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Proposal details

Title: Study 329 paroxetine
Status: Proposal Answered
Submitted: 28 Oct 2013

This proposal has been submitted. You may not change anything that has been submitted. However you may be asked to provide additional information. This can be provided using the "Provide requested information" and "Attachments" tabs below.

Summary | Provide requested information | Attachments | Email notifications

Summary

Reference Name
Study 329 paroxetine

Reference Number
669

Proposal Review Outcome

Required fields are marked with an *

*Have you received an answer to a previous enquiry related to this research proposal?
Yes
Please provide the enquiry Reference Name and Number
638 Study 329 paroxetine
*Is this research proposal a re-submission of a previous research proposal that has been reviewed by the Independent Review Panel?
No

Following approval, access is provided after we receive a signed Data Sharing Agreement. This includes requirements for the research team to:

a. Only use the data for the agreed research purpose and not download or transfer the data for future use.
b. Protect the privacy and confidentiality of research participants; the researchers must not attempt to establish the individual identities of research participants.
c. Obtain any regulatory or ethics approvals necessary to conduct the analysis.
d. Inform us and regulatory authorities of any safety concerns as soon as they are identified.
e. Post a summary of the analysis plan and summary results on internet registers and websites and seek publication of the research in a peer reviewed journal.
f. Include in the publication a description of the strengths and weaknesses of the analysis.
g. Provide other researchers with additional details of the analysis on request.
h. Provide us with an advance copy of any public disclosure of the results, including a copy of the manuscript at the time of submission to a peer reviewed journl. Also provide us with the citation after publication.
i. Allow us to use any invention coming out of the research that would impact our ability to commercialise the product used in the analysis and any related product. Such use will be free of charge and throughout the world. If we request additional rights, you agree to negotiate in good faith with us. This does not prevent you from offering rights to another party in addition to us. However, if you do, then you agree to give us first refusal on the same terms before you can conclude those terms with the third party.
j. Confirm that you do not have, and do not plan to have, any other agreements which would prevent you from complying with "i" above.
k. Meet any additional requirements identified by the Independent Review Panel.

The Data Sharing Agreement template is provided here.
*I have read and understood these requirements. Where relevant I have provided the Data Sharing Agreement template to relevant legal staff at my institution.

*I have read and accept the terms of GSK's Privacy Website Statement.

*By completing a submission, you accept that after GSK receives a signed Data Sharing Agreement, GSK may publish the name and affiliation of the lead researcher, the title of the proposed research, the requested studies, lay summary, funding source and any potential conflicts of interest that are provided.

Research Proposal Format
Please complete this form in English.

- SECTION A : Research Plan
- SECTION B : Information about the Research Team
- SECTION C : Funding of the Proposed Research
- SECTION D : Potential Conflicts of Interest
- SECTION E : Other Information

If you already have a protocol or analysis plan for the research, please "cut" and "paste" information from that document to complete this form.

SECTION A: RESEARCH PLAN

***A.1 Title of the Proposed Research**

Limited to 200 characters.
A multi-center, double-blind, placebo controlled study of paroxetine and imipramine in adolescents with unipolar major depression - efficacy and adverse outcomes.

***A.2 Lay Summary**

Please provide a plain English summary of the proposed research suitable for a general or lay audience, explaining:

- The background to the research
- How the research will add to medical science or improve patient care
- The aims and objectives of the research
- How the research will be conducted
- How the findings will be interpreted and communicated

Limited to 3,000 characters.
Study 329 investigated the effectiveness of the antidepressant paroxetine (Paxil) in the treatment of adolescent depression. The published report, an article in the Journal of the American Academy of Child and Adolescent Psychiatry, concluded that Paxil was safe and effective. That publication was widely publicised and has contributed to increased rates of prescribing of paroxetine to children and adolescents. However, since shortly after the publication of the study, there have been concerns about the way in which the study was analysed and reported.
Our proposed research project is to re-analyse the data from the study (at the individual level) and report all findings objectively. This is part of an international movement to improve the integrity of medical trials. The findings will be submitted for publication in the BMJ. If we honestly and accurately re-analyse and republish the findings, we will enable doctors to make more informed prescribing decisions, thus benefiting patients.

***A.3 Study Design**

Limited to 2,500 characters.
Double-blind randomised controlled trial, analysed for efficacy and adverse outcomes (see analytic plan below).

***A.4 Studies Selected and Study Populations**

Limited to 2,500 characters.
Study 329 has been chosen because of its misrepresentation in the publication in the Journal of the American Academy of Child and Adolescent Psychiatry in 2001. The study population is as per the original analytic plan, below.

***A.5 Primary and Secondary Endpoints for the Study**

Limited to 2,500 characters.
The primary and secondary endpoints are as designated in PROTOCOL NUMBER 29060/329 dated 12 June 1993 and (subject to protocol amendments as documented on page 26-29 of the final clinical report):

1.1 Primary efficacy variables
a) The change in total HAM-D score from beginning of the treatment phase to the endpoint of the acute phase.
b) The proportion of responders at the end of the eight week acute treatment phase.
1.2 Secondary efficacy variables
a) Changes from baseline to endpoint in the following parameters:
• Depression items in K –SAD-P
• Global Impressions
• Autonomic Function Checklist
• Self Perception Profile
• Sickness Impact Scale.
b) Predictors of response (endogenous subtypes, age, prior episodes. duration and severity of present episode. comorbidity with separate anxiety, attention deficit. and conduct disorder).

c) The number of patients who relapse during the maintenance phase

In addition, we will report as a primary outcome, serious adverse events, and as a secondary outcome, all adverse events.

***A.6 Statistical Analysis Plan**

Please provide the statistical analysis plan for the proposed research

The following is provided as guidance for items to include in the statistical analysis plan:

- Effect measure of interest (e.g. for inferential studies: risk or rate ratio, risk or rate difference, absolute difference; for descriptive studies: rate with confidence intervals)
- Methods to control for bias (e.g. restriction, matching, stratification, covariate adjustment)
- Assumptions and any planned adjustments for covariates or meta-regression or modelling of covariates
- The statistical approach (e.g. Bayesian or frequentist (classical), fixed or random effects)
- Meta-analysis approach where applicable (e.g. random effects meta-analysis, stratified meta-analysis)
- Statistical tests and methods (e.g. Fisher's exact test, Kaplan-Meier curves, log-rank test to compare groups, multiplicity adjustments)
- Power to detect an effect, or the precision of the effect estimate given the sample size available
- Statistical power calculations and levels of significance
- Model fit tests, sensitivity or heterogeneity analyses (e.g. Chi-Squared Test, I squared statistic)
- Analysis of subgroups (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose)
- Handling of missing data

Limited to 25,000 characters.
Our statistical analysis plan is identical to that proposed in PROTOCOL NUMBER 29060/329 dated 12 June 1993

Criteria for Efficacy
1.1 Primary efficacy variables
a) The change in total HAMD score from beginning of the treatment phase to the endpoint of the acute phase.
b) The proportion of responders at the end of the eight week acute treatment phase.
1.2 Secondary efficacy variables
a) Changes from baseline to endpoint in the following parameters:
• Depression items in K –SAD-P
• Global Impressions
• Autonomic Function Checklist
• Self Perception Profile
• Sickness Impact Scale.
b) Predictors of response (endogenous subtypes, age, prior episodes. duration and severity of present episode. comorbidity with separate anxiety, attention deficit. and conduct disorder).
c) The number of patients who relapse during the maintenance phase.
2 Statistical Methods
2.1 Comparisons of interest
The comparison of primary interest is active treatment versus placebo. Hypotheses concerning these comparison will be tested at the alpha level of 0.05
2.2 Sample size determination
This study is designed to have adequate power to detect a clinically meaningful difference in both active-placebo comparisons at a two tailed alpha level of 0.05 and power 0.80. The sample size estimates are further based on an effect size of 0.40.
The rationale tor this effect size is as follows:
• A difference of 4 in the HAMD Total change from baseline scores at endpoint. This is a smaller difference than that seen in previous studies with antidepressants in adults, yet it is large enough to be clinically meaningful, and
• A standard deviation of 10. This is 20% larger than observed in studies with anti-depressants in adults and should reflect the greater variability in response expected in adolescent depression.
These parameter estimates result in 100 patients per treatment group.
3 Efficacy Analysis
3.1 Intent to Treat Analysis
All patients who receive double-blind medication will be considered as part of the ITT population. This patient population will be considered the primary population.
3.2 Patients Valid For The Efficacy Analysis
All patients randomized to study treatment and for whom at least one valid post-treatment efficacy evaluation is available will be valid for inclusion in an 'intent-to-treat' analysis. Patients who meet the following criteria will be eligible for the efficacy analysis:
a) No major protocol violation exists with regard to inclusion or exclusion criteria
b) No other major protocol violation during the first 8 weeks at active treatment has occurred.
Only primary efficacy variables will be analyzed using this population. Patients to be excluded from the efficacy analysis will be identified before the randomization code is broken.
3.3 Statistical Methodology
Psychometric scales using at least an ordinal measurement scale will be analyzed using parametric analysis of variance. Effects in the model will include treatment investigator and treatment by Investigator interaction. If the treatment by investigator interaction is not significant ($p > 0.1$) the interaction term will be dropped from the model. This analysis will be performed using the General Linear Models processing of the SAS system. The ordinal scales which have very few levels (such as the Severity of Illness) will also be analyzed using non parametric methodology so that the results are consistent across modes of analysis.
Dichotomous variables such as response (based on HAMO criteria) will be analyzed using Logistic Regression methodology. Effects in the model will include treatment, investigator, and treatment by investigator interaction; if the interaction is not significant then it will be dropped from the model. These

analyses will be performed using the LOGISTIC procedure of the SAS system.
Summary statistics will be presented for demography, disease history, and baseline measures of efficacy.
An analysis of covariance will be performed to evaluate the effect of possibly important prognostic variables on the HAMD total score at endpoint. These include endogenous subtype, age at onset, gender, number of prior episodes, duration and severity of current episode, comorbidity with separate anxiety disorder, attention deficit disorder and conduct disorder.
3.4 Test of Significance
Tests of hypothesis regarding model assumptions such as the significance of treatment by investigator interactions will be made at the 10% level.
All other statistical tests will be two-tailed and performed at the 5% significance level.
3.5 Patient Characteristics At Baseline
Demographic and diagnostic variables at baseline will be checked for homogeneity between the treatment groups. If major differences exist for variables predictive of treatment response, their impact on the trial results will be investigated.
4 Safety Analysis
4.1 patients Valid for Clinical Safety & Tolerability
All patients who receive coded medication will be assessed for clinical safety and tolerability.
4.2 Adverse Experiences
Adverse experiences will be coded for each subject with reference to body system and preferred terms. The treatment groups will be compared regarding the incidence at the reported adverse experiences with reference to both preferred term and body system. The comparison between treatments with regard to incidence of adverse experiences will be performed primarily by using descriptive statistics.
4.3 Other Clinical Safety Variables
Information regarding demographic data, vital signs, physical examination, adverse experiences and abnormal laboratory values will be presented as listings and tables. All deviations from the study protocol and study withdrawals will be documented.

***A.7 Publication Plan**

Limited to 2,500 characters.
The report of our analysis will be submitted to BMJ.

SECTION B: INFORMATION ABOUT THE RESEARCH TEAM

Please note that a statistician with a degree in statistics or a related discipline should be part of the research team.

GSK pays fees for research team members to access data and use the statistical software. For each approved research proposal, up to two members of the research team are able to use the statistical software and up to a further four team members are able to access the data.

For this section, please include all researchers on your team. We should be notified where there is a change in membership of the research team.

Up to 20 researchers can be entered.

Lead Researcher

*Name:	Jon Jureidini
*Post or Position:	Professor, Discipline of Psychiatry
*Employer, Company, Research Institution or Affiliation:	University of Adelaide
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	Child Psychiatrist, PhD, MBBS, FRANZCP

Add Researcher (Unchecking this box will delete all research team members below)

Researcher 1

*Name:	Mickey Nardo
*Post or Position:	RETIRED PSYCHIATRIST
*Employer, Company, Research Institution or Affiliation:	EMORY UNIVERSITY
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	INTERNAL MEDICINE, NIH FELLOW, PSYCHIATRY, PSYCHOANALYSIS

Add Researcher (Unchecking this box will delete all research team members below)

Researcher 2

*Name:	David Healy
*Post or Position:	Professor of Psychiatry
*Employer, Company, Research Institution or Affiliation:	Bangor University

*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	MD FRCPsych

Add Researcher (Unchecking this box will delete all research team members below)

Researcher 3

*Name:	Catalin Tufanaru
*Post or Position:	Research Associate; Administrator of the JBI Connect Mental Health Node (evidence-based point of care resources for mental health professionals)
*Employer, Company, Research Institution or Affiliation:	The Joanna Briggs Institute (JBI), School of Translational Health Science, Faculty of Health Sciences, The University of Adelaide, Adelaide, South Australia, Australia
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	Research Associate in Evidence-Based Health Care, MD, MPH Note, Tufanaru is a public health specialist with training in biostatistics.

Add Researcher (Unchecking this box will delete all research team members below)

Researcher 4

*Name:	Elia Abi-Jaoude
*Post or Position:	Research Fellow
*Employer, Company, Research Institution or Affiliation:	University of Toronto, Toronto Western Hospital – University Health Network
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	Psychiatrist, MSc, MD, PhD Candidate, FRCPC

Add Researcher (Unchecking this box will delete all research team members below)

Researcher 5

*Name:	Melissa Raven
*Post or Position:	Research Fellow
*Employer, Company, Research Institution or Affiliation:	Flinders University
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	MMedSci(ClinEpid), MPsych(Clin), PhD

SECTION C: FUNDING OF THE PROPOSED RESEARCH

***Source of funding for the Proposed Research.**

Please provide the name (e.g. NIH, MRC) of the funding source(s) that is being used or is planned to be used solely or in part for the proposed research.

Please include research grants from governments or government agencies, other grants or donations, funding from employers through employment contracts, other contracts, consultancies, honoraria and other payments that will be used for the research.

Please including any funding from commercial (e.g. for profit) organisations.

If there is no funding for the research, enter "None".

Limited to 2,500 characters.
None

SECTION D: POTENTIAL CONFLICTS OF INTEREST

***D.1 Potential Conflicts of Interest Outside the Funding of the Proposed Research**

For each member of the research team, please provide information on financial relationships that could be perceived to influence the planning, conduct or interpretation of the proposed research. This should include but not be limited to financial relationships with GSK and other pharmaceutical or biotechnology companies within the last three years. It should include:

- Board memberships
- Consultancies
- Employments
- Grants/grants pending
- Patents (planned, pending or issued)
- Royalties
- Stocks or shares (including options)

Please also include any other (e.g. non-financial) real or potential conflicts of interest that could be perceived to influence the planning, conduct or interpretation of the proposed research. For example potential biases based on pre-existing personal views, academic or commercial competition, personal relationships, political or religious beliefs and institutional affiliations.

If none, please enter "None".

***Lead Researcher**	Jureidini has been a critic of study 329 since it was first published and, as a result, has been contracted to provide expert advice for Baum Hedlund in a class action against GSK in relation to the prescribing of paroxetine to children and adolescents. He is a member of Healthy Scepticism. He reports no other conflicts.
***Researcher 1**	None
***Researcher 2**	Healy has been an expert witness on behalf of plaintiffs in legal cases involving paroxetine. He has also been a former consultant to and clincal triallist for SmithKline Beecham, and has consulted extensively with other pharmaceutical companies.
***Researcher 3**	None
***Researcher 4**	None
***Researcher 5**	Raven is a member of Healthy Skepticism. She has participated in lobbying for the published article (Keller et al. 2001) to be retracted. She reports no other conflicts.

***D.2 Management of Real or Potential Conflicts of Interest**

Please summarise how real or potential conflicts of interest related to the funding of the proposed research, other financial relationships, or other real or potential conflicts of interest will be managed. For example through disclosure of interests when the research is presented and published.

If none, please enter "None".

All real or potential conflicts will be published.

SECTION E: OTHER INFORMATION

Please provide any additional information that should be considered when reviewing this proposal

On the basis of the adverse event reports in the CSR, it is clear that not all adverse events have been included in the master tables of adverse events. We already have found 200 adverse events in the records on the website that it would appear are either not listed in your summary tables of adverse events or else are coded inappropriately by GSK.

In the circumstances it is important to have access to the de-identified case report forms (CRFs) for all subjects in study 329 so that we can increase our confidence in the final codings that we arrive at.