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Department of Psychological Medicine
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Australia

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James Shannon
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Dear Dr Shannon

**Re: Responding to serious adverse events in Study 329**

Thank you for your letter dated 11 March 2014. We are puzzled by your assumption that the right way to establish whether a drug is responsible for an adverse outcome is to require that RCTs demonstrate a statistically significant increase for the adverse effect in question.

We are also surprised that, having set your standard as statistical significance in RCTs, you describe the ultimate demonstration of a statistically significant increase in suicidal behaviour in those taking paroxetine only as a 'signal'.

We do however note that your approach is in keeping with GSK's commercial interests.

Authorities agree that an RCT can provide evidence that helps to identify an adverse outcome, but that the failure to reach statistical significance does not preclude a causal role for a drug in producing adverse outcomes. Moreover RCTs can be misleading if the study population is selected (wittingly or unwittingly) in such a way as to minimise possible adverse outcomes.

Our understanding is that in the case of Paxil, GSK already had compelling evidence from internally assessed cases from the late 1980s that paroxetine caused suicidality, and the finding of increased suicidal events in Study 329 should have heightened already existing concerns about the dangers of the drug, even if that increase was not *statistically* significant.

We will therefore be grateful if you can respond to the following requests/questions:

1. Please provide us with references to support your approach of downplaying the role of Paxil in inducing suicidal thinking and behaviour on the grounds that those increases did not reach statistical significance.

2. Once the "signal" of increased suicidality emerged, did GSK pursue other methods of trying to clarify the role of paroxetine, such as N of 1 trials and Challenge – DeChallenge – ReChallenge and other established and respected forms of pharmacovigilance?

   If not, can you tell us why you have rejected these alternative approaches?

3. Finally, on the basis that it is likely that even more children became suicidal on Paxil than those reported in the Clinical Study Reports or Case Report Forms, we once again ask you to write to all participants who took Paxil, pointing out that if they became suicidal in this trial it may have stemmed from taking Paxil.

   In terms of good clinical care participants should be informed of the implications for other antidepressants they may take and also for their image of themselves and the view health professionals may have of them.

   We understand the learned intermediary argument that you are making but it seems to us that GSK are in the best position to discharge the duty to tell all children in this trial who were on medication that any suicidality experienced was more likely to be treatment related than not.

Yours sincerely

Jon Jureidini

On behalf of the Study 329 RIAT team

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