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27 October 2014

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

Dear Professor Jureidini,

Thank you for your letter to Dr. Shannon of 14 October 2014.

Dr. Shannon is currently out of the office. In his absence I have responded to your questions below.

Should variables that were developed prior to opening the blind be analyzed, this should be done in accordance with the study protocol. This states that the study was powered to detect differences between placebo and active groups and Section 9.3.3 of the protocol states that psychometric scales were to be analyzed using parametric analysis of variance.

I believe 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.

With regard to your question about the HAM-D depression item, this was designated as an outcome variable before breaking the blind. A request was made in August 1997 to analyze this item and a program was prepared to run this analysis in the same month. The blind for the study was broken in October 1997 and the program was run at the end of that month.

This is described in the Method section of the Keller et al manuscript where the change in the depressed mood item of the HAM-D is described as a depression related variable declared *a priori*. The clinical study report (Sections 3.9 and 13.13.4) also states this item was identified prior to opening the blind.

Thank you again for seeking Dr. Shannon's views on these questions. I know that he was pleased to have been able to offer help with your research over the past few months and I am pleased that you have reached the point where it has been submitted to a journal.

Kind regards,

John E. Kraus, MD, PhD, DFAPA
VP, Medicines Development Leader