

April 26, 2013

Sir Andrew Witty  
CEO, GlaxoSmithKline  
980 Great West Rd  
Brentford, Middlesex TW8 9GS  
United Kingdom

Dear Sir Andrew,

**Study 329: A multi-center, double blind, placebo controlled study of paroxetine and imipramine in adolescents with unipolar major depression.**

I write to you as the CEO of GlaxoSmithKline in regard to an on-going complaint about a fraudulent journal article under the lead authorship of Martin Keller entitled 'Efficacy of paroxetine in the treatment of adolescent major depression: A randomized, controlled trial' that was sponsored by GSK and appeared in the July 2001 issue of the *Journal of the American Academy of Child & Adolescent Psychiatry*.<sup>1</sup> This frequently cited paper has misled clinicians and academics; at least 75 scientific articles have reproduced its false claims about outcomes, thereby supporting off-label prescribing of paroxetine.

Study 329 clearly failed to demonstrate efficacy or safety for paroxetine in adolescents, and yet the paper claimed "paroxetine is generally well tolerated and effective for major depression in adolescents". I, along with other scientists, have documented the many problems with this paper that contributed to misreporting of efficacy and safety outcomes in study 329.<sup>2</sup>

In light of a recent \$3 billion settlement in which your corporation pleaded guilty to misbranding of paroxetine (Paxil), we request that you write to Dr. Andrés Martin, the editor of *Journal of the American Academy of Child & Adolescent Psychiatry* to request retraction of the Keller *et al.* article, which was a key piece of evidence in the government's case for off-label promotion by GSK.

Your corporation has so far failed to take responsibility for a published report that has harmed young patients who were prescribed paroxetine on the basis of this misleading article. As the CEO of GSK, you have the opportunity to correct the scientific record. I respectfully urge you to do so.

Yours sincerely,

Jon Jureidini, MB, PhD  
Clinical Professor  
Discipline of Psychiatry

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<sup>1</sup> MB Keller, ND Ryan, M Strober, RG Klein, SP Kutcher, B Birmaher et al. (2001) Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 40:762-772

<sup>2</sup> Jureidini, J. and McHenry, L., Mansfield, P. (2008). Clinical trials and drug promotion: selective reporting of study 329. *International Journal of Risk and Safety in Medicine*, 20(1–2):73–81; McHenry, L. and Jureidini, J. (2008). Industry-sponsored ghostwriting in clinical trial reporting: A case study. *Accountability in Research*, 15(3):152–167; Newman, M., (2010) *BMJ* 341: c6985.



GlaxoSmithKline

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May 3, 2013

Jon Jureidini, MB, PhD  
The University of Adelaide  
Department of Psychological Medicine  
Women's and Children's Hospital  
North Adelaide, 5006, South Australia

Dear Dr. Jureidini:

I am responding to your letter addressed to Andrew Witty dated April 26, 2013, regarding an article published in the July 2001 issue of The Journal of the American Academy of Child and Adolescent Psychiatry ("JAACAP") on Paroxetine Study 329 entitled, "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial."

GSK does not agree that the article is false, fraudulent or misleading. The article, which was subjected to peer review on three occasions prior to publication, accurately reflects the honestly-held views of the clinical investigator authors. It is my understanding that you recently requested both Brown University and JAACAP retract the article and that both Brown and JAACAP declined to do so. Indeed, according to an e-mail from Dr. Andres Martin, Editor-in-Chief of JAACAP, to you that was apparently sent December 21, 2012 and reprinted in a post by Ed Silverman on January 9, 2013 on [www.pharmalot.com](http://www.pharmalot.com), "Journal Refuses to Retract Controversial Paxil Study," in response to your request, the JAACAP editorial board undertook a "comprehensive and extensive review" and "found no basis for retraction or other editorial action."

In light of the above, GSK does not believe it appropriate to request retraction of the article.

Very truly yours,

A handwritten signature in black ink, appearing to read "John E. Kraus", written over a horizontal line.

John E. Kraus, MD, PhD, DFAPA  
Head of Medical Governance  
Neurosciences Therapy Area Unit  
GlaxoSmithKline Research & Development



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Department of Psychological Medicine  
Women's and Children's Hospital  
North Adelaide, 5006  
Australia

September 4, 2013

Sir Andrew Witty  
CEO, GlaxoSmithKline  
980 Great West Road  
Brentford, Middlesex TW8 9GS  
United Kingdom

Dear Sir Andrew

You may recall that I wrote to you (April 26, 2013) expressing concerns about the published report of SmithKline Beecham and GlaxoSmithKline's Study 329 of paroxetine in children and adolescents. I received a response from Dr Kraus (May 3, 2013) declining to request retraction of the published paper.

Following the publication of the restoring invisible and abandoned trials (RIAT) paper by Doshi et al. in the BMJ<sup>1</sup>, your company was notified by the RIAT authors by email on 14 June 2013 that Study 329 was amongst the studies requiring restoration. This gave GSK 30 days to signal its intent to publish a corrected version.

GSK did not signal its intent to do so within 30 days. Consequently on 15 July 2013, I declared my intent to work with a team of scientists to republish Study 329, in accordance with the RIAT guidelines.

Shortly afterwards, GSK set up an online process for researchers to 'submit research proposals and request anonymised data from clinical studies'.<sup>2</sup> Although this process was for studies conducted since 2007, there was an opportunity to 'enquire about the availability of data from our clinical studies that are not listed on the site'.

I made such an enquiry in relation to Study 329 on 4 August. However, I have had no response. The GSK website still designates the status of my query as 'under review', and there is no means to find anything more through that website. I am therefore seeking your help in gaining access to the anonymised case report forms for all participants in Study 329.

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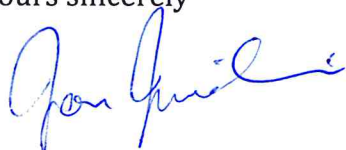
<sup>1</sup> <http://www.bmj.com/content/346/bmj.f2865>

<sup>2</sup> <https://clinicalstudydata.gsk.com/>

Your company had already agreed to make data from study 329 public as a consequence of the 2004 consent order of the New York State Attorney General's office.<sup>3</sup> The response that I received from Dr Kraus stated that "GSK does not agree that the article is false, fraudulent or misleading", so your company will want the individual level data made publicly available to confirm that.

I therefore trust that you will arrange for the data to be made available to me in a timely manner, and I look forward to hearing from you. Please let me know if you will be unable to provide me with a definitive response within 10 days.

Yours sincerely

A handwritten signature in blue ink, appearing to read 'Jon Jureidini', with a stylized flourish at the end.

Jon Jureidini  
Clinical Professor  
Discipline of Psychiatry  
[jon.jureidini@adelaide.edu.au](mailto:jon.jureidini@adelaide.edu.au)

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<sup>3</sup> Consent Order, dated 08/26/2004, for Civil Action No. 04- CV-5304 MGC, People of the State of New York vs. GlaxoSmithKline <http://tinyurl.com/84226ly>, see page 7:

"In addition, for the same period, GSK shall make available to the public on-line Clinical Study Reports of GSK-Sponsored Clinical Studies of Paxil® in adolescent and pediatric patients, to the extent such Clinical Study Reports are not otherwise included in the CTR."

"Clinical Study Report" (p.2) is defined as:

"Clinical Study Report" of a Clinical Study means a description of the protocol, all the Data, and the clinically relevant conclusions drawn from the Data, including the answers to the questions posed in the protocol."



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6 September 2013

Dear Professor Jureidini

Thank you for your letter to Sir Andrew's office which was passed on to me.

I have checked on the status of your enquiry about access to anonymised patient level data from paroxetine Study 329.

Information for this study and other studies of paroxetine in paediatric and adolescent patients is available on our external website, [www.gsk.com](http://www.gsk.com). The following information can be accessed directly from this link: - (<http://www.gsk.com/media/resource-centre/paroxetine/paroxetine-paediatric-and-adolescent-patients.html#reports>):

- Clinical Study Report(s)
- Protocol and blank Case Report Form (Appendix A)
- Patient data listings (Appendices B to H). This contains the information directly from the case report forms.

In addition, I can confirm that we are able to provide access to the anonymised raw datasets from this study in an electronic database as described in our request site. In order for you to gain access to this we would ask that you complete and submit a formal research proposal via the request site which will be reviewed by the Independent Review Panel. A decision from the panel can be expected within 30 days (usually 5-10 days) of receipt of your research proposal. In addition we will require a signed Data Sharing Agreement. The Agreement template is also available via the request site. Given the age of this study we anticipate that anonymisation of the data may take 4-6 weeks after we receive a research proposal that is approved by the Independent Review Panel.

I hope that this is satisfactory and if you have additional questions please do not hesitate to contact me directly.

Yours sincerely

A handwritten signature in black ink, appearing to read 'J Shannon', is written over a white background.

James Shannon  
Chief Medical Officer



Department of Psychological Medicine  
Women's and Children's Hospital  
North Adelaide, 5006  
Australia

September 30, 2013

Sir Andrew Witty  
CEO, GlaxoSmithKline  
980 Great West Road  
Brentford, Middlesex TW8 9GS  
United Kingdom

Dear Sir Andrew

As you know, I am coordinating a multidisciplinary team which has declared its intent to restore Paroxetine trial 329.<sup>1</sup>

I have already corresponded with you, most recently on 4 September 2013. You will have seen the responses that were written by Dr John Kraus (3 May 2013) about the proposed retraction of the published report of Study 329, and from Dr James Shannon (6 September 2013) about my request for de-identified case report forms (CRFs) for all subjects in study 329.

As you may know, part of the restoration process is the re-running of the original analyses reported in the Clinical Study Reports (CSRs) and any linked paper(s). Before running any analyses we need to check the datasets both for acute and maintenance (continuation) phases of participant exposure to paroxetine and imipramine with special regard to harms. This check is aimed at ensuring completeness and reliability of the dataset.

On June 25, GSK (through Perry Nisen) expressed support for the RIAT process, telling Peter Doshi, as first author of the RIAT declaration, "However, by making the Clinical Study Reports available we are very happy for others to publish on the records if they wish to and if journals consider the work to be of scientific merit."

Unfortunately it appears that even after publication in 2012 of most of the remaining appendices on your website following involvement with the New York State Attorney General's Office, CRFs are not yet available.

Your website points out 'GSK will consider requests for additional information from the reports that is required for a defined research question and methodology'.<sup>2</sup>

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<sup>1</sup> <http://www.bmj.com/content/346/bmj.f2865?tab=responses>

<sup>2</sup> <http://www.gsk.com/media/resource-centre/paroxetine/paroxetine-paediatric-and-adolescent-patients.html>

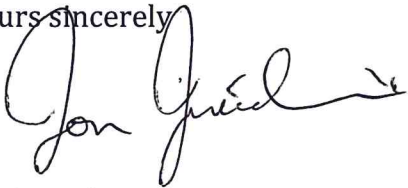
Our Enquiry (#638) on your website eventually elicited a response (13 September 2013) that informed us that we could apply for access via the Data Access System, but the response raises three concerns:

1. is not clear that the Data Access System provides access to CRFs
2. the clinical study report and appendices posted on GSK's are not searchable because they are scanned images
3. the application process requires submission of an analysis plan, but such a plan is irrelevant when restoring a publication where our primary focus is the original analysis plan drawn up and implemented by your own statisticians.

In summary, I am writing to you to ask you to authorize release of the original de-identified CRFs for trial 329 as well as searchable copies of the electronic patient level data, in a format such as SAS XPORT, so that we can restore the publication of trial 329 in a fair, complete and publicly transparent way.

I look forward to your answer.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Jon Jureidini', with a stylized flourish at the end.

Jon Jureidini  
Clinical Professor  
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[jon.jureidini@adelaide.edu.au](mailto:jon.jureidini@adelaide.edu.au)



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11 October 2013

Dear Professor Jureidini

Thank you for your follow-up letter to Sir Andrew dated September 30<sup>th</sup> 2013.

I wanted to follow up to my last letter to you of September 6<sup>th</sup> to clarify the information available for this study and our approach to providing electronic anonymised patient level data for further research in a SAS environment.

As you document, Dr. Nisen expressed GSK's support for the RIAT process and we will, as he noted, make Clinical Study Reports (CSRs) available for our studies. Normally, Case Report Forms (CRFs) are not included in a CSR. For study 329, some CRFs are included in Appendix H, namely CRFs for patients having Adverse Experiences leading to withdrawal, serious adverse experiences or death. The narratives for these events are included in the CSRs. The content of Appendix H is not posted on our website because it contains information (such as names) that can be used to readily identify the patients concerned.

All of the data that study 329 was set up to obtain, including that from the CRFs in Appendix H, is contained in the CSRs and the associated appendices which are posted on our website.

We do not publicly disclose Case Report Forms (CRFs) and we do not provide them to other researchers. Complete CRFs are available to regulatory authorities for audit and for them to assure the integrity of the data sets and CSRs. This use of patients' information for these audit purposes is part of the informed consent process for clinical trials and patients' confidentiality is protected.

With regard to the electronic database, we have established a process to provide researchers with access to the electronic anonymised patient level data from our studies; following this process will enable you to request access to these data so that you can conduct your analysis of both the acute and maintenance (continuation) phases of study 329. As with every other investigator requesting access to such data, I would ask that you do indeed submit an analysis plan via the website and sign a data sharing agreement. I have an obligation to protect patient confidentiality and appropriate use of patients' data and so I must insist on these steps.

In conclusion, I believe that you have the complete study data from the CRFs available to you in the listings of the CSR, we have offered (under the conditions noted above) to make the patient level data available to you in an electronic searchable format in a SAS environment and I therefore believe that you have the ability to access the data from study 329 to complete your analysis.

Please let me know if you need any additional assistance.

Yours sincerely

A handwritten signature in black ink, appearing to read 'James Shannon', written in a cursive style.

James Shannon  
Chief Medical Officer



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October 29 2013

James Shannon  
Chief Medical Officer  
GlaxoSmithKline  
980 Great West Road  
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Dear Dr Shannon

Thank you for your letter dated 11 October 2013. You asked that we submit an analysis plan via the GSK website. The group working to restore Study 329 does not accept that an analytic plan should be required for access to Clinical Trial Data. Having said this, the RIAT process involves following the original analytic plan, which we thought would be obvious from reading about RIAT. We have anyway proceeded to make our application (Reference Number 669), submitting GSK's original analytic plan.

Second, as a group we do not accept your argument about patient confidentiality. Study 329 does not involve a rare diseases group where it is likely that a patient might be identified. It is an empirical question whether when patients signed consent forms to enter into Study 329, they wanted their data hidden for ever from independent scrutiny or whether they thought that they were contributing to science and expected independent scrutiny. This question is not something GSK have a right to prejudge. I suspect a lot of people would not feel comfortable with the notion of GSK as a gatekeeper – especially in the case of this study which has led to charges of fraud and large fines against GSK.

The blank case report forms (CRFs) in the Clinical Study Reports (CSRs) make it clear that the only patient identifiers in any CRF not contained in the CSRs were initials. Redacting initials is the work of minutes. Even if it were possible to identify someone in these data, this is not our intention. We think anyone in our group attempting to do this would do significant damage to the data access cause. We are happy to sign agreements that there will be no effort to identify anyone and that the de-identified CRFs will not be shared with anyone outside the 329 group, with access limited to two to three designated individuals within our group.

Thirdly, to make explicit the reason for requesting the extra material: on the basis of the adverse event reports you allude to, 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. For instance many patients, including 065, 113, 195 and 236, have adverse events of tachycardia or suicide related events that do not appear in the master summary. There are many other patients coded by GSK with emotional lability, hyperkinesia or tremor that as you are aware, would best have been otherwise coded.

Finally, noting the concern you expressed in your letter for the wellbeing of patients who participate in clinical trials, can we enquire as to GSK's follow-up of patients who were in Study 329? For instance, were those who became suicidal or violent on Paxil subsequently advised of the possible role of the drug in their dangerous and distressing feelings/actions and counselled that it may be better for them to avoid SSRIs in future?

In the circumstances it is important to have access to the CRFs so that we can increase our confidence in the final codings that we arrive at. We seek your help in facilitating the prompt provision of data in response to our application.

Yours sincerely

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5 November 2013

Dear Professor Jureidini

Many thanks for your letter dated 29 October 2013 and for submitting your research proposal (Reference Number 669) using our online system. The proposal has been sent to the Independent Review Panel. GSK is not involved in the decisions made by the panel. Under normal circumstances they complete their review within 30 days and so I imagine you will be notified of their decision within the month.

As I stated in my previous letter to you, we do not provide access to case report forms (CRFs) through the online system as the clinical study data from the CRFs is in the anonymised electronic datasets we provide. Therefore access to these documents is not part of the panel's remit; they will consider your proposal with regard to access to the anonymised electronic datasets.

I recognise, however, that you believe you need to see the CRFs and I would like to explore with you how we can help with this. Please could we arrange a telephone call to discuss this more fully and agree a way forward? We could also use that conversation to discuss your reference to the adverse event reporting for study 329. I am obviously very keen to receive further information that you have related to this issue. I have asked my administrative assistant to follow-up with you to arrange a time for this discussion.

Yours sincerely



James Shannon  
Chief Medical Officer



From: Jureidini, Jon (Health)  
Sent: Friday, 8 November 2013 9:29 PM  
To: Eileen Milligan  
Subject: Attention Dr Shannon

Dear Dr Shannon

Thank you for your preparedness to help our team gain access to CRFs from study 329, and your offer to discuss by telephone and agree a way forward.

On reflection, I do not think that a telephone conversation is the best way to proceed. Can we instead interact by email?

So to begin, I would be grateful if you could indicate what in your opinion is the safest way of getting all CRFs from study to me, suitably de-identified, but otherwise complete with narrative elements intact.

Our purpose is to ensure the fidelity of transfer of information from CRFs to the study 329 CSR, especially adverse events.

If you could begin by answering this question, and posing any questions you have for us, I hope that we will be able to rapidly make progress towards a greater understanding of the outcomes of study 329.

Sincerely

Jon Jureidini