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Research proposal details

Title: Post-hoc analysis of placebo-controlled trials in children and adolescents with depression
Status: Access Expiration Pending
Submitted: 08 Jun 2015
This proposal included the following clinical studies listed on this site:

- GSK-BRL-029060/329: Acute Phase
- GSK-BRL-029060/377
- GSK-BRL-029060/701
- GSK-29060/329_1

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 “Contact administrator” and “Attachments” tabs below.

Summary | Contact administrator | Attachments | Email notifications

Summary

Reference Name
Post-hoc analysis of placebo-controlled trials in children and adolescents with depression

Reference Number
1273

Proposal Review Outcome
Approved by IRP

Required fields are marked with an *

*Do you understand that access to data will only be provided in the secure data access system. SAS and “R” statistical software are provided and there are controls to prevent the original study datasets from being downloaded.
Yes

*Have you previously submitted or plan to submit an enquiry to add studies to this research proposal?
Yes

Please provide the enquiry Reference Name and Number
Post-hoc analysis of placebo-controlled trials in children and adolescents with depression. 1227.

*Is this research proposal a re-submission of a previous research proposal that has been reviewed by the Independent Review Panel?
No

*Does your proposed research require Ethics Committee or Institutional Review Board (IRB) approval? (If No, please provide further details below).
No

Where required, Bayer require this approval before research proposals are sent to the Independent Review Panel. If your research proposal includes Bayer studies, you will be contacted and asked to provide a copy of the approval.

*Please provide the reason why Ethics Committee or IRB approval is not needed. Note: The applicability of local regulations depends on the location where the research will be performed (usually the location of the lead researcher or the location of the lead researcher’s institution or affiliation).

The Ethical Committee of the University of Gothenburg recently stated that this kind of research on de-identified data is not encompassed by the Law of Ethical Trials, but also that they had no objections to the planned study (regarding a corresponding analysis of trials on depression in adults).

Following approval, access is provided after the relevant study sponsor or sponsors 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.
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. Notify sponsor of any replacement of Lead Researcher and/or Statistician as approved by the Independent Review Panel.
e. Inform the relevant sponsor(s) and regulatory authorities of any safety concerns as soon as they are identified.
f. Consent to the posting of the information contained in the Research Proposal (e.g. title, lay summary, requested clinical studies, the Lead Researcher's name, affiliation, funding source and potential conflicts of interest) on ClinicalStudyDataRequest.com after the Data Sharing Agreement has been signed.
g. Publish the results of the analysis in a scientific journal within one year of analysis completion or for failed publications ensure that any analyses performed and associated outcomes are disclosed on an open access journal or publishing platform.
h. Consent to the posting of a summary of the analysis plan, and a link to the publication citation or publically disclosed results (for failed publications) on ClinicalStudyDataRequest.com after the research is published.
i. Provide the relevant sponsor(s) with a copy of any public disclosure of the results, including a copy of the manuscript. (Some sponsors include a provision for prior review of the manuscript; refer to the terms specified in Exhibit E of the actual Data Sharing Agreement.) Also provide the relevant sponsor(s) with the citation after publication.
j. Acknowledge the relevant sponsor(s) and ClinicalStudyDataRequest.com in the publication.
k. Allow the relevant sponsor(s) to use any invention coming out of the research that impacts the ability of the sponsor to develop or commercialise their products. Such use will be free of charge and throughout the world. If the sponsor requests additional rights, you agree to negotiate in good faith with the sponsor.
l. Confirm that you do not have, and do not plan to have, any other agreements which would prevent you from complying with the above.
m. Meet any additional requirements identified by the Independent Review Panel.

Note this is a legal document and so may require legal review within your organisation prior to signing.

The Data Sharing Agreement template is provided here. Your actual Data Sharing Agreement may have minor modifications. **Please note that the sponsors do not anticipate negotiation on the provisions in this template.**

*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 the Privacy Website Statement. I also understand that if I, or any member of my research team, fail to comply with the terms of the Data Sharing Agreement, information related to this matter may be shared among study sponsors.

*By completing a submission, you accept that the name and affiliation of the lead researcher, the title of the proposed research, the statistical analysis plan, the requested studies, lay summary, funding source and any potential conflicts of interest that are provided may be published on this site. For approved requests, the statistical analysis plan for the proposed research will be posted on this site after the research is published.

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**
Post-hoc analysis of placebo-controlled trials in children and adolescents with depression

***A.2 Lay Summary**
Background

Whereas >7% of the population in many countries are medicating with selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression and other conditions, many influential researchers and debaters have recently gained considerable attention when presenting the theory that these drugs are in fact devoid of any specific pharmacological antidepressant effect. Needless to say, the lack of consensus on this important matter is highly unsatisfactory, especially given the gravity of the disorders in question.

The questioning of the SSRIs has to a large extent been based on post hoc analyses of drug company-sponsored placebo-controlled trials. According to the critics, such analyses hence reveal that the possible superiority of the SSRIs over placebo is too small to be clinically meaningful, and possibly caused by side-effects breaking the blind so that the psychological placebo effect is enhanced in those given active treatment. Also, it has been argued that post-hoc analyses provide support for the conclusion that SSRIs enhance rather than reduce suicidal ideation.

The analyses underlying these conclusions have however been marred by considerable methodological shortcomings, including dealing with trial-level rather than subject-level data and/or focusing on a subjective selection of trials. We have hence started an extensive project aiming to solve the controversies regarding the SSRIs which is based on the fact that we have access to patient-level data from all company-sponsored placebo-controlled trials in adult depression regarding three of the four major first-generation SSRIs: paroxetine, sertraline and citalopram.

While the use of SSRIs for adult depression is controversial, their use in depressed children and adolescents is even more so. For this reason, we now aim to repeat all analyses we conduct on trials of adults also on trials in the young.

Aims

By conducting post hoc analyses of patient-level data from all drug company sponsored trials regarding paroxetine, citalopram and sertraline we hope to shed new light on the pros of cons of using SSRIs for the treatment of depression in the young. For example, we will assess i) the result of replacing the sum of the rating of all symptoms on a rating scale as effect parameter, ii) the possible relationship between side-effects and response, iii) the influence of drug treatment on the suicidality item at different time points and iv) the possible association between baseline symptom profile and response.

Design

Post hoc analyses will be conducted on the data received from GSK, as well as on corresponding data received from other companies (Lundbeck, Pfizer). These will largely follow a statistical plan decided upon a priori, but permitting certain deviations prompted by the results obtained.

Dissemination of results

The results will be published in an international scientific journal.

***A.3 Study Design**
With respect to our ongoing project regarding depression in adults (see above), we show, in a first publication, recently published online in Molecular Psychiatry, that the actual efficacy of SSRIs in adult depression has been grossly underrated by the use of an inadequate primary effect parameter (i.e. the sum score on the Hamilton depression rating scale). In two subsequent papers, which are shortly to be submitted, we report on the dose-response relationship and time of onset of these drugs, as well as on the possible initial anxiety- and suicide-enhancing effect of the SSRIs (the latter of these papers showing a reduction in suicidal ideation in SSRI-treated patients already from week 1). In a fourth paper we will address the “side effect breaking the blind” hypothesis (see above) by comparing effect sizes in patients with or without side effects (preliminary data refuting this theory).

The present study will address all these issues but with respect to trials conducted in children and adolescents rather than adults. The strategies will be the same as in our analyses of adult depression: we will thus re-analyze i) individual trials, ii) all trials for a certain compound pooled and iii) all SSRI trials pooled. For example, we will assess i) the result of replacing the sum of the rating of all symptoms on the scale as effect parameter, ii) the possible relationship between side-effects and response, iii) the influence of drug treatment on the suicidality item at different time points and iv) the possible association between baseline symptom profile and response.

***A.4 Studies Selected and Study Populations**
We would need patient-level data on all GSK-sponsored placebo-controlled trials of paroxetine in children and adolescents with depression, and believe that the requested trials are all that have been conducted and from which data are available. In a previous request (ref number 1227) we also asked for data from trial 29060/511; however, we

were informed (in an e-mail dated May 6, 2015) that these data are not available; hence this trial is not included in this request.

***A.5 Primary and Secondary Endpoints for the Study**
The issue of end-point is discussed under the heading "Statistical Analysis Plan" below.

***A.6 Statistical Analysis Plan**
The assumption underlying this project is that the presentation of outcome of placebo-controlled trials in the depression field has been grossly misleading (usually indicating the studied drug to be less effective than it actually is) because of the fact that the drug companies, when analyzing the results, for formal reasons have been limited by what was decided beforehand with respect to effect parameter, statistical approach etc.

In the present project, we will hence be guided by an approach that we believe are far sounder from a scientific point of view, i.e. to allow for a considerable flexibility with respect to how to analyze the data, i.e. to allow the results of one analysis to partly guide the forthcoming ones. From this follows, needless to say, that all analyses undertaken and presented in future publications must be scientifically sound and convincingly justified.

For the above-mentioned reason, we prefer to refrain from presenting a very detailed statistical plan from which we should not be allowed to deviate. However, this is how we, at this stage, plan to analyze the data:

1. One objective of this study being to assess the result of using different effect parameters, we will conduct all analysis both using the parameter named primary in the original trial protocol (which we assume will usually be the sum score of the used rating scale) and using various alternative parameters, the most important of which will be the “depressed mood” item in this scale. For completeness, additional analyses using each of the various items on the scale as effect parameter will be undertaken. Of special importance from the perspective of tolerability will be any possible effects on items that may be negatively influenced by the active drug, such as anxiety and suicidality.

2. For all comparisons of placebo and active drug we will both use the technique usually adopted by the companies and authorities when these trials were undertaken, i.e. ANCOVA with center as co-variate, and more modern approaches, such as the mixed model repeated measures (MMRM) technique with treatment as factor and including appropriate interactions (including gender, age and baseline symptom profile).

3. For all analyses we will study both the ITT population (using the LOCF principle) and those completing the trial.

4. For addressing the “side effects breaking the blind” hypothesis we will conduct the above-mentioned analyses after having split the population into those with or wi

***A.7 Publication Plan**
The results will be published in an international scientific journal. Registration at clinicaltrial.gov is not applicable for this kind of project.

SECTION B: INFORMATION ABOUT THE RESEARCH TEAM

Lead Researcher

*Name:	Elias Eriksson
*Post or Position:	Professor
*Employer, Company, Research Institution or Affiliation:	University of Gothenburg
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	Med dr. 30 years of experience in the field.

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

Researcher 1

Name:	Fredrik Hieronymus
Post or Position:	PhD student
Employer, Company, Research Institution or Affiliation:	University of Gothenburg
Education, Professional Qualifications and Memberships that are	MD

Relevant to the Proposed Research:	

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

Researcher 2

Name:	Jakob Näslund
Post or Position:	PhD student
Employer, Company, Research Institution or Affiliation:	University of Gothenburg
Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	MD

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

Researcher 3

Name:	Johan Fredrik Emilsson
Post or Position:	PhD student
Employer, Company, Research Institution or Affiliation:	Sahlgrenska University Hospital
Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	MD

Statistician

*Name:	Staffan Nilsson
*Post or Position:	PhD, senior lecturer
*Employer, Company, Research Institution or Affiliation:	Chalmers University of Technology
*Education, Professional Qualifications and Memberships that are Relevant to the Proposed Research:	PhD in statistics. Senior lecturer in statistics.

SECTION C: FUNDING OF THE PROPOSED RESEARCH

***Source of Funding for the Proposed Research.**
Supported by the Swedish Medical Council, Hållsten's Foundation, Söderberg's Foundation and the Swedish Brain Foundation. No funding from commercial organisations.

SECTION D: POTENTIAL CONFLICTS OF INTEREST

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

***Lead Researcher**	Elias Eriksson has previously been on advisory boards for Lilly, Lundbeck and Pfizer, and has also received speaker honoraria from these companies. In addition, he has previously received research grants from Lundbeck.
***Researcher 1**	None
***Researcher 2**	None
***Researcher 3**	None
***Statistician**	None

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

Disclosure of interests will be made when the results are presented and published.

SECTION E: OTHER INFORMATION

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