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24<sup>th</sup> September 2014

Dear Professor Jureidini,

Thank you for your letter of September 9 2014. I am pleased that the systems and processes we launched in May 2013, enabling researchers to request access to patient-level data from our clinical studies via an independent review panel, have enabled you to conduct your research.

BMJ asked one of our physicians to be a peer reviewer for your paper. This was declined as we believe it is not appropriate for a GSK employee to be part of the journal process that determines whether or not to publish the paper. >

As you have written to me separately welcoming comments on your paper outside the peer review process I have provided some suggestions below that I believe are important to correct inaccuracies and strengthen your manuscript. I hope you will find these useful.

As I have stated in previous letters, our review of data from a number of studies of paroxetine in paediatrics, including Study 329, showed a statistically significant association with an increased risk of possibly suicide related adverse events among adolescent patients taking paroxetine (see Apter et al referenced in my letter from 12 December 2013). In addition, research commissioned by the FDA and published by Hammad et al (also referenced in my letter from 12 December 2013) also concluded that the use of SSRI antidepressant drugs in paediatric patients is associated with a modestly increased risk of suicidality.

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This, together with the inconsistent and variable pattern of efficacy we saw in our studies, gives an unfavourable benefit-risk profile for paroxetine in children and adolescents and it is therefore not recommended for use in this population – I believe we agree on this important point.

These conclusions were reached after a review of the entire body of clinical trial data for paroxetine in paediatric and adolescent patients and not just from Study 329 alone.

I believe there are a number of methodological aspects to your re-analysis of Study 329 alone that can be made clearer in your paper, to help readers to better understand your work. I have also identified some inaccuracies that should be corrected. Given the wide body of research now available on paediatric use of SSRIs I also believe it would be worthwhile comparing and discussing your findings with other relevant published literature.

I have listed my main suggestions below, which I hope you will find helpful.

#### **Context and discussion in relation to other published literature**

- The paper claims that the original published paper of Study 329, authored by Keller et al, was misreported and I am pleased that you have included our view that we do not agree that the article is false, fraudulent or misleading and that it accurately reflects the honestly held views of the clinical investigator authors. Including a statement that we, and the authors of the Keller paper, do not agree that the paper was “ghostwritten” would inform readers that there are different views.
- The paper does not reference as background, or discuss your findings in relation to, studies that have already re-analysed safety data for suicidality from Study 329 and other paediatric studies such as the Apter et al study and the Hammad et al study (as above).

I believe it is important that you discuss your findings in relation to these studies and whether any differences (for example related to the number of assessors, their expertise and whether they were blind to the study drug) may be contributing to different findings.

## **Efficacy assessment**

- Your analysis includes the primary and secondary outcomes described in the original protocol. It does not include analyses that were developed prior to opening the blind as described in the publication by Keller et al (see METHOD, Efficacy and Safety Evaluation) and the clinical study report (CSR).

As the intent of the RIAT initiative is to address concerns of misreporting, may I suggest your paper includes these analyses with a factual description that they were not included in the protocol but were identified before breaking the blind. I also believe it is very important that the findings from these analyses be put in the context of other studies that did not show evidence of efficacy and that Study 329 was designed when there was little consensus on endpoints for assessing the efficacy of antidepressants in this population.

- The definition of relapse that you have used differs from that in the protocol and, I believe, should be described as a post-hoc analysis.

## **Safety assessment**

- As you selected the sample of case report forms (CRFs) for your review, am I correct to assume your review was not conducted blind to the study drug? I believe this should be made clear in your paper.

If the review of CRFs was conducted blind, the paper would benefit from a description of the method of achieving this (as well as the method of achieving the blind for the review of the CSRs).

- Your assessment of safety would best be described as a post-hoc analysis as a coding dictionary is used that was not available at the time Study 329 was conducted (MedDRA was developed in the late 1990s) and your approach differs from that stated in the protocol – for example:



- (i) The identification of “additional AEs” from CRFs and narratives does not align with the protocol which states that the investigator who was blind to the study drug records AEs according to the protocol definition.
  - (ii) In a number of instances you assign different reasons for withdrawal compared to those given by the investigator. This does not align with the protocol which states that this is done by the treating investigator.
- The source of additional AEs is not made clear in your paper which implies the CSR and safety database do not contain AEs from the AE section of CRFs – this is not the case yet is described as “discrepancies between CRFs and the CSR”. This should be amended.

AEs in the AE section of CRFs are listed in Appendix D and G of the CSR. These are AEs that were considered AEs by the investigator according to the protocol. In addition, a number of your tables misreport these as AEs identified by GSK as opposed to the investigator – this should also be corrected.

- You have interpreted the data (including handwritten notes on the CRFs) to make clinical judgements that are different to the clinical judgements of the investigator who was treating the patient. These judgements should be documented in the paper. There is documentation as an example for one judgement (Box 1) where “more depressed” and “superficial scratches” is coded by you as “suicide attempt”.

Readers may or may not agree with your judgement. I would ask that your other interpretations be detailed in a similar manner so readers can make an informed assessment of the judgements that have been made particularly as they differ from those of the investigator who was treating the patient at the time and was blind to the study drug.

- The paper should include the criteria for determining AEs such as akathisia and whether C-CASA criteria (used by FDA) were used to identify possibly suicide-related adverse events. If criteria such as these were not used, and instead subjective judgements were used, I believe the paper would benefit from including this.

- The paper states that the reviewers chose not to review all the CRFs and that the population for the CRF audit (patients withdrawn from the study and patients previously identified to have had a suicide related AE) differs from the overall population. It is therefore questionable whether it is valid to extrapolate the findings from the CRF audit population to the overall study population as described in the paper. This introduces the potential for significant misreporting and so is something to be included in the paper as part of the discussion rather than a finding.
- The comparison of your analysis with adverse experiences described in Keller et al in Table 6 does not compare like with like and because of this it could be misleading for readers. I think it is important that the differences (below) are made clear in the column headings:
  - (i) Keller et al presented data for AEs reported for 5% of patients or more.
  - (ii) You have moved adverse experiences to different system-organ-classes.
  - (iii) You have used a different coding dictionary (developed after Study 329).
  - (iv) You have included AEs not considered AEs by the investigator who was treating the patient at the time.
  - (v) You have included AEs following the acute phase of the study.
- You state that your analysis reveals evidence consistent with dependence and withdrawal from paroxetine. The possibility of adverse events associated with discontinuation is included in the prescribing information for paroxetine but a risk of substance dependence is not included. I was unable to find evidence in your paper that substantiates this conclusion. Evidence from your analysis that suggests substance dependence should be clearly described with any confounding factors (for example imbalance between groups) and discussed with the other conclusions<sup>1</sup> that there is no clear evidence that drugs in this class have a significant substance dependence liability or show development of a substance dependence syndrome.
- You state that approximately 1000 pages were missing from the CRFs you reviewed. I think it would benefit your paper to include details of the missing pages (which patients, sections missing etc). This will enable readers to assess whether the missing pages negatively impacted the conduct of your research.

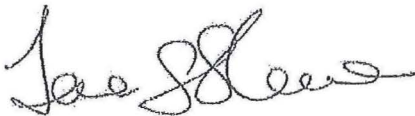
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<sup>1</sup> <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf>

- We provided you with a breakdown of the CRFs provided in the ReadMe file that was included with the data and documents. As stated in this document, we were aware that there were missing CRF pages for one patient (007.000265). This is a very small fraction (less than 1%) of the total number of pages provided and I don't believe this patient was included in your review.
- Throughout "adverse events/experiences" are often described as "harms". As stated in the protocol an adverse experience is identified whether or not it is considered drug related. The term "harms" implies that the adverse events are related to the study drug. Given the term "adverse experiences" was used in the original protocol I believe it would be more appropriate to use this in your paper.

I hope you find these comments useful and I would be happy to discuss them with you in more detail.

Yours sincerely

A handwritten signature in black ink, appearing to read 'James Shannon', with a stylized, cursive script.

James Shannon

Chief Medical Officer