.9%)
487	PAROXETINE	214	70.2	6.32	70.0	60	88	100 (46.7%)	114 (53.3%)	11 (5.1%)	203 (94.9%)
	PLACEBO	109	69.4	5.40	70.0	60	82	40 (36.7%)	69 (63.3%)	5 (4.6%)	104 (95.4%)
625	PAROXETINE	112	64.3	11.39	67.0	22	85	61 (54.5%)	51 (45.5%)	15 (13.4%)	97 (86.6%)
	PLACEBO	117	65.6	10.51	67.0	38	82	64 (54.7%)	53 (45.3%)	14 (12.0%)	103 (88.0%)
442	PAROXETINE	41	46.9	11.81	48.0	21	69	6 (14.6%)	35 (85.4%)	0 (0.0%)	41 (100.0%)

Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation

Paroxetine Adult Suicidality Analysis
Major Depressive Disorder, Short Term Trials
Table 1.01. Demographic Characteristics by Trial

			Age					Gender		Baseline Suicidal Ideation	
Trial	Treatment	N	Mean	Standard Deviation	Median	Minimum	Maximum	Males	Females	Present	Absent
442	PLACEBO	48	49.0	11.49	48.0	31	79	2 (4.2%)	46 (95.8%)	0 (0.0%)	46 (95.8%)
785	PAROXETINE	197	41.3	12.19	43.0	18	65	76 (38.6%)	121 (61.4%)	46 (23.4%)	151 (76.6%)
	PLACEBO	105	40.4	11.36	40.0	18	63	46 (43.8%)	59 (56.2%)	22 (21.0%)	83 (79.0%)
810	PAROXETINE	306	38.9	11.53	38.0	18	74	131 (42.8%)	175 (57.2%)	3 (1.0%)	303 (99.0%)
	PLACEBO	148	38.5	11.78	37.0	18	65	57 (38.5%)	91 (61.5%)	2 (1.4%)	146 (98.6%)
NKD20006	PAROXETINE	124	38.0	11.85	38.5	18	64	46 (37.1%)	78 (62.9%)	0 (0.0%)	124 (100.0%)
	PLACEBO	125	37.7	11.20	37.0	18	63	53 (42.4%)	72 (57.6%)	0 (0.0%)	125 (100.0%)
874	PAROXETINE	341	67.1	6.36	66.0	60	91	136 (39.9%)	205 (60.1%)	6 (1.8%)	335 (98.2%)
	PLACEBO	180	68.0	6.73	66.0	60	87	67 (37.2%)	113 (62.8%)	1 (0.6%)	179 (99.4%)

Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation

Paroxetine Adult Suicidality Analysis
Table 2.01
Number and Percent of Subjects with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	31/3455 (0.90%)	11/1978 (0.56%)	1.3 (0.7, 2.8)	0.493	(527.4)
Overall (Mantel Haenszel)	31/3455 (0.90%)	11/1978 (0.56%)	1.1 (0.6, 2.1)	0.709	(1437.4)
Trial 276	0/ 20 (0.00%)	0/ 21 (0.00%)	Not Enough Events		
Trial 279	2/ 21 (9.52%)	1/ 10 (10.00%)	0.9 (0.1, 30.9)		210.0
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	1/ 170 (0.59%)	2/ 171 (1.17%)	0.5 (0.0, 6.6)		172.0
Trial 009	5/ 421 (1.19%)	0/ 53 (0.00%)	inf (0.2, inf)		(84.2)
Trial 003	0/ 241 (0.00%)	2/ 244 (0.82%)	0.0 (0.0, 3.5)		122.0
Trial 115	5/ 283 (1.77%)	3/ 117 (2.56%)	0.7 (0.2, 3.5)		125.4
Trial 128	8/ 357 (2.24%)	2/ 140 (1.43%)	1.6 (0.4, 11.0)		(123.1)
Trial 251	2/ 125 (1.60%)	0/ 129 (0.00%)	inf (0.3, inf)		(62.5)
Trial 448	3/ 212 (1.42%)	0/ 103 (0.00%)	inf (0.3, inf)		(70.7)
Trial 449	1/ 223 (0.45%)	0/ 110 (0.00%)	inf (0.0, inf)		(223.0)
Trial 487	2/ 214 (0.93%)	0/ 109 (0.00%)	inf (0.1, inf)		(107.0)
Trial 625	1/ 112 (0.89%)	0/ 117 (0.00%)	inf (0.1, inf)		(112.0)
Trial 442	0/ 41 (0.00%)	0/ 48 (0.00%)	Not Enough Events		
Trial 785	1/ 197 (0.51%)	0/ 105 (0.00%)	inf (0.0, inf)		(197.0)
Trial 810	0/ 306 (0.00%)	1/ 148 (0.68%)	0.0 (0.0, 9.2)		148.0
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	0/ 341 (0.00%)	0/ 180 (0.00%)	Not Enough Events		

*Zelen's test of homogeneity, p=0.566
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)

Paroxetine Adult Suicidality Analysis
Table 2.02
Number and Percent of Subjects with Rating Scale Emergent Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	37/3414 (1.08%)	32/1930 (1.66%)	0.6 (0.4, 1 0)	0.050	154.3
Overall (Mantel Haenszel)	37/3414 (1.08%)	32/1930 (1.66%)	0.6 (0.4, 1 0)	0.035	152.4
Trial 276	1/ 20 (5.00%)	0/ 21 (0.00%)	inf (0.1, inf)		(20.0)
Trial 279	0/ 21 (0.00%)	1/ 10 (10.00%)	0.0 (0.0, 9.0)		10.0
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	1/ 170 (0.59%)	4/ 171 (2.34%)	0.2 (0.0, 2.0)		57.1
Trial 009	6/ 421 (1.43%)	1/ 53 (1.89%)	0.8 (0.1, 17.7)		216.6
Trial 003	3/ 241 (1.24%)	7/ 244 (2.87%)	0.4 (0.1, 1.6)		61.6
Trial 115	5/ 283 (1.77%)	0/ 117 (0.00%)	inf (0.5, inf)		(56.6)
Trial 128	6/ 357 (1.68%)	5/ 140 (3.57%)	0.5 (0.1, 1.7)		52.9
Trial 251	2/ 125 (1.60%)	1/ 129 (0.78%)	2.1 (0.2, 61.8)		(121.2)
Trial 448	0/ 212 (0.00%)	1/ 103 (0.97%)	0.0 (0.0, 9.2)		103.0
Trial 449	6/ 223 (2.69%)	3/ 110 (2.73%)	1.0 (0.2, 4.9)		2725.6
Trial 487	2/ 214 (0.93%)	1/ 109 (0.92%)	1.0 (0.1, 30.3)		(5831.5)
Trial 625	1/ 112 (0.89%)	1/ 117 (0.85%)	1.0 (0.0, 41.1)		(2620.8)
Trial 785	3/ 197 (1.52%)	4/ 105 (3.81%)	0.4 (0.1, 1.9)		43.7
Trial 810	0/ 306 (0.00%)	2/ 148 (1.35%)	0.0 (0.0, 1.7)		74.0
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	1/ 341 (0.29%)	1/ 180 (0.56%)	0.5 (0.0, 20.6)		381.2

*Zelen's test of homogeneity, p=0.461
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
NOTE: Rating Scale Emergent Suicidal Behaviour and Ideation data was not available in Study 442

Paroxetine Adult Suicidality Analysis
Table 2.03
Number and Percent of Subjects with Composite Suicidal Behaviour and Ideation by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	62/3414 (1.82%)	40/1930 (2.07%)	0.8 (0.5, 1.2)	0.275	226.2
Overall (Mantel Haenszel)	62/3414 (1.82%)	40/1930 (2.07%)	0.8 (0.5, 1.2)	0.241	223.5
Trial 276	1/ 20 (5.00%)	0/ 21 (0.00%)	inf (0.1, inf)		(20.0)
Trial 279	2/ 21 (9.52%)	2/ 10 (20.00%)	0.4 (0.0, 4.8)		9.5
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	2/ 170 (1.18%)	6/ 171 (3.51%)	0.3 (0.0, 1.6)		42.9
Trial 009	10/ 421 (2.38%)	1/ 53 (1.89%)	1.3 (0.2, 28.2)		(204.7)
Trial 003	3/ 241 (1.24%)	7/ 244 (2.87%)	0.4 (0.1, 1.6)		61.6
Trial 115	7/ 283 (2.47%)	3/ 117 (2.56%)	1.0 (0.2, 4.7)		1103.7
Trial 128	14/ 357 (3.92%)	7/ 140 (5.00%)	0.8 (0.3, 2.1)		92.7
Trial 251	4/ 125 (3.20%)	1/ 129 (0.78%)	4.2 (0.5, 105.5)		(41.2)
Trial 448	3/ 212 (1.42%)	1/ 103 (0.97%)	1.5 (0.2, 38.9)		(225.1)
Trial 449	6/ 223 (2.69%)	3/ 110 (2.73%)	1.0 (0.2, 4.9)		2725.6
Trial 487	4/ 214 (1.87%)	1/ 109 (0.92%)	2.1 (0.3, 51.3)		(105.1)
Trial 625	2/ 112 (1.79%)	1/ 117 (0.85%)	2.1 (0.2, 62.7)		(107.4)
Trial 785	3/ 197 (1.52%)	4/ 105 (3.81%)	0.4 (0.1, 1.9)		43.7
Trial 810	0/ 306 (0.00%)	2/ 148 (1.35%)	0.0 (0.0, 1.7)		74.0
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	1/ 341 (0.29%)	1/ 180 (0.56%)	0.5 (0.0, 20.6)		381.2

*Zelen's test of homogeneity, p=0.604
Note. *NNT numbers in brackets denote number-needed-to-harm (NNH)*
NOTE: Composite Suicidal Behaviour and Ideation data was not available in Study 442

Paroxetine Adult Suicidality Analysis
Table 2.04
Number and Percent of Subjects with Definitive Suicidal Behaviour by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	11/3455 (0.32%)	1/1978 (0.05%)	6.7 (1.1, 149.4)	0.058	(345.2)
Overall (Mantel Haenszel)	11/3455 (0.32%)	1/1978 (0.05%)	1.6 (0.6, 4.2)	0.363	(3515.9)
Trial 276	0/ 20 (0.00%)	0/ 21 (0.00%)	Not Enough Events		
Trial 279	1/ 21 (4.76%)	0/ 10 (0.00%)	inf (0.0, inf)		(21.0)
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	1/ 170 (0.59%)	1/ 171 (0.58%)	1.0 (0.0, 39.4)		(29070.0)
Trial 009	1/ 421 (0.24%)	0/ 53 (0.00%)	inf (0.0, inf)		(421.0)
Trial 003	0/ 241 (0.00%)	0/ 244 (0.00%)	Not Enough Events		
Trial 115	1/ 283 (0.35%)	0/ 117 (0.00%)	inf (0.0, inf)		(283.0)
Trial 128	1/ 357 (0.28%)	0/ 140 (0.00%)	inf (0.0, inf)		(357.0)
Trial 251	1/ 125 (0.80%)	0/ 129 (0.00%)	inf (0.1, inf)		(125.0)
Trial 448	2/ 212 (0.94%)	0/ 103 (0.00%)	inf (0.1, inf)		(106.0)
Trial 449	1/ 223 (0.45%)	0/ 110 (0.00%)	inf (0.0, inf)		(223.0)
Trial 487	0/ 214 (0.00%)	0/ 109 (0.00%)	Not Enough Events		
Trial 625	1/ 112 (0.89%)	0/ 117 (0.00%)	inf (0.1, inf)		(112.0)
Trial 442	0/ 41 (0.00%)	0/ 48 (0.00%)	Not Enough Events		
Trial 785	1/ 197 (0.51%)	0/ 105 (0.00%)	inf (0.0, inf)		(197.0)
Trial 810	0/ 306 (0.00%)	0/ 148 (0.00%)	Not Enough Events		
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	0/ 341 (0.00%)	0/ 180 (0.00%)	Not Enough Events		

*Zelen's test of homogeneity, p=1.000
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)

Paroxetine Adult Suicidality Analysis
Table 2.05
Number and Percent of Subjects with Rating Scale Emergent Suicidal Behaviour by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	1/3414 (0.03%)	0/1930 (0.00%)	inf (0.0, inf)	1.000	
Overall (Mantel Haenszel)	1/3414 (0.03%)	0/1930 (0.00%)	0.4 (0.0, 9.5)	0.542	
Trial 276	0/ 20 (0.00%)	0/ 21 (0.00%)	Not Enough Events		
Trial 279	0/ 21 (0.00%)	0/ 10 (0.00%)	Not Enough Events		
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	0/ 170 (0.00%)	0/ 171 (0.00%)	Not Enough Events		
Trial 009	1/ 421 (0.24%)	0/ 53 (0.00%)	inf (0.0, inf)		(421.0)
Trial 003	0/ 241 (0.00%)	0/ 244 (0.00%)	Not Enough Events		
Trial 115	0/ 283 (0.00%)	0/ 117 (0.00%)	Not Enough Events		
Trial 128	0/ 357 (0.00%)	0/ 140 (0.00%)	Not Enough Events		
Trial 251	0/ 125 (0.00%)	0/ 129 (0.00%)	Not Enough Events		
Trial 448	0/ 212 (0.00%)	0/ 103 (0.00%)	Not Enough Events		
Trial 449	0/ 223 (0.00%)	0/ 110 (0.00%)	Not Enough Events		
Trial 487	0/ 214 (0.00%)	0/ 109 (0.00%)	Not Enough Events		
Trial 625	0/ 112 (0.00%)	0/ 117 (0.00%)	Not Enough Events		
Trial 785	0/ 197 (0.00%)	0/ 105 (0.00%)	Not Enough Events		
Trial 810	0/ 306 (0.00%)	0/ 148 (0.00%)	Not Enough Events		
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	0/ 341 (0.00%)	0/ 180 (0.00%)	Not Enough Events		

*Test of homogeneity not carried out due to insufficient data
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
NOTE: Rating Scale Emergent Suicidal Behaviour data was not available in Study 442

Paroxetine Adult Suicidality Analysis
Table 2.06
Number and Percent of Subjects with Composite Suicidal Behaviour by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)*	12/3414 (0.35%)	1/1930 (0.05%)	6.9 (1.1, 151.9)	0.036	(329.0)
Overall (Mantel Haenszel)	12/3414 (0.35%)	1/1930 (0.05%)	1.6 (0.6, 4.3)	0.340	(3239.3)
Trial 276	0/ 20 (0.00%)	0/ 21 (0.00%)	Not Enough Events		
Trial 279	1/ 21 (4.76%)	0/ 10 (0.00%)	inf (0.0, inf)		(21.0)
Trial 274	0/ 22 (0.00%)	0/ 23 (0.00%)	Not Enough Events		
Trial 001	0/ 25 (0.00%)	0/ 25 (0.00%)	Not Enough Events		
Trial 002	1/ 170 (0.59%)	1/ 171 (0.58%)	1.0 (0.0, 39.4)		(29070.0)
Trial 009	2/ 421 (0.48%)	0/ 53 (0.00%)	inf (0.0, inf)		(210.5)
Trial 003	0/ 241 (0.00%)	0/ 244 (0.00%)	Not Enough Events		
Trial 115	1/ 283 (0.35%)	0/ 117 (0.00%)	inf (0.0, inf)		(283.0)
Trial 128	1/ 357 (0.28%)	0/ 140 (0.00%)	inf (0.0, inf)		(357.0)
Trial 251	1/ 125 (0.80%)	0/ 129 (0.00%)	inf (0.1, inf)		(125.0)
Trial 448	2/ 212 (0.94%)	0/ 103 (0.00%)	inf (0.1, inf)		(106.0)
Trial 449	1/ 223 (0.45%)	0/ 110 (0.00%)	inf (0.0, inf)		(223.0)
Trial 487	0/ 214 (0.00%)	0/ 109 (0.00%)	Not Enough Events		
Trial 625	1/ 112 (0.89%)	0/ 117 (0.00%)	inf (0.1, inf)		(112.0)
Trial 785	1/ 197 (0.51%)	0/ 105 (0.00%)	inf (0.0, inf)		(197.0)
Trial 810	0/ 306 (0.00%)	0/ 148 (0.00%)	Not Enough Events		
Trial NKD20006	0/ 124 (0.00%)	0/ 125 (0.00%)	Not Enough Events		
Trial 874	0/ 341 (0.00%)	0/ 180 (0.00%)	Not Enough Events		

*Zelen's test of homogeneity, p=1.000
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
NOTE: Composite Suicidal Behaviour data was not available in Study 442

Paroxetine Adult Suicidality Analysis
Table 2.07
Number and Percent of Subjects with Any Adverse Event by Indication, Treatment Group and Trial
Indication = MDD

Trial	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (Mantel Haenszel)	2843/3414 (83.27%)	1370/1930 (70.98%)	1.9 (1.7, 2.2)	<0.001	(8.7)
Trial 276	16/ 20 (80.00%)	13/ 21 (61.90%)	2.4 (0.6, 11.1)		(5.5)
Trial 279	20/ 21 (95.24%)	8/ 10 (80.00%)	4.7 (0.3, 154.1)		(6.6)
Trial 274	19/ 22 (86.36%)	13/ 23 (56.52%)	4.7 (1.1, 24.9)		(3.4)
Trial 001	18/ 25 (72.00%)	9/ 25 (36.00%)	4.4 (1.4, 15.6)		(2.8)
Trial 002	138/ 170 (81.18%)	99/ 171 (57.89%)	3.1 (1.9, 5.1)		(4.3)
Trial 009	327/ 421 (77.67%)	31/ 53 (58.49%)	2.5 (1.3, 4.5)		(5.2)
Trial 003	209/ 241 (86.72%)	169/ 244 (69.26%)	2.9 (1.8, 4.6)		(5.7)
Trial 115	260/ 283 (91.87%)	99/ 117 (84.62%)	2.1 (1.0, 4.0)		(13.8)
Trial 128	328/ 357 (91.88%)	116/ 140 (82.86%)	2.3 (1.3, 4.2)		(11.1)
Trial 251	105/ 125 (84.00%)	103/ 129 (79.84%)	1.3 (0.7, 2.5)		(24.1)
Trial 448	190/ 212 (89.62%)	82/ 103 (79.61%)	2.2 (1.1, 4.3)		(10.0)
Trial 449	200/ 223 (89.69%)	89/ 110 (80.91%)	2.0 (1.1, 3.9)		(11.4)
Trial 487	196/ 214 (91.59%)	95/ 109 (87.16%)	1.6 (0.7, 3.4)		(22.6)
Trial 625	43/ 112 (38.39%)	37/ 117 (31.62%)	1.3 (0.8, 2.3)		(14.8)
Trial 785	157/ 197 (79.70%)	80/ 105 (76.19%)	1.2 (0.7, 2.2)		(28.5)
Trial 810	245/ 306 (80.07%)	113/ 148 (76.35%)	1.2 (0.8, 2.0)		(26.9)
Trial NKD20006	97/ 124 (78.23%)	82/ 125 (65.60%)	1.9 (1.1, 3.3)		(7.9)
Trial 874	275/ 341 (80.65%)	132/ 180 (73.33%)	1.5 (1.0, 2.3)		(13.7)

*Breslow-Day test of homogeneity, p=0.157
Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
NOTE: Exact analyses were not possible due to the large number of events
NOTE: Adverse event data was not available in Study 442

Paroxetine Adult Suicidality Analysis
Table 2.08
Number and Percent of Subjects with Definitive Suicidal Behaviour and Ideation by Indication, Treatment Group and Risk Factors
Indication = MDD

Description	Subgroup	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)		31/3455 (0.90%)	11/1978 (0.56%)	1.3 (0.7, 2.8)	0.493	(527.4)
Baseline Suicidal Ideation	Missing	0/ 0	0/ 2 (0.00%)			
	Absent	24/3042 (0.79%)	7/1736 (0.40%)	2.0 (0.9, 4.9)		(259.3)
	Present	7/ 413 (1.69%)	4/ 240 (1.67%)	1.0 (0.3, 4.0)		(3536.2)
Age Group	18-24	5/ 230 (2.17%)	0/ 104 (0.00%)	inf (0.6, inf)		
	25-64	23/2713 (0.85%)	10/1567 (0.64%)	1.3 (0.6, 2.9)		(477.2)
	>=65	3/ 512 (0.59%)	1/ 307 (0.33%)	1.8 (0.2, 47.6)		(384.9)
Gender	Female	18/2031 (0.89%)	5/1190 (0.42%)	2.1 (0.8, 6.4)		(214.6)
	Male	13/1424 (0.91%)	6/ 788 (0.76%)	1.2 (0.5, 3.4)		(660.3)

Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation
Note. Tests of heterogeneity for Baseline Suicidal Ideation, Age Group and Gender are 0.439, 0.810, 0.492

Paroxetine Adult Suicidality Analysis
Table 2.09
Number and Percent of Subjects with Definitive Suicidal Behaviour by Indication, Treatment Group and Risk Factors
Indication = MDD

Description	Subgroup	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (exact, adjusted)		11/3455 (0.32%)	1/1978 (0.05%)	6.7 (1.1, 149.4)	0.058	(345.2)
Baseline Suicidal Ideation	Missing	0/ 0	0/ 2 (0.00%)			
	Absent	9/3042 (0.30%)	0/1736 (0.00%)	inf (1.4, inf)		
	Present	2/ 413 (0.48%)	1/ 240 (0.42%)	1.2 (0.1, 34.4)		(1481.9)
Age Group	18-24	3/ 230 (1.30%)	0/ 104 (0.00%)	inf (0.3, inf)		
	25-64	8/2713 (0.29%)	0/1567 (0.00%)	inf (1.3, inf)		
	>=65	0/ 512 (0.00%)	1/ 307 (0.33%)	0.0 (0.0, 11.4)		(1.0)
Gender	Female	7/2031 (0.34%)	1/1190 (0.08%)	4.1 (0.6, 93.5)		(383.9)
	Male	4/1424 (0.28%)	0/ 788 (0.00%)	inf (0.5, inf)		

Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation
Note. Tests of heterogeneity for Baseline Suicidal Ideation, Age Group and Gender are 0.254, 0.091, 1.000

Paroxetine Adult Suicidality Analysis
Table 2.10
Subjects with Definitive Suicidal Behaviour and Ideation by Age
Indication = MDD

Age (years)	Paroxetine	Placebo
18	2/ 17 (11.76%)	0/ 6 (0.00%)
19	1/ 30 (3.33%)	0/ 12 (0.00%)
20	1/ 28 (3.57%)	0/ 9 (0.00%)
21	1/ 36 (2.78%)	0/ 13 (0.00%)
22	0/ 36 (0.00%)	0/ 20 (0.00%)
23	0/ 42 (0.00%)	0/ 18 (0.00%)
24	0/ 41 (0.00%)	0/ 26 (0.00%)
25	1/ 49 (2.04%)	0/ 33 (0.00%)
26	0/ 56 (0.00%)	1/ 35 (2.86%)
27	1/ 62 (1.61%)	1/ 42 (2.38%)
28	1/ 67 (1.49%)	0/ 44 (0.00%)
29	2/ 76 (2.63%)	0/ 34 (0.00%)
30	2/ 72 (2.78%)	0/ 47 (0.00%)
31	1/ 80 (1.25%)	2/ 50 (4.00%)
32	0/ 91 (0.00%)	0/ 40 (0.00%)
33	0/ 78 (0.00%)	0/ 52 (0.00%)
34	2/ 84 (2.38%)	1/ 47 (2.13%)
35	1/ 82 (1.22%)	0/ 39 (0.00%)
36	1/ 89 (1.12%)	0/ 39 (0.00%)
37	0/ 82 (0.00%)	0/ 48 (0.00%)
38	3/ 88 (3.41%)	1/ 60 (1.67%)
39	0/ 84 (0.00%)	1/ 47 (2.13%)
40	0/ 88 (0.00%)	0/ 50 (0.00%)
41	0/ 78 (0.00%)	1/ 47 (2.13%)
42	1/ 68 (1.47%)	0/ 54 (0.00%)

Paroxetine Adult Suicidality Analysis
Table 2.10
Subjects with Definitive Suicidal Behaviour and Ideation by Age
Indication = MDD

Age (years)	Paroxetine	Placebo
43	0/ 87 (0.00%)	0/ 48 (0.00%)
44	0/ 82 (0.00%)	0/ 32 (0.00%)
45	1/ 83 (1.20%)	0/ 47 (0.00%)
46	1/ 74 (1.35%)	0/ 40 (0.00%)
47	0/ 68 (0.00%)	0/ 35 (0.00%)
48	0/ 60 (0.00%)	0/ 46 (0.00%)
49	3/ 69 (4.35%)	1/ 33 (3.03%)
50	0/ 58 (0.00%)	0/ 43 (0.00%)
51	1/ 53 (1.89%)	0/ 26 (0.00%)
52	0/ 56 (0.00%)	0/ 36 (0.00%)
53	0/ 50 (0.00%)	0/ 29 (0.00%)
54	0/ 49 (0.00%)	0/ 32 (0.00%)
55	0/ 56 (0.00%)	0/ 29 (0.00%)
56	0/ 52 (0.00%)	0/ 27 (0.00%)
57	0/ 39 (0.00%)	0/ 21 (0.00%)
58	1/ 31 (3.23%)	0/ 27 (0.00%)
59	0/ 38 (0.00%)	0/ 24 (0.00%)
60	0/ 82 (0.00%)	1/ 49 (2.04%)
61	0/ 72 (0.00%)	0/ 42 (0.00%)
62	0/ 70 (0.00%)	0/ 32 (0.00%)
63	0/ 52 (0.00%)	0/ 33 (0.00%)
64	0/ 58 (0.00%)	0/ 28 (0.00%)
65	0/ 44 (0.00%)	0/ 30 (0.00%)
66	0/ 52 (0.00%)	0/ 21 (0.00%)
67	0/ 45 (0.00%)	1/ 27 (3.70%)

Paroxetine Adult Suicidality Analysis
Table 2.10
Subjects with Definitive Suicidal Behaviour and Ideation by Age
Indication = MDD

Age (years)	Paroxetine	Placebo
68	0/ 42 (0.00%)	0/ 24 (0.00%)
69	0/ 38 (0.00%)	0/ 16 (0.00%)
70	0/ 36 (0.00%)	0/ 23 (0.00%)
71	0/ 40 (0.00%)	0/ 26 (0.00%)
72	1/ 40 (2.50%)	0/ 17 (0.00%)
73	0/ 28 (0.00%)	0/ 18 (0.00%)
74	0/ 22 (0.00%)	0/ 17 (0.00%)
75	1/ 19 (5.26%)	0/ 17 (0.00%)
76	0/ 17 (0.00%)	0/ 17 (0.00%)
77	0/ 18 (0.00%)	0/ 10 (0.00%)
78	0/ 18 (0.00%)	0/ 16 (0.00%)
79	0/ 10 (0.00%)	0/ 9 (0.00%)
80	0/ 7 (0.00%)	0/ 6 (0.00%)
81	0/ 3 (0.00%)	0/ 4 (0.00%)
82	1/ 8 (12.50%)	0/ 5 (0.00%)
83	0/ 6 (0.00%)	0/ 1 (0.00%)
84	0/ 7 (0.00%)	0/ 1 (0.00%)
85	0/ 3 (0.00%)	0/ 0
86	0/ 4 (0.00%)	0/ 1 (0.00%)
87	0/ 1 (0.00%)	0/ 1 (0.00%)
88	0/ 3 (0.00%)	0/ 0
89	0/ 0	0/ 0
90	0/ 0	0/ 0
91	0/ 1 (0.00%)	0/ 0

Paroxetine Adult Suicidality Analysis
Table 2.11
Subjects with Either Definitive Suicidal Behaviour or Rating Scale Emergent Suicidal Behaviour
Indication = MDD

Subject ID	Study Number	Randomized Treatment	Age (years)	Gender	Baseline Suicidal Ideation	Definitive Suicidal Behaviour	Rating Scale Emergent Suicidal Behaviour
02.001.009	002	PLACEBO	67	Female	Yes	Yes	No
02.004.089	002	PAROXETINE	19	Female	No	Yes	No
09.01A.006	009	PAROXETINE	35	Male	No	No	Yes
09.01E.260	009	PAROXETINE	51	Female	No	Yes	No
1 12 037	279	PAROXETINE	20	Male	Yes	Yes	No
115.003.0062	115	PAROXETINE	29	Female	No	Yes	No
128.001.0759	128	PAROXETINE	30	Male	No	Yes	No
251.002.0285	251	PAROXETINE	30	Male	No	Yes	No
448.010.00044	448	PAROXETINE	25	Female	No	Yes	No
448.019.00391	448	PAROXETINE	27	Female	No	Yes	No
449.021.00788	449	PAROXETINE	18	Female	No	Yes	No
625.500.02062	625	PAROXETINE	49	Male	Yes	Yes	No
785.720.00695	785	PAROXETINE	34	Female	No	Yes	No

Paroxetine Adult Suicidality Analysis
Table 3.01
Change from Baseline on HAMD Total Score to LOCF Endpoint by Treatment Group
Indication = MDD

Population	Category	N	Paroxetine LS mean	Placebo LS mean	Estimated Treatment Effect	95% CI	P-value
Overall		4609	-10.9	-8.4	-2.5	(-3.0, -2.1)	<0.001
Baseline Suicidal Ideation	Missing	2	.	.	.		
	Absent	4090	-10.9	-8.5	-2.5	(-2.9, -2.0)	
	Present	517	-11.1	-8.0	-3.1	(-4.7, -1.5)	
Age Group	18-24	282	-10.8	-9.9	-0.9	(-2.8, 0.9)	
	25-64	3671	-10.9	-8.2	-2.7	(-3.2, -2.1)	
	>=65	656	-11.3	-8.8	-2.5	(-3.7, -1.4)	
Gender	Female	2745	-11.5	-8.5	-3.0	(-3.6, -2.4)	
	Male	1864	-10.1	-8.3	-1.8	(-2.6, -1.1)	

Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation

Paroxetine Adult Suicidality Analysis
Table 3.02
Change from Baseline on MADRS Total Score to LOCF Endpoint by Treatment Group
Indication = MDD

Population	Category	N	Paroxetine LS mean	Placebo LS mean	Estimated Treatment Effect	95% CI	P-value
Overall		1759	-12.2	-8.5	-3.7	(-4.7, -2.7)	<0.001
Baseline Suicidal Ideation	Absent	1361	-11.8	-8.0	-3.8	(-4.9, -2.7)	
	Present	398	-13.7	-10.4	-3.2	(-5.6, -0.8)	
Age Group	18-24	105	-11.9	-8.9	-3.1	(-7.7, 1.6)	
	25-64	1479	-12.2	-8.3	-3.9	(-5.0, -2.8)	
	>=65	175	-12.1	-9.8	-2.3	(-5.2, 0.5)	
Gender	Female	903	-12.7	-8.5	-4.3	(-5.7, -2.9)	
	Male	856	-11.6	-8.6	-3.0	(-4.4, -1.6)	

Paroxetine Adult Suicidality Analysis
Table 3.03
Change from Baseline on HAMD Item 3 to LOCF Endpoint by Treatment Group
Indication = MDD

Population	Category	N	Paroxetine LS mean	Placebo LS mean	Estimated Treatment Effect	95% CI	P-value
Overall		4524	-0.6	-0.5	-0.2	(-0.2, -0.1)	<0.001
Baseline Suicidal Ideation	Absent	4007	-0.5	-0.4	-0.2	(-0.2, -0.1)	
	Present	517	-1.4	-1.0	-0.4	(-0.6, -0.2)	
Age Group	18-24	281	-0.7	-0.7	0.0	(-0.1, 0.2)	
	25-64	3595	-0.6	-0.4	-0.2	(-0.2, -0.2)	
	>=65	648	-0.5	-0.4	-0.1	(-0.2, -0.1)	
Gender	Female	2668	-0.7	-0.5	-0.2	(-0.2, -0.1)	
	Male	1856	-0.6	-0.4	-0.2	(-0.3, -0.1)	

Note. Baseline HAMD Item 3 Scores were not available in study 442

Paroxetine Adult Suicidality Analysis
Table 3.04
Change from Baseline on MADRS Item 10 to LOCF Endpoint by Treatment Group
Indication = MDD

Population	Category	N	Paroxetine LS mean	Placebo LS mean	Estimated Treatment Effect	95% CI	P-value
Overall		1759	-0.9	-0.6	-0.3	(-0.4, -0.2)	<0.001
Baseline Suicidal Ideation	Absent	1361	-0.6	-0.3	-0.3	(-0.4, -0.2)	
	Present	398	-1.9	-1.4	-0.5	(-0.8, -0.3)	
Age Group	18-24	105	-0.9	-0.4	-0.5	(-1.0, -0.1)	
	25-64	1479	-1.0	-0.6	-0.3	(-0.5, -0.2)	
	>=65	175	-0.7	-0.4	-0.3	(-0.5, -0.0)	
Gender	Female	903	-0.9	-0.5	-0.4	(-0.5, -0.3)	
	Male	856	-0.9	-0.6	-0.3	(-0.4, -0.1)	

Paroxetine Adult Suicidality Analysis
Table 3.05
Number and Percent of Subjects with Declining Suicidal Ideation by Indication, Treatment Group and Risk Factors
Indication = MDD

Description	Subgroup	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (Mantel Haenszel)		263/ 413 (63.68%)	121/ 240 (50.42%)	1.7 (1.2, 2.4)	0.002	7.6
Age Group	18-24	18/ 28 (64.29%)	10/ 19 (52.63%)	1.6 (0.5, 5.3)		8.6
	25-64	223/ 359 (62.12%)	104/ 206 (50.49%)	1.6 (1.1, 2.3)		8.6
	>=65	22/ 26 (84.62%)	7/ 15 (46.67%)	6.3 (1.4, 27.4)		2.6
Gender	Female	154/ 237 (64.98%)	71/ 129 (55.04%)	1.5 (1.0, 2.3)		10.1
	Male	109/ 176 (61.93%)	50/ 111 (45.05%)	2.0 (1.2, 3.2)		5.9

Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
Note. Declining Suicidal Ideation was not assessable in study 442
Note. Tests of heterogeneity for Age Group and Gender are 0.355, 0.895

Paroxetine Adult Suicidality Analysis
Table 3.06
Number and Percent of Subjects with >=50% Reduction in HAMD or MADRS Baseline Score by Indication, Treatment Group and Risk Factors
Indication = MDD

Description	Subgroup	Paroxetine	Placebo	OR (95% CI)	P-value	NNT
Overall (Mantel Haenszel)		1688/3227 (52.31%)	702/1890 (37.14%)	1.8 (1.6, 2.0)	<0.001	7.2
Baseline Suicidal Ideation	Missing	0/ 0	0/ 2 (0.00%)	Not Enough Events		
	Absent	1500/2843 (52.76%)	625/1661 (37.63%)	1.9 (1.6, 2.1)		6.6
	Present	188/ 384 (48.96%)	77/ 227 (33.92%)	1.9 (1.3, 2.6)		6.6
Age Group	18-24	102/ 214 (47.66%)	45/ 98 (45.92%)	1.1 (0.7, 1.7)		57.3
	25-64	1317/2525 (52.16%)	538/1497 (35.94%)	1.9 (1.7, 2.2)		6.2
	>=65	269/ 488 (55.12%)	119/ 295 (40.34%)	1.8 (1.4, 2.5)		6.8
Gender	Female	1022/1887 (54.16%)	424/1129 (37.56%)	2.0 (1.7, 2.3)		6.0
	Male	666/1340 (49.70%)	278/ 761 (36.53%)	1.7 (1.4, 2.1)		7.6

Note. NNT numbers in brackets denote number-needed-to-harm (NNH)
Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation
Note. Tests of heterogeneity for Baseline Suicidal Ideation, Age Group and Gender are 0.960, 0.062, 0.264

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Paroxetine Adult Suicidality Analysis

Figure 2.01. Definitive Suicidal Behaviour and Ideation

Indication = MDD

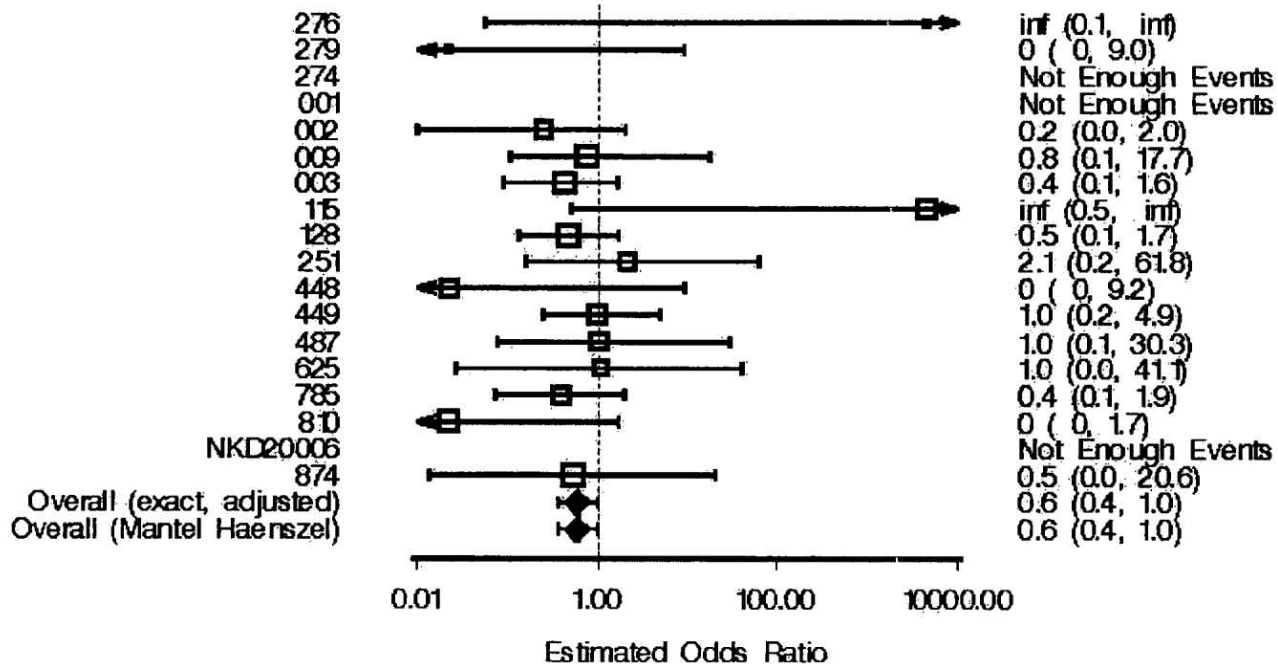
PAR004372169

DX 101-048

Paroxetine Adult Suicidality Analysis

Figure 2.02. Rating Scale Emergent Suicidal Behaviour and Ideation

Indication = MDD

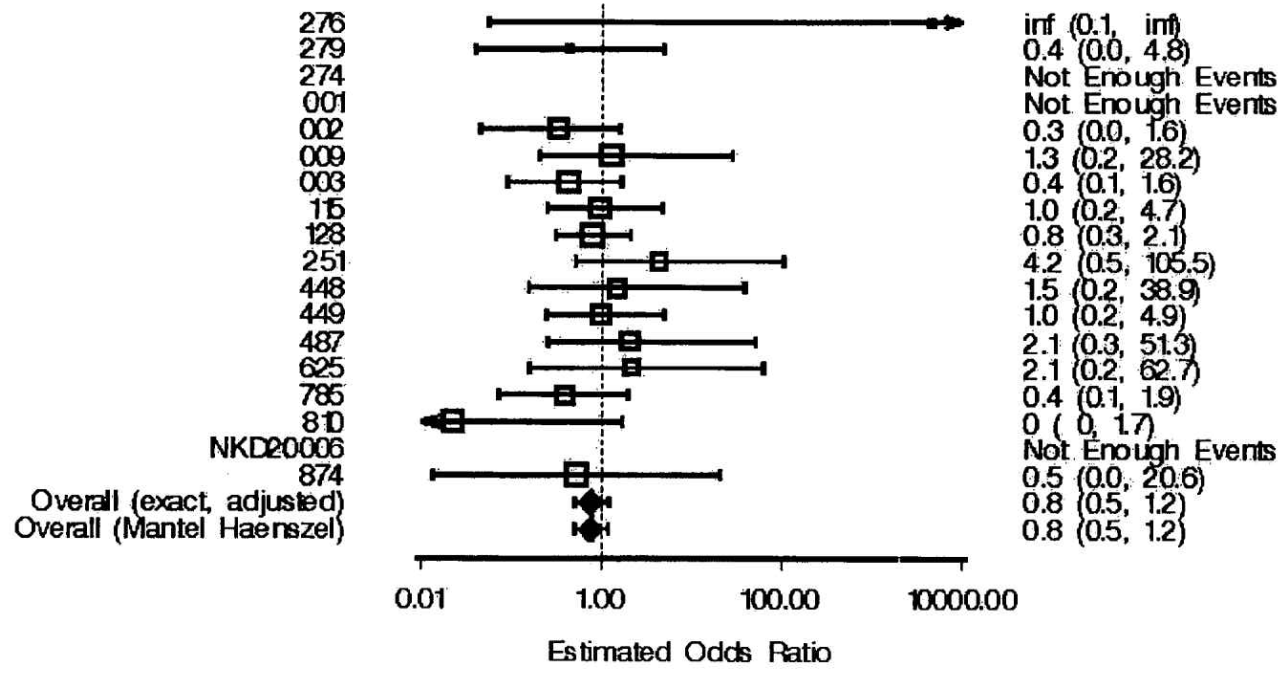


NOTE: Rating Scale Emergent Suicidal Behaviour and Ideation data was not available in Study 442

Paroxetine Adult Suicidality Analysis

Figure 2.03. Composite Suicidal Behaviour and Ideation

Indication = MDD



NOTE: Composite Suicidal Behaviour and Ideation data was not available in Study 442

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Paroxetine Adult Suicidality Analysis
Figure 2.04. Definitive Suicidal Behaviour
Indication = MDD
276
279
274
001
002
009
003
115
128
251
448
449
487
625
442
785
810
NKD20006
874
Overall (exact, adjusted)
Overall (Mantel Haenszel)
Not Enough Events
inf (0.0, inf)
Not Enough Events
Not Enough Events
1.0 (0.0, 39.4)
inf (0.0, inf)
Not Enough Events
inf (0.0, inf)
inf (0.0, inf)
inf (0.1, inf)
inf (0.1, inf)
inf (0.0, inf)
Not Enough Events
inf (0.1, inf)
Not Enough Events
inf (0.0, inf)
Not Enough Events
Not Enough Events
Not Enough Events
6.7 (1.1, 149.4)
1.6 (0.6, 4.2)
0.01
1.00
100.00
10000.00
Estimated Odds Ratio
NOTE: Composite Suicidal Behaviour and Ideation data was not available in Study 442

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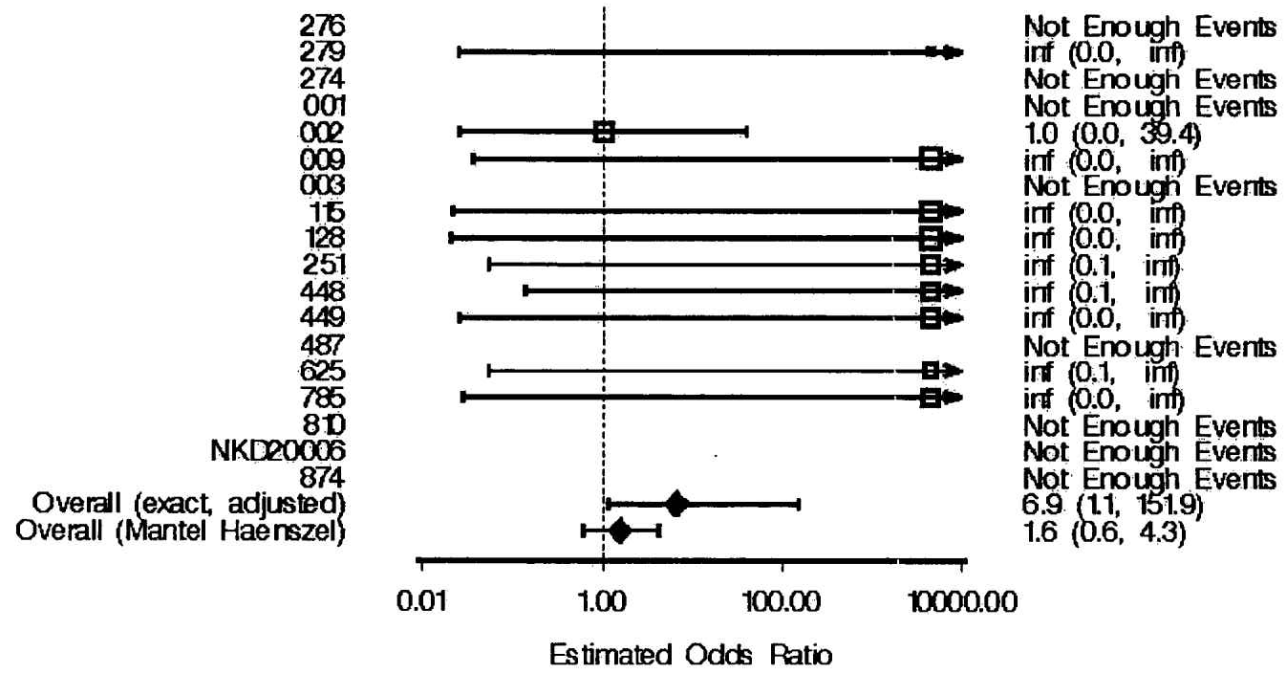
/bloenw/dsn10/sbbri29060_cdal/lega2/list/and_mddadsui_gsk_2005_plots.jpg and_mddadsui_gsk_2005_plots.sas 28FEB2006:12:08 kk45592
Paroxetine Adult Suicidality Analysis
Figure 2.05. Rating Scale Emergent Suicidal Behaviour
Indication = MDD
276
279
274
001
002
003
003
15
128
251
448
449
487
625
785
810
NKD20006
874
Overall (exact, adjusted)
Overall (Mantel Haenszel)
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
inf (0.0, inf)
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
Not Enough Events
inf (0.0, inf)
0.4 (0.0, 9.5)
0.01
1.00
100.00
10000.00
Estimated Odds Ratio
NOTE: Rating Scale Emergent Suicidal Behaviour data was not available in Study 442

Paroxetine Adult Suicidality Analysis

Figure 2.06. Composite Suicidal Behaviour

Indication = MDD



NOTE: Composite Suicidal Behaviour data was not available in Study 442

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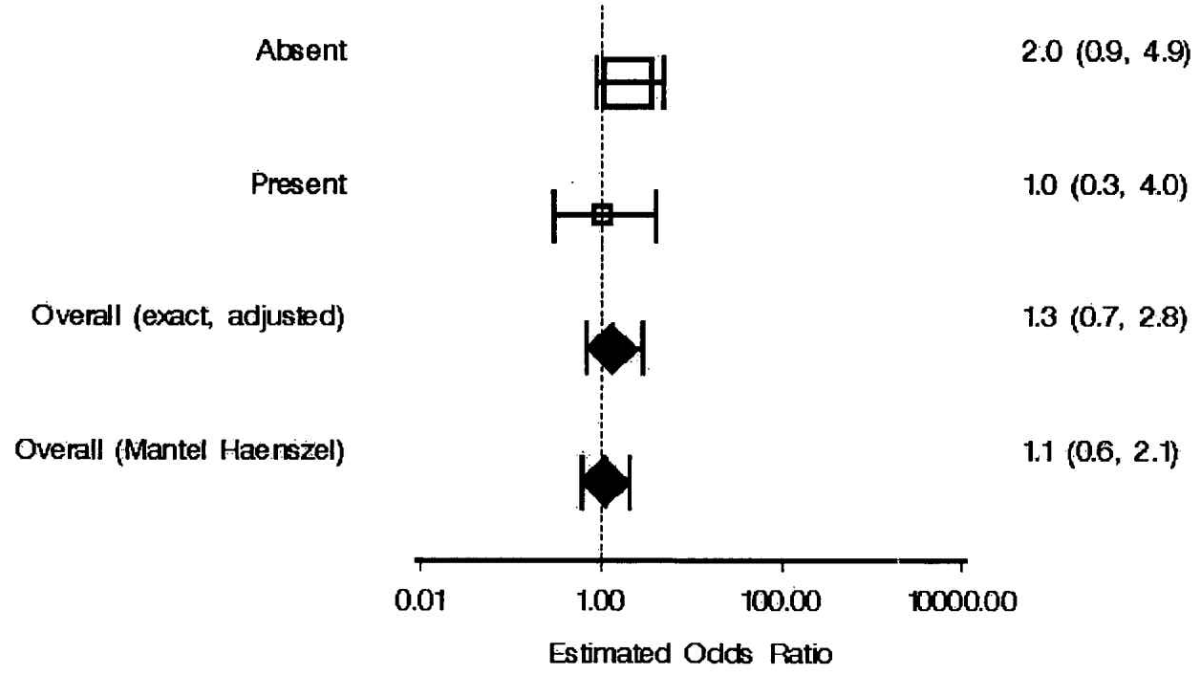
Paroxetine Adult Suicidality Analysis

Figure 2.07. Definitive Suicidal Behaviour and Ideation by Baseline Suicidal Ideation

Indication = MDD



Note. For two subjects in study 442 it was not possible to assess baseline suicidal ideation

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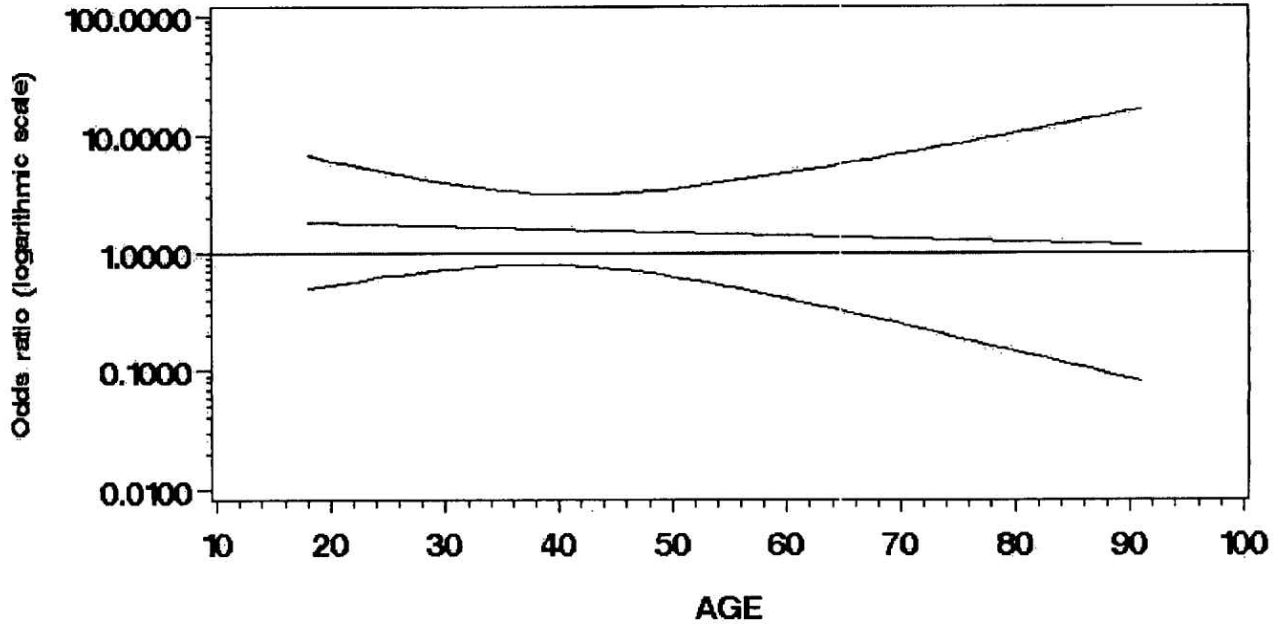
Figure 2.08: Definitive Suicidial Behaviour and Ideation by indication and Age

Indication= Major Depressive Disorder

Odds Ratio and 95% Confidence Intervals



An odds ratio < 1 corresponds to a paroxetine benefit

Model: logit(y)= treatment + age + treatment*age

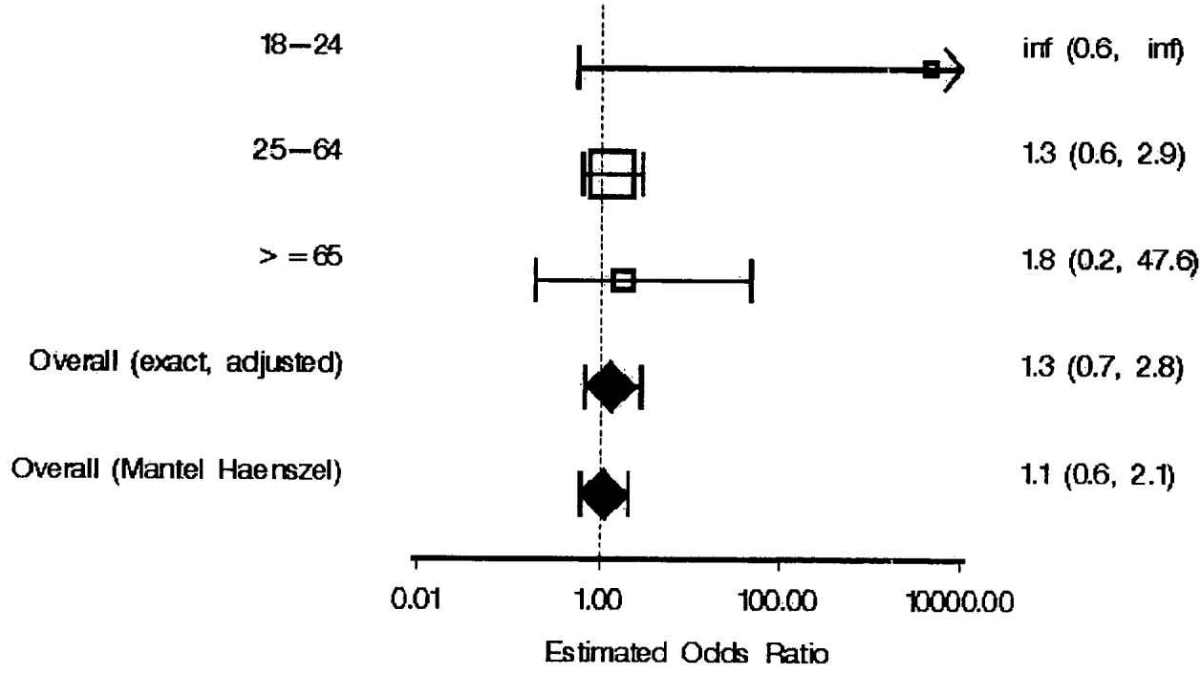
Note: treatment*age term not sig. at 5% level, added to model for plotting puposes

 /biocenv/dart10/ebbr129060_cda/legal2/list/anal_mddadsui_gsk_2005_risk_plots.jpg anal_mddadsui_gsk_2005_risk_plots.sas 23FEB2006:12:27 kk45592

Paroxetine Adult Suicidality Analysis

Figure 2.09. Definitive Suicidal Behaviour and Ideation by Age Group

Indication = MDD



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Paroxetine Adult Suicidality Analysis

Figure 2.10. Definitive Suicidal Behaviour and Ideation by Gender

Indication = MDD

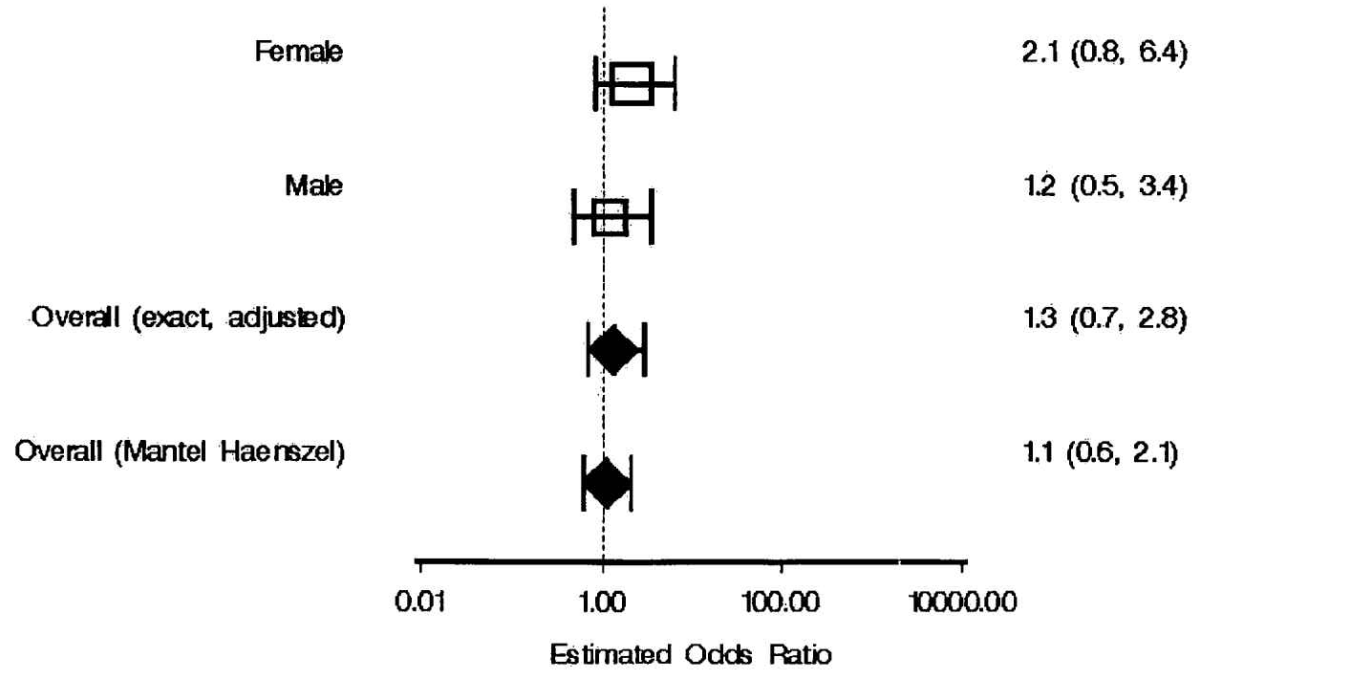

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Figure 2.11: Percentage of Patients with Definitive Suicidal Behaviour and Ideation by Treatment group and Trial
Indication=Major Depressive Disorder

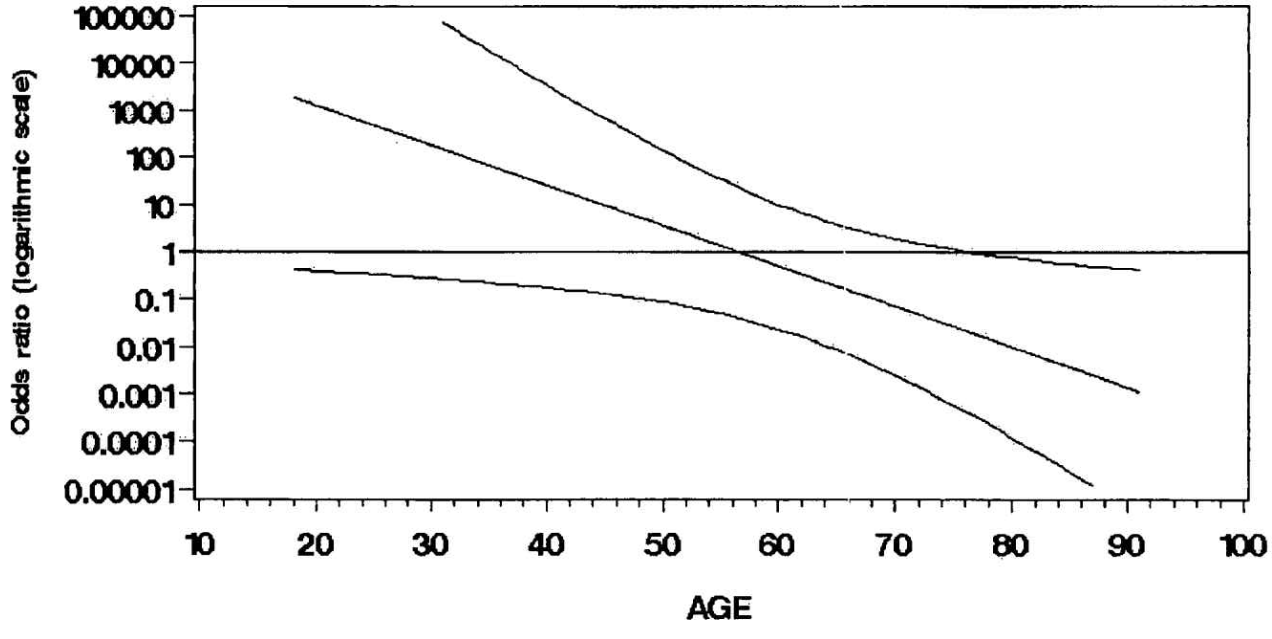
Figure 2.12: Percentage of Patients with Any Adverse Event by Treatment group and Trial

Indication = Major Depressive Disorder

Figure 2.13: Percentage of Patients with Definitive Suicidal Behaviour and Ideation by Treatment group and Age
Indication = Major Depressive Disorder

GSK Confidential /bioenv/dart10/sbbrl_29060_cda/legal2/fig2_8.jpg anal_mddadsui_gsk_2005_agecont.sas 17FEB2006:09:52 axp45559

Figure 2.14: Definitive Suicidial Behaviour by indication and Age
Indication= Major Depressive Disorder
Odds Ratio and 95% Confidence Intervals



An odds ratio < 1 corresponds to a paroxetine benefit
Model: logit(y)= treatment + age + treatment*age
Note: treatment*age term sig. at 5% level, p= 0.030

APPENDIX IV: Unblinded Case Narratives

The case narratives contained herein reflect subjects with either definitive suicidal behavior or rating scale emergent suicidal behavior. The case narratives are in the order presented in Table 2.11 of Appendix 2.

Protocol Id:	02
Subject Number:	02.001.009
Treatment Group:	Placebo
Serious Adverse event Preferred term(s):	
Serious Adverse event Verbatim term(s):	Suicide Gesture by Suffocation

This patient is a 67-year-old white female with a diagnosis of major depressive disorder, recurrent with melancholia (DSM-III: 296.3). She has no significant medical history. She received chloral hydrate 500 mg/day (6/12-16185) for severe insomnia and FI0RINA (butalbital) 2 tablets/day (6/12-13/85) for headache.

Screen ECG was an abnormal record which could have reflected recent change. Further ECG showed that lead V-2 was technically unsatisfactory, but there was no change from screen. Left ventricular hypertrophy could have been responsible for the reading wholly or in part. No other clinical information is available.

The patient began placebo on 6/19186 and continued treatment until 6/25/85, when she made a suicide gesture by suffocation. Her husband prevented her suicide, she was brought to the investigator that same day, and her termination visit was completed. She was dropped for lack of efficacy because of the profound and rapid deterioration of her condition prior to her suicide attempt. No laboratory abnormalities were recorded and she reported no adverse clinical experiences. Post-study follow-up visit on 6/26/85 revealed her condition continued to deteriorate. She reported no withdrawal effects.

Additional Information:

This 67-year-old female was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression, with melancholia (DSM-III: 296.33).

This subject reported no concurrent clinical conditions, but she had recently been treated for headache and severe insomnia. Additionally, the patient had a previous history of depression. The subject's family history was positive for non-psychotic psychiatric disturbance (father), other major affective disturbance (mother), and suicide (mother).

The subject had previously received unspecified psychiatric treatment, including outpatient treatment for 15 years and hospitalization for two weeks. Information pertaining to medicinal treatment was not provided. The episode of major depression for which the subject was enrolled in the study was of 6-12 month's duration, and no concurrent medications were reported at study entry. The subject's current condition was best characterized as a recurrence of a similar previous condition with onset of the present episode being gradual (one or more months). A precipitating external event was

probably present. It was also noted that the subject was experiencing moderate psychosocial stressors at the time of study recruitment.

The subject had a history of suicidal ideation prior to treatment. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2, and the total HAMD-17 score at randomization was 27 and the HAMD-21 score was 30. The verbal, behaviour, and secondary symptoms of depressions scores at screening and randomization on the Raskin Depression Scale were 5,5; 5,4; and 4,4; respectively. The randomization score on MADRS item #10, reflecting suicidality, was 4, and the total MADRS score at randomization was 45.

Six days after the first dose of study medication, (placebo), the subject experienced a profound and rapid deterioration in clinical state with suicidal gesture by suffocation. Corrective treatment included immediate hospitalization. The investigator did not make a relatedness statement.

At the time of the adverse event the subject was receiving placebo at a dosage equivalent to Paxil, 20 mg/day. No concurrent medications were reported at the time of the event.

Treatment with study medication was discontinued the same day as the event and the subject was withdrawn from the study.

Observed efficacy scores by study week for the subject are listed below.

	HAMD		
Day of HAMD visit	HAMD item 3: suicide	HAMD-17 total*	HAMD-21 total
Day -6	2	24	25
Day 0	2	27	30
Day 7	3	36	41

	Raskin Depression Scale		
Day of visit	Verbal report	Behavior	Secondary symptoms of depression
Day -6	5	5	4
Day 0	5	4	4
Day 7	5	5	4

MADRS

Day of MADRS visit	MADRS item 10: suicide	MADRS total*
Day 0	4^	45
Day 7	5	50

^ History of suicidal ideation prior to treatment.

Symptom checklist - 56 Day of visit	Item 35 - 'Thoughts of ending your life'
Day 0	2
Day 7	3

Protocol Id:	002
Subject Number:	004.089
Treatment Group:	Paxil
Adverse event Preferred term(s):	Overdose
Adverse event Verbatim term(s):	Overdose

Clinical Study Report Summary for PAR 02-04-089:

The patient is a 19-year-old white female who entered the study on 03/09/87 with a diagnosis of major depression, recurrent (DSM-III: 296.3). The patient reported a history of severe menstrual cramps, but was otherwise in good health. Concomitant medication used during the study was Tylenol (acetaminophen) 1000 mg on 03/18/97 for a headache.

Screening laboratory values revealed no significant abnormalities. ECG was normal.

On 03/16/87, the patient was begun on paroxetine 20 mg/day (days 1-8); decreased to 10 mg/day (days 9-16) because of adverse experiences; returned to 20 mg/day (days 17-40). She was on medication for 40 days. Adverse clinical experiences reported during the study were moderate dizziness and lack of energy (probably drug-related), and moderate headaches (possibly drug-related). There were no adverse laboratory experiences reported.

On 04/24/87, the patient had a fight with her spouse and in anger consumed 150 mg to 200 mg of paroxetine. The patient had no serious adverse effects and did not require hospitalization. She was able to continue on her job immediately after the overdose.

The patient was originally dropped from the study for a non-drug-related reason; however, her overdose was entered in the case report form as an adverse clinical experience and as the primary reason for termination. Because of this, the sponsor recoded her dropout reason as a drug-related experience.

Follow-up was attempted for final safety studies and physical exams. In phone contact of 05/05/87 the patient reported that she was doing well. She was then lost to follow-up. She failed to keep two scheduled appointments. The patient was contacted by telephone on 11/02/87; at that time the patient reported good general health.

Additional Information:

This 19-year-old female was enrolled in a double-blind clinical study for the treatment of major depressive disorder. According to DSM-III criteria, no personality or developmental disorder was noted (Axis II: V71.09), nor were any psychosocial stressors

identified (Axis IV), but a history of poor adaptive function over the past year was assessed (Axis V). No psychiatric history in any lineal or conjugal family members was noted.

At screening the subject's height and weight were reported as 65.25 inches and 199.25 lbs, respectively.

No prior or current treatment for depression was reported. The episode of major depression for which the subject was enrolled in the study was of more than one year in duration and was characterized as a recurrence of a previous condition. The onset of the current episode of depression was very gradual (one or more years), and no precipitating external event was identified. The subject had not received any psychiatric treatment for the current episode or prior to this episode.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were 2 and 1, respectively, and the total HAMD-17 score at randomization was 23. Additionally, the HAMD-21 score at randomization was 26. The randomization score on the MADRS item #10, reflecting suicidality, was 2, and total MADRS score at randomization was 30. The subject's Raskin Depression Score values were all four (4-considerably) in the areas of verbal report, behaviour, and secondary symptoms of depression at screening and randomization. On the 56 point Symptom Checklist item # 35, 'thoughts of ending your life,' the screening and randomization scores were both 1 (not at all).

Three days after the first dose of study medication, Paxil at a dose of 20 mg/day, the subject experienced headache, dizziness, and no energy. Her dose of study medication was subsequently reduced to Paxil 10 mg/day due to the events of dizziness and no energy, which were both assessed as moderate in intensity and probably related to study medication by the investigator. The headache was assessed as moderate in intensity and possibly related to study medication. The subject received treatment with acetaminophen, and the headache was considered resolved the same day. The dizziness and lack of energy were ongoing.

Twelve days later, while receiving Paxil at a dose of 10 mg/day, she experienced another headache that was also assessed as moderate in intensity and possibly related to study medication. She continued on study medication and the event resolved five days later. On Day 18 of study treatment the subject's dose of Paxil was advanced to a dose of 20 mg/day due to lack of efficacy.

Forty days after the first dose of study medication and while receiving Paxil at a dose of 20 mg/day, the subject contacted the investigational site to report that she had had a fight with her husband and subsequently ingested 15-20 study drug capsules in anger. She reported that she was at her job and was not experiencing any adverse effects. It was noted that the investigator did not think this was a suicide attempt. The study blind was broken and the investigator was instructed to discontinue the subject from the study

immediately. A follow-up appointment was scheduled with the subject for four days later, but the appointment was not kept. The subject was contacted at this time and another appointment was scheduled for a week later. At the time of scheduling, the subject reported that she was feeling fine and was reluctant to set-up the appointment, but she agreed to return to the investigational site to have all of her follow-up tests and return any unused medication. She did not keep this appointment and was considered lost to follow-up.

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD visit		HAMD item 3: suicide	HAMD-17 total	HAMD-21 total
Day	-6	2	22	24
Day	1	1	23	26
Day	9	0	10	13
Day	17	0	10	12
Day	23	0	10	12
Day	31	0	10	12

Raskin Depression Scale

Day of visit		Verbal report	Behaviour	Seconday symptoms of depression
Day	-6	4	4	4
Day	1	4	4	4
Day	9	2	3	3
Day	17	2	3	2
Day	23	2	2	2
Day	31	2	2	2

Symptom checklist - 56

Day of visit		Item 35 - 'Thoughts of ending your life'
Day	1	1
Day	9	1
Day	17	1
Day	23	1
Day	31	1

MADRS

Day of MADRS visit		MADRS item 10: suicide	MADRS total*
Day	1	2	30
Day	9	1	16
Day	17	0	9
Day	23	0	10
Day	31	0	11

Protocol Id:	09_01A
Subject Number:	006
Treatment Group:	Paxil
Adverse event Preferred term(s):	Emotional Lability
Adverse event Verbatim term(s):	Suicidal Threats

This 35-year-old male was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression, recurrent: moderate (DSM-III 296.32).

This subject also reported concurrent clinical conditions of major affective disorder, unipolar and a possible ulcer. Additionally, the patient had a family history of non-psychotic psychiatric disturbance involving his mother and imprisonment of a sibling.

The subject had no reported previous treatment for depression. The episode of major depression for which the subject was enrolled in the study was of six to twelve months duration, and concurrent medications administered at the time of study entry were reported as cimetidine. The onset of the current depressive episode was described as gradual (one or more months) and was best characterized as a recurrence of a similar previous condition. A precipitating external event was definitely present. At the time of study recruitment it was also noted that in the past three years the subject was employed full-time but was experiencing some decline in work performance and some decline in competence with regard to social functioning.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 1, and the total HAMD-17 and HAMD-21 scores at randomization were 31 and 33, respectively. The randomization score on MADRS item #10, reflecting suicidality, was 2 and the total MADRS score at randomization was 36. Screening and randomization scores for the Raskin Depression Scale on verbal report, behaviour and secondary symptoms of depression were all 3 (moderate) at screening and all 4 (considerable) at randomization. On the Symptom Checklist-56, item #35, the subject's score at randomization was 1, (no thoughts of ending your life).

On day one of treatment with study medication (Paxil), the subject experienced generalized depression that was considered severe in intensity and unrelated to study medication by the investigator. Subsequently that same day, the subject expressed suicidal threats, which were considered moderate in intensity and unrelated to study medication by the investigator. At the time of the adverse events, the subject was receiving Paxil at a dose of 10mg/day. There were no reported concomitant medications being taken at the time of the events as cimetidine had been stopped two days earlier. At the time of the events it was also noted that the subject was experiencing difficulties with a precipitating external event. He had moderate psychosocial stressors noted prior to and upon multiaxial evaluation.

Treatment with study medication was discontinued the same day as the adverse events described previously, and the subject was terminated prematurely from the study. The adverse events remained unresolved at the time of study termination.

The subject's EKG record noted that he did not undergo a final EKG exam due to hospitalization (dates not provided).

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD visit		HAMD item 3: suicide	HAMD-17 total*	HAMD-21 total
Day	-6	1	30	32
Day	0	1	31	33
Day	2	4	39	43

Raskin Depression Scale

Day of visit		Verbal report	Behaviour	Seconday symptoms of depression
Day	-6	3	3	3
Day	0	4	4	4
Day	2	5	4	4

MADRS

Day of MADRS visit		MADRS item 10: suicide	MADRS total*
Day	0	2	36
Day	2	5	42

Symptom checklist - 56

Day of visit		Item 35 - 'Thoughts of ending your life'
Day	0	1

Protocol Id:	09_01E
Subject Number:	260
Treatment Group:	Paxil
Adverse event Preferred term(s):	Emotional Lability
Adverse event Verbatim term(s):	Suicide Attempt

This 51-year-old female was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression, recurrent: severe (DSM-III 303.91).

This subject also reported concurrent clinical conditions of alcohol dependence, mixed personality disorder, and Meniere's Syndrome. Additionally, she had a history of kidney infections, abdominal hysterectomy for fibroids, head injury, nasal surgery, and left ear surgery. The subject's family psychiatric history included children with major affective disturbance, children hospitalized for psychiatric disturbance, a spouse who engaged in excessive use of alcohol and was physically abusive toward her, and imprisonment of her spouse. The physical beatings she received from her spouse resulted in fractures of the face, requiring five nasal surgeries.

The subject had previously received outpatient treatment for three months and hospitalization for one week for depression and first received psychiatric treatment at the age of 43. The episode of major depression for which the subject was enrolled in the study was of more than one year duration, and there were no concurrent medications administered at the time of study entry. The onset of the present episode of depression was best characterized as an exacerbation of a chronic condition with a very gradual onset (one or more years). A precipitating external event was definitely present, and the subject had severe psychosocial stressors noted on multi-axial evaluation. At the time of study recruitment it was noted that the subject was employed full-time and was divorced.

The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2 and the total HAMD-17 and HAMD-21 score at randomization was 21 and 22, respectively. On the Raskin Depression Scale for verbal report, behaviour and secondary symptoms of depression, the screening and randomization scores were 4 (considerable) and 4, 4 and 3 (moderate) and 2 (somewhat) and 3, respectively. The randomization scores on the MADRS item #10, reflecting suicidality, was 2, and the total MADRS score at randomization was 20. On the Symptom Checklist-56, item #35 'thoughts of ending your life', the subject scored 2 (a little) at randomization.

The subject received 41 days of study treatment with Paxil at a dose of 30 mg/day. On day 42 of study treatment the subject was admitted to a detoxification unit for alcohol abuse. During this admission all laboratory studies were within normal limits but the subject's blood alcohol level was 0.182. She did not require treatment with chlorodiazepoxide (Librium).

Forty-four days after the first dose of study medication, the subject attempted suicide. The event was assessed as severe in intensity and possibly related to study medication by the investigator. On the same day, the subject was noted to have an ear infection and to be engaging in alcohol abuse. The alcohol abuse was also assessed as severe in intensity and possibly related to study medication, and the ear infection was considered moderate in intensity and unrelated to study medication. At the time of the adverse events, the subject was not receiving study medication as she had been hospitalized from days 42-50 of study treatment for detoxification. There were no reported concomitant medications being taken at the time of the adverse events.

Hospital records available from an admission for detoxification during the study noted that the subject felt that the study medication helped, but she continued to be overwhelmed by the situational distress in her life.

Treatment with study medication was interrupted during hospitalization and the subject was treated with amoxicillin and erythromycin for the ear infection. It was reported that the subject attempted suicide via an overdose with alcohol and amoxicillin. The final diagnoses made during her hospitalization were: acute chronic alcoholism, hearing loss, and depression. The reported events of suicide attempt, alcohol abuse, and ear infection were all considered resolved one day after onset. Fifty one days after the first dose of study drug and following hospitalization, the subject resumed treatment with Paxil at a dose of 30mg/day.

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD visit		HAMD item 3: suicide	HAMD-17 total	HAMD-21 total
Day	-8	2	19	20
Day	0	2	21	22
Day	7	0	8	9
Day	14	0	4	4
Day	21	0	7	8
Day	27	0	4	4
Day	41	0	5	5
Day	63	2	11	12

Raskin Depression Scale

Day of visit		Verbal report	Behaviour	Seconday symptoms of depression
Day	-8	4	4	2
Day	0	4	3	3
Day	7	3	3	1
Day	14	1	2	1
Day	21	2	3	1
Day	27	1	2	1
Day	41	1	2	1
Day	63	2	2	2

MADRS

Day of MADRS visit	MADRS item 10: suicide	MADRS total*
Day 0	2	20
Day 7	0	11
Day 14	0	5
Day 21	0	8
Day 27	0	6
Day 41	0	3
Day 63	2	20

Symptom checklist - 56

Day of visit	Item 35 - 'Thoughts of ending your life'
Day 0	2
Day 7	2
Day 14	1
Day 21	1
Day 27	2
Day 41	2
Day 63	2

Protocol Id:	279
Subject Number:	1.12.037
Treatment Group:	PAROXETINE
Adverse event Preferred term(s):	Trauma
Adverse event Verbatim term(s):	Patient Stabbed His Abdomen

This 20 year old male patient had a history of alcohol intolerance. He did not have any concurrent illnesses or medication during the study. The patient made an attempt to stab himself in the abdomen on day 49 which resulted in minor injury only. This was not considered a true suicide attempt by the investigator and no action was taken. He had one double flagged laboratory value: a transient increase in blood urea level, rising from 4.5 mol/l at baseline to 7.6 mol/l at week 1, which returned to and stayed within the normal range for the remainder of the study. Hence it was not considered to be clinically significant. There were no other double flagged laboratory values or vital signs.

Additional Information:

This 20-year-old male was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression according to DSM-III criteria.

This subject reported no concurrent clinical conditions; however, the subject's family medical history included a father who has suffered from manic depressive psychosis, paternal grandmother with possible depressive illness, and mother and maternal grandmother who were both treated for depressive illness. The subject reported weekend alcohol intake, use of LSD on two occasions, as well as use of marijuana.

The subject had previously received treatment for depression with lorazepam for three weeks and Prothiaden for six weeks and had a poor response to treatment with both of these medications. The episode of major depression for which the subject was enrolled in the study was of 14 days duration, and there were no concurrent medications administered at the time of study entry. The subject's current episode of depression included symptoms of irrational fears, self-pity, and moderate loss of pleasure. It was also noted that the subject was unemployed at the time of study entry.

The subject had a history of suicidal ideation prior to treatment. The screening score on the HAMD item #3, reflecting suicidality, was 3, and the total HAMD-17 and HAMD-21 scores at screening were 20 and 21, respectively. No HAMD evaluation was performed at the time of treatment randomization.

Forty-nine days after the first dose of study medication, Paxil, the subject stabbed himself in the abdomen. At the time of the adverse event, the subject was receiving Paxil at a dose of 30mg/day. There were no reported concomitant medications being administered

at the time of the event. It was also noted that, at the time of the event, the subject lost his flatmate who had also stolen his girlfriend, and his puppy had died the day prior to the event.

Treatment with study medication was discontinued and the subject was withdrawn from the study.

During the course of the double-blind phase of the study, the subject also experienced alcohol intolerance and epigastric pain eight and 15 days, respectively, after the first dose of study medication. Both of these events were assessed as mild in intensity and related to study medication by the investigator. The alcohol intolerance lasted for greater than two weeks, and the epigastric pain lasted over a period of two weeks.

One day after the last dose of study medication and 50 days after commencing study treatment, the subject experienced lethargy, constipation, diarrhea and sweating. The sweating was assessed as being related to study medication. The outcome of these events was unknown.

Observed efficacy scores by study week for the subject are listed below.

	HAMD		
Day of HAMD Visit	HAMD item 3: suicide	HAMD-17 total	HAMD-21 total
-6	3^	20	21
8	0	19	20
15	0	14	16
36	0	12	13
50	2	15	18
64	3	18	21
78	2	10	12

^History of suicidal ideation prior to treatment

Protocol Id:	115
Subject Number:	003.0062
Treatment Group:	Paxil
Adverse event Preferred term(s):	Emotional Lability
Adverse event Verbatim term(s):	Suicide attempt

This 29-year-old female was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression, single episode (DSM-IIIR 296.22).

No concurrent clinical conditions were reported at the time of study entry; however, the patient reported a previous history of allergic reaction (nausea) to meperidine, kidney removal, and bladder infections. The subject had previously received treatment with amitriptyline, nortriptyline (for > 8 weeks), and temazepam (for 0-2 weeks) for this episode of depression; with a good treatment response noted for both amitriptyline and nortriptyline. The episode of major depression for which the subject was enrolled in the study was of five years duration.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2. The total HAMD-17 score at randomization was 24 and the total HAMD-21 score was 27.

Fifty-five days after the first dose of study medication (Paxil), the subject attempted suicide. The event was assessed by the investigator as moderate in intensity and unrelated to the use of study medication. The subject allegedly ingested approximately 20 chloral hydrate 500mg capsules after leaving a suicide note and picture for her daughter. A clinical drug safety note reflecting a discussion between the safety group and investigator reported his assessment of the event as "possibly related to study medication, but probably unrelated (this category can not be captured)." It was also noted that the subject was involved in a pending divorce proceeding. At the time of the event, the subject was receiving Paxil 30mg/day and had been on this dose for approximately one month. There were no reported concomitant medications. She survived the suicide attempt and the event was considered resolved that day. Treatment with study medication was discontinued and the subject was withdrawn from the study.

The subject also experienced increased insomnia which commenced 14 days after the start of study medication while the subject was receiving 20mg dose of study medication. The investigator assessed the event as mild in intensity and probably unrelated to study medication. Corrective therapy was prescribed and the event was noted as unresolved at the time of study discontinuation.

During the course of the double-blind study, the subject also reported the following non-serious adverse events: sinus congestion (beginning three days before starting study medication) and indigestion (beginning four days after starting study medication). The subject was treated with Sinutab for 11 days following randomization, and the event was assessed by the investigator as unrelated and resolved during the study. The indigestion resolved in four days, with corrective therapy (Tums), and was considered probably related by the investigator.

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD Visit	HAMD item 3: suicide	HAMD-17 total*	HAMD-21 total*
-7	2	28	32
0	2	24	27
7	2	29	30
14	0	16	17
21	0	21	23
29	2	18	19
42	0	10	11

Raskin Depression Scale

Day of Visit*	Verbal Report	Behavior	Secondary Symptoms Depression
-7	5	3	5
0	4	3	4
7	5	4	4
14	2	2	3
21	2	1	4
29	2	1	4
42	2	2	3

Symptom Checklist SCL-90

Day of Visit	Thoughts of Ending Your Life	Thoughts of Death or Dying
0	1	2
7	1	1
14	0	0
21	0	0
29	0	0
42	0	0

Protocol Id:	29060 128
Subject Number:	128.001.0759
Treatment Group:	Paxil
Case ID Number:	B0152218A
Adverse event Preferred term(s):	Emotional Lability
Adverse event Verbatim term(s):	Suicide Attempt

Medical Monitor Comments: 23-Aug-1991 (Dr. Arias) This thirty year old male patient, was enrolled in study PAR128 on 16-Jul-1991. On 21-Aug-1991, the patient decided to discontinue the study coded medication. On this same date, while at his girlfriend's apartment having "some drinks," he was involved in a serious argument with her. The police were called in, and the patient taken into custody. At the police station he attempted suicide by hanging with his belt. The clinical investigator requested the immediate opening of this patient's coded study medication. The code was opened at SKB, the patient was receiving PAROXETINE study medication. Following the suicide attempt, the patient was hospitalized at a State Hospital. The investigator categorized this patient's suicide attempt as not related to PAROXETINE. . WORLDWIDE CLINICAL SAFETY - 26-AUG-1991: NON-EXPEDITE PER CLINICAL SAFETY PHYSICIAN. . ae coordinator comments: 27-Aug-1991 (cc) per WWCS mail request the following change has been made to the "m" page: - study med. = PAROXETINE . WORLDWIDE CLINICAL SAFETY - 27-AUG-91: CASE MAINTENANCE NOTED; FILED. . ae coordinator comments: 29-Oct-1991 (cc) per CRF review the following changes were made to the "m" page: - birth date = 07-Nov-1960 - weight = 84.5 Kg. . CLIN. SAFETY: 29-OCT-1991: CASE MAINTENANCE NOTED; FILED. F/U Clinical Safety Analyst (sc) Narrative Per CRF Review: 21-Nov-1991 Probably unrelated on CRF = not related in WWCS data base. ae coordinator comments: 22-Nov-1991 (cc) per CRF review the following changes were made to the "m" page: - severity = mod - complete = y - outcome = rec - clear date = 21-Aug-1991 - rx start = 17-Jul-1991 - rx stop = 20-Aug-1991 (est) - abate = y - reintro. = n . CLINICAL SAFETY - 25-NOV-1991 CASE UPDATE REVIEWED; CIRCULATED. F/U Clinical Safety Analyst (mw) Narrative: 16-Dec-1991 Per CRF: There are three documented ae's that caused study drug withdrawl: - argumentative - 21-Aug to 22-Aug-91/severe/unrelated. - increased hopelessness - 20-Aug to 23-Aug-1991/severe/unrelated. - anxiety - 21-Aug to 25-Aug-91/severe/probably related. Both increased hopelessness and anxiety were noted as present before or at baseline. ae coordinator comments: 16-Dec-1991 (dg) per CRF review: est was deleted from rx end date. . CLINICAL SAFETY: 16-DEC-1991 CASE NOTE REVIEWED; CIRCULATED. ae coordinator comments: 10-Jan-1992 (cc) in response to WWCS mail request relevant medical history has been added to the "h" page. . CLINICAL SAFETY - 10-JAN-1992: CASE MAINTENANCE NOTED; FILED.

Additional Information:

This 30-year-old male was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression (DSM-IIIR: 296.22) and personality disorder, not otherwise specified (DSM-IIIR 301.90).

This subject reported no concurrent clinical conditions. Additionally, the patient had a previous history of an unspecified personality disorder.

The subject had previously received treatment with trazodone, lithium carbonate, isocarboxazid, desipramine, nortriptyline, fluoxetine, sibutramine, and Wellbutrin for depression and reported a poor to fair response to each of these medications. The episode of major depression for which the subject was enrolled in the study was of more than one year in duration with the first appearance of symptoms 10 years previously. No concurrent medications were reported as being administered at the time of study entry. At the time of study entry it was also noted that the subject had stopped working because of his present illness.

The subject had no documented history of suicide attempt or self-harm at the time of study entry, but suicidal thoughts were identified at baseline in the context of the Symptom Checklist- 90. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2, and the total HAMD-17 and HAMD-21 scores at randomization were 26 and 29, respectively. The scores at the baseline visit on the Symptom Checklist- 90 were both 3 (quite a bit) for "thoughts of ending your life" and "thoughts of death or dying."

Thirty-six days after the first dose of study medication (Paxil) that the subject discontinued study medication and withdrew himself from the study. On the same date, the subject was at his girlfriend's apartment having "some drinks" and was subsequently involved in a serious argument with her. The police were notified and the subject was taken into custody. At the police station the subject attempted suicide by hanging with his belt. The investigator requested immediate breaking of the study blind. The investigator subsequently assessed the event as moderate in intensity and probably unrelated to study medication. Corrective treatment included hospitalization, and the event was considered resolved within one day.

Prior to discontinuing study treatment the subject was receiving Paxil at a dose of 50mg/day and no reported concomitant medications were being taken at the time of the adverse event.

The subject also experienced agitation (two episodes), increased hopelessness, anxiety, and being argumentative during the course of the study. The agitation commenced two days and 21days after the start of study medication while the subject was receiving Paxil 20mg/day and Paxil 30mg/day, respectively. The investigator assessed the events as moderate in intensity and probably unrelated to study medication. The agitation resolved 18 days after the first episode and 19 days after the second episode. The increased hopelessness occurred 35 days after the start of study medication while the subject was

receiving Paxil 50mg/day. The investigator assessed the event as severe in intensity and unrelated to study medication. Study medication was discontinued on this date, and the event resolved after three days. The events of anxiety and being argumentative commenced one day after the subject discontinued study medication. The investigator assessed both of these events as severe in intensity and felt that the argumentativeness was unrelated to study medication and the anxiety was probably unrelated to study medication. The anxiety resolved after four days, and the argumentativeness resolved after one day.

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD Visit	HAMD item 3: suicide	HAMD-17 total	HAMD-21 total
-7	2	23	26
0	2	26	29
8	2	25	28
14	1	21	24
21	1	18	21
28	1	20	23
37	4	34	38

Raskin Depression Scale

Day of Visit*	Verbal Report	Behavior	Secondary Symptoms of Depression
-7	4	3	3
0	4	3	3
8	3	3	3
14	3	3	3
21	3	3	3
28	3	3	3

Symptom Checklist SCL-90

Day of Visit	Thoughts of Ending Your Life	Thoughts of Death or Dying
0	3	3
8	1	2
14	1	1
21	1	2
28	1	2

Protocol Id:	251
Subject Number:	002.0285
Treatment Group:	Paxil
Adverse event Preferred term(s):	Emotional lability
Adverse event Verbatim term(s):	Suicide gesture

This 30-year-old male was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the patient had a diagnosis of major depression, single chronic episode, moderate (DSM 296.2).

This subject also reported concurrent clinical conditions of dependent personality (DSM 301.60), daily headaches, exogenous obesity, environmental allergies and allergy to penicillin.

The subject had no reported previous treatment for depression. The episode of major depression for which the subject was enrolled in the study was of 14 years duration and paracetamol was reported as a concurrent medication at the time of study entry. It was also noted that the subject was unemployed at the time of study recruitment.

The subject had no documented history of suicide attempt or self-harm at the time of study entry, but he did experience suicidal thoughts. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2, and the total HAMD-17 and HAMD-21 scores at Randomization were 27 and 32, respectively. For the Symptom Checklist-90, item #15 (thoughts of ending your life) the subject's score at screening and randomization was 3 (quite a bit) and 2 (moderately), respectively.

Twenty-five days after the first dose of study medication (Paxil), the subject demonstrated suicidal gestures. The subject took two diphenhydramine 25mg capsules, eight over the counter diphenhydramine 25mg capsules and anti-anxiety medications which he could not identify(small blue and white capsules) to help him sleep, not caring "whether or not he woke up." Concomitant medication records later documented the subject's use of diphenhydramine (a total of 300 mg) and hydroxyzine (100 mg) related to the suicide gesture. He awoke the next morning feeling dizzy and groggy but with no problems or sequelae. The subject was not suicidal when seen by the study coordinator three days after the event. The coordinator stated that the event was probably due to psychosocial stressors and not related to study medication. The event was considered to be of mild intensity and probably unrelated to study drug by the investigator. The event was considered resolved within 18 hours of onset.

At the time of the adverse event, the subject was receiving Paxil at a dose of 30 mg/day. Reported concomitant medications being taken at the time of the adverse event included paracetamol and vitamins, of which the vitamins had been started after treatment with study medication had been initiated.

Treatment with study medication was discontinued three days after the onset of the adverse event, and the subject was terminated from the study prior to completion due to lack of efficacy as well as the adverse event.

Observed efficacy scores by study week for the subject are listed below.

HAMD

Day of HAMD Visit	HAMD item 3: suicide	HAMD-17 total	HAMD-21 total
-7	2	23	28
0	2	27	32
7	0	18	21
18	0	17	21
28	3	25	30

Symptom Checklist SCL-90

Day of Visit	Thoughts of Ending Your Life	Thoughts of Death or Dying
-7	3	3
0	2	2
7	0	0
18	2	2
28	4	3

Protocol Id:	29060 448
Investigator Number:	010
Patient Number:	00044
Treatment Number:	
Case Id:	A0251781A
Suspect Drugs:	Paxil IR
Serious Events Preferred terms:	Emotional Lability
Serious Events Verbatim terms:	Suicide Attempt Overdose

Patient was randomized to a double-blind placebo controlled depression/affective disorders study Protocol 448. On 06 December 1996 the patient overdosed on Flexeril (cyclobenzaprine), Valium (diazepam), Anaprox (naproxen sodium), and possibly study medication. The investigator indicated that the event was of severe intensity. The patient was hospitalized for approximately 48 hours and was doing well. She was last seen at the study site on 02 December 1996 where there was a mild improvement in her mood. On 18 December 1996 she came in for visit #7 and reported that she had taken a drug overdose (06 December 1996) after an argument with her boyfriend. Study medication was discontinued on 28 December 1996. The patient was terminated from the study and entered the taper phase. The event resolved. Investigator attribution: not related to study medication. Investigator Assessment: the experience could be associated with the primary condition. Further information will be forthcoming. OVERDOSE

Additional Information:

At the time of study entry, this 25 year old female had a diagnosis of major depressive disorder according to DSM-IV criteria. The subject also reported the concurrent clinical condition of irritable bowel syndrome. The subject had previously received treatment with fluoxetine and sertraline, and it was reported that she had a fair response to both medications. The subject had received trazodone for treatment of the current episode of major depression to which she had a fair response. The episode of major depression for which the subject was enrolled in the study was of one year duration, and at the time of study entry she received dofamium concurrently.

She had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were 1 and 2, respectively, and the total HAMD score at randomization was 27.

Forty-nine days after the first dose of study medication, the subject attempted suicide by overdose. At the time of the adverse event, the subject was receiving Paxil IR at a dose of 40mg/day.

During the course of the double-blind phase of the study the subject also experienced dizziness, nausea, dilated pupils (two days after first dose of investigational product),

backache, diarrhea (three days after first dose of study medication), sinus infection (17 days after first dose of study medication), bloody nose and cold symptoms (19 days after first dose of study medication). All events resolved during the course of the study.

Observed efficacy scores by study week for the subject are listed below.

		HAMD		
Date of HAMD visit	Day of HAMD visit		HAMD item 3: suicide	HAMD-17 total
11OCT1996	Day	-7	1	23
17OCT1996	Day	-1	2	27
25OCT1996	Day	7	2	27
04NOV1996	Day	17	2	27
11NOV1996	Day	24	1	21
18NOV1996	Day	31	1	16
02DEC1996	Day	45	1	14
19DEC1996	Day	62	4	24

Protocol Id:	29060 448
Investigator Number:	019
Patient Number:	00391
Treatment Number:	
Case Id:	A0254833A
Suspect Drugs:	Paxil IR
Serious Events Preferred terms:	Emotional Lability
Serious Events Verbatim terms:	Suicide Attempt Via Overdose

Patient entered double-blind, placebo-controlled study on 20-Dec-96. Patient was seen in week 3 visit on 21-Jan-97 admitting to feeling that "life was empty," but denied thoughts of death or suicide. Patient continued on level 3 of study medication dosing. On 24-Jan-97, the patient's husband reported that the patient was hospitalized subsequent to an overdose the previous night following a fight between the patient and her husband (23-Jan-97) with chloral hydrate 500 mg (possible 9 {tablets}), and Tylenol with codeine (number of tablets and dosage unknown). The patient did not take an overdose of the study medication. The investigator considered the event severe in intensity, life-threatening, unrelated to the study medication, and attributable to the patient's primary condition. The patient was discharged from the hospital on 24-Jan-97 and study medication was stopped on 23-Jan-1997, after 24 days of therapy. Medical records indicated that the patient was dysphoric and patient reported "being tired of feeling down," but denied active suicidal ideation. Following discussion of patient's goals, it was decided to terminate the patient from the protocol and to initiate treatment with Serzone 50 mg bid starting the next day (25-Jan-97). Patient was instructed to increase Serzone dosing to 100 mg bid on 28-Jan-97, and it was noted that she was not suicidal after 1 week. OVERDOSE

Additional Information:

This 27-year-old female was enrolled in a double-blind clinical study for the treatment of major depressive disorder. At the time of study entry, the subject had a diagnosis of major depressive disorder according to DSM-IV criteria. Thie subject reported concurrent clinical conditions of frequent headaches and hypoglycaemia. Additionally, the subject had a previous history of miscarriages and a motor vehicle accident.

The subject had previously received treatment for the current episode of depression with an unknown antidepressant and nefazodone. The subject had a fair response to the unknown antidepressant and a good response to the nefazodone. The episode of major depression for which the subject was enrolled in the study was of six years and eleven months duration.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the HAMD item #3, reflecting suicidality, were both 2, and the total HAMD score at randomization was 22.

It was noted that one day after the first dose of study medication, the subject experienced insomnia, which was assessed as moderate in intensity and probably related to study medication. The subject was taking Paxil IR at a dose of 20mg/day at the time of the event. The insomnia remained unresolved at the time of discontinuation of study medication.

On day eleven of study treatment the subject was up-titrated to Paxil IR at a dose of 30 mg/day. Five days later (16 days after the first dose of study medication) she was subsequently advanced to Paxil IR at a dose of 40 mg/day.

Twenty days after the first dose of study medication medication she experienced the non-serious events of chills, diarrhea, fever, and headache. All of the events resolved within one day and she continued on study treatment.

Twenty-four days after the first dose of study medication, the subject attempted suicide by overdose while receiving study treatment with Paxil IR at a dose of 40mg/day. Reported concomitant medications being taken at the time of the suicide attempt were ibuprofen and Ovcon-50, both of which had been started after starting treatment with study medication.

It was also noted at the time of the subject's early termination visit that she had not been to work in a week because of her depression.

Observed efficacy scores by study week for the subject are listed below.

		HAMD	
Date of HAMD visit	Day of HAMD visit	HAMD item 3: suicide	HAMD-17 total
20DEC1996	Day -10	2	24
30DEC1996	Day 0	2	22
09JAN1997	Day 10	2	24
14JAN1997	Day 15	2	20
21JAN1997	Day 22	1	17

Protocol Id:	29060 449
Investigator Number:	021
Patient Number:	00788
Treatment Number:	000777
Case Id:	A0258041A
Suspect Drugs:	Paxil IR
Serious Events Preferred terms:	Emotional Lability
Serious Events Verbatim terms:	Drug Overdose

This patient with major depression was enrolled in study 29060/449, a double-blind, placebo controlled trial to evaluate the clinical effects of immediate release paroxetine and modified release paroxetine in the treatment of major depression. She began blinded study medication on 10-Jan-1997. On 20-Jan-1997 the patient began to experience mild fatigue, which is considered by investigator as ongoing, non-serious and possibly related to study medication. On 16-Mar-1997 after having a fight with her boyfriend, the patient took an overdose of 70 Motrin tablets and eight Robaxacet tablets as a suicide gesture. Gastric lavage with charcoal was performed in the emergency unit at a local hospital. Patient experienced moderate nausea, considered by investigator as a non-serious event unrelated to study medication, for four hours. She was given Gravol 50 mg intravenously for nausea. Patient was then discharged from the hospital. The patient spoke with the investigator by phone on 17-Mar-1997 and stated she was fine. She was to meet with the investigator on 18-Mar-1997. Per case report form, study medication was discontinued on 18-Mar-1997 and Paxil 20 mg daily was initiated on 27-Mar-1997. The investigator reported that the overdose was severe, unrelated to the study medication and could be associated with the patient's primary condition. DRUG OVERDOSE

Additional Information

At the time of study entry, this 18 year old female had a diagnosis of major depression according to DSM-IV criteria. The subject reported a concurrent clinical condition of vaginitis, and she had a previous history of post traumatic stress disorder. The episode of major depression for which the subject was enrolled in the study was of three months duration, and concurrent use of ethinylestradiol/levonorgestrel (Triphasil) was reported at the time of study entry.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on HAMD item #3, reflecting suicidality, were 2 and 1, respectively, and the total HAMD score at randomization was 21.

Fifty-two days after the start of study medication and two weeks before the subject's drug overdose, she experienced a dislocated left shoulder while receiving Paxil IR at a dose of

20 mg/day. The event was considered resolved the next day. The investigator assessed the event as moderate in intensity and unrelated to study medication.

In the setting of the subject's drug overdose (66 days after the start of study medication, at a dose of Paxil IR, 20 mg/day), she also sustained abrasions on the knees and experienced left hand pain and excoriations on the hands. These events subsequently resolved approximately one month following the subject's withdrawal from the study.

Observed efficacy scores by study week for the subject are listed below.

		HAMD		
Date of HAMD visit	Day of HAMD visit		HAMD item 3: suicide	HAMD-17 total*
02JAN1997	Day	-7	2	25
09JAN1997	Day	0	1	21
16JAN1997	Day	7	0	17
23JAN1997	Day	14	2	23
30JAN1997	Day	21	2	23
04FEB1997	Day	26	0	8
20FEB1997	Day	42	1	9
04MAR1997	Day	54	0	0
18MAR1997	Day	68	3	23

Protocol Id:	29060 625
Investigator Number:	500
Patient Number:	02062
Treatment Number:	
Case Id:	A0301493A
Suspect Drugs:	Paxil
Serious Events Preferred terms:	Emotional Lability
Serious Events Verbatim terms:	Tylenol Overdose

Case reference number 1999008231-1 is a clinical trial report from study 29060/625, a double-blind, placebo-controlled multi-centre study to evaluate the efficacy and tolerability of paroxetine in the treatment of post-stroke depression. This case refers to a 50-year-old male (patient identification number 625.500.02062). The patient started the blinded study medication on 09-Feb-99 at a dose of 1 tablet per day. On 24-Mar-99, the dose was increased to 2 tablets per day. The patient's relevant medical history includes post stroke depression. Concomitant medications include Diabinese (chlorpropamide), Norvasc (amlodipine), Bezalip SR (bezafibrate), Avapro (irbesartan), ASA (acetylsalicylic acid), Altace (ramipril), and Risperidone. On 05-Apr-99, the patient overdosed on Tylenol (paracetamol) extra strength by taking 12 to 15 tablets at one time. The event resolved on the 05-Apr-99, he was not admitted to the hospital. The patient discontinued blinded study medication on 06-Apr-1999, and has been switched to open-label paroxetine. The investigator reported this event to be unrelated to treatment with the blinded study medication and associated the overdose to be related to the patient's primary condition. On 26-Apr-1999, the patient again overdosed on Tylenol (paracetamol) extra strength, taking 23 tablets at one time. The event was reported to be resolved later that day. The investigator reported the event to be unrelated to treatment with the blinded study medication, and probably associated with the patient's primary condition. OVERDOSE OVERDOSE

Additional Information:

At the time of study entry, the subject met the diagnostic criteria for a current depressive episode (moderate depressive episode; F32.2) according to ICD-10 diagnostic criteria. The subject also reported concurrent clinical conditions of angina pectoris, diabetes mellitus, hypertension, speech dysfunction, high cholesterol and a non-specific T-wave abnormality. The episode of major depression for which the subject was enrolled in the study was of 91 days duration. Concurrent medications administered at the time of study entry were reported as chlorpropamide, amlodipine, bezafibrate, irbesartan, acetylsalicylic acid, and ramipril.

The subject had a history of suicidal ideation prior to treatment as evidenced by his MADRS item #10 results related to suicidal thoughts. The screening and randomization

scores on MADRS item #10, reflecting suicidality, were 2 and 3 respectively, and the total MADRS score at randomization was 32.

The subject experienced the serious adverse event of Tylenol overdose described above on day 56 of study treatment while receiving Paxil at a dose of 30mg/day.

During the course of the double-blind phase of the study, the subject also experienced biting of the tongue and feeling lightheaded, 53 and 57 days after the first dose of study medication, respectively. Both of these non-serious adverse events were assessed as mild in intensity and unrelated to study medication by the investigator. The events resolved without corrective treatment. At the time of these adverse events, the subject was receiving Paxil at a dose of 30mg/day.

Observed efficacy scores by study week for the subject are listed below.

MADRS

Date (Day)		MADRS Item 10: Suicidal Thoughts	MADRS Total Score
02FEB1999	(Day -6)	2	30
08FEB1999	(Day 0)	3^	32
15FEB1999	(Day 7)	0	12
23FEB1999	(Day 15)	0	11
08MAR1999	(Day 28)	0	14
23MAR1999	(Day 43)	0	9
06APR1999	(Day 57)	4	36

^History of suicidal ideation prior to treatment

Protocol Id:	29060 785
Investigator Number:	720
Patient Number:	00695
Treatment Number:	10309
Case Id:	A0349686A
Suspect Drugs:	Paxil CR
Serious Events Preferred terms:	Abnormal Laboratory Value, Emotional Lability, Emotional Lability
Serious Events Verbatim terms:	Accidental Overdose, Suicidal, Suicide Attempt

Case reference number 2001016626-1 is a clinical trial report from double-blind study 29060/785 for the treatment of major depressive disorder with anxiety. This report refers to a 34-year-old female (patient identification number 785.720.00695). The patient's medical history included bilateral tubal ligation, chronic lower back pain, constipation, facial acne, fever blisters, fungal infection toenail right foot, heartburn, insomnia, intermittent headaches, and intermittent urinary tract infections. The patient had no concomitant medication use. The patient received study medication from 12-Jun-2001 to 09-Jul-2001. On 08-Jul-2001, 26 days after the start of study medication, the patient indicated she may have taken an extra study medication pill by mistake. Upon receiving the study medication bottle back from the patient, it was noted the bottle contained only two capsules instead of three capsules from the original number of ten capsules. The patient was diagnosed with overdose (accidental/ asymptomatic). Treatment with study medication was not stopped due to this event. The event was reported as resolved on 08-Jul-2001. The investigator reported the overdose (accidental/asymptomatic) as not related to treatment with study medication. On 08-Jul-2001, 26 days after the start of treatment with study medication, the patient attempted suicide and it was noted the attempted suicide was not related to the accidental overdose. The patient had suicidal feelings and on 10-Jul-2001, she was hospitalized. The patient was treated with valproate semisodium (Depakote). The patient discharged herself from the hospital on 14-Jul-2001 against medical advice. The investigator reported that the patient's follow-up visit to the clinic on 18-Jul-2001 revealed the patient was doing well. Treatment with study medication was discontinued due to these events. The event of attempted suicide resolved on 08-Jul-2001 and the event of suicidal feelings resolved on 12-Jul-2001. The investigator reported the suicidal attempt and suicidal feelings as life-threatening and not related to treatment with study medication, and probably associated with condition under study. OVERDOSE (ACCIDENTAL/ASYMPTOMATIC)

Additional Information

At the time of study entry, the patient had a diagnosis of major depressive disorder according to DSM-IV criteria. The episode of major depression for which the subject was enrolled in the study was of approximately10 years (3814 days) duration.

The subject had no documented history of suicidal thoughts, suicide attempt or self-harm at the time of study entry. The screening and randomization scores on the MADRS item #10, reflecting suicidality, were both 1, and the total MADRS score at randomization was 30.

Eight days after the first dose of study medication (Paxil CR) and one day after up-titration from Paxil CR 12.5 mg/day to Paxil CR 25 mg/day, the subject experienced moderate dizziness, nausea, decreased appetite, and lack of concentration. All of the events resolved without corrective therapy, and the subject continued on study drug. Sixteen days after the first dose of study medication, the subject experienced moderate fatigue and a mildly increased appetite. Both events resolved and there was no interruption in study treatment.

Twenty-two days after the first dose of study medication (Paxil CR, 25 mg/day) and five days before the serious adverse event (SAE) described above (Accidental Overdose and Suicide Attempt), the subject experienced a severely decreased appetite that resolved over a period of eight days. On the same day she also experienced a moderate panicky feeling. The panicky feeling was evaluated as probably unrelated to study medication and resolved after 13 days without corrective therapy. At the time of these adverse events and the SAE, the subject was receiving Paxil CR at a dose of 25 mg/day.

Observed efficacy scores by study week for the subject are listed below.

Date (Day)		MADRS Item 10: Suicidal Thoughts	MADRS Total Score
01JUN2001	(Day -10)	1	28
11JUN2001	(Day 0)	1	30
18JUN2001	(Day 7)	1	26
26JUN2001	(Day 15)	1	17
02JUL2001	(Day 21)	1	15
10JUL2001	(Day 29)	5	32