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October 30 2014

John E. Kraus, MD, PhD, DFAPA
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GlaxoSmithKline
P.O. Box 13398
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Dear Dr Kraus

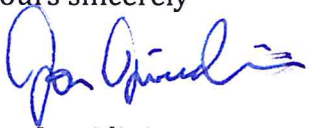
Thank you for your letter dated 27 October, responding to our letter to Dr Shannon (14 October).

We appreciate your acknowledgement that post hoc measures should be analysed per protocol, but we disagree that 'the statistical approach to conduct pairwise comparisons, as reported in the Keller et al manuscript and the clinical study report, is consistent with the protocol'. In both the CSR and the published paper, the analyses appear to be the result of pairwise comparisons without first evaluating the omnibus statistic. As you would know, the omnibus statistic tests to see if the grouping by treatment subdivides the dataset in a non-random way. In this case, it does not. Consequently the pairwise comparisons are meaningless. We can find no justification for your methodology in the CSR, the published paper, or the mainstream statistical literature.

With regard to the designation of the HAM-D depression item as an outcome variable, we asked for *evidence* that this occurred prior to the breaking of the blind. Instead you have recapitulated the often-stated *claim* that there was an 'analytical plan' (see, for example, clinical study report 3.9.2 [where it is referred to as an 'analysis plan'] and 3.13.4 [not 13.13.4]). We have looked in vain for documentation of this analytical plan, including searching the archived discovery documents. It was not submitted as an amendment to the IRB. Is there some reason why GSK cannot provide it?

Unless the analytical plan is produced, we can only assume that it does not exist.

Yours sincerely



Jon Jureidini
On behalf of the Study 329 RIAT team

cc James Shannon, Chief Medical Officer, GlaxoSmithKline