Marty doesn't have email (still, despite my prompting) but his secretary does and can print stuff form him. It is:

Barbara_ryan@brown.edu

NR

-----Original Message-----
From: James_P_McCafferty@sbphrd.com [mailto:James_P_McCafferty@sbphrd.com]
Sent: Tuesday, March 09, 1999 2:02 PM
To: SallyL@stimedinfo.com
Cc: Ryannd@MSX.UPMC.EDU; MStrober@NPIH.MEDSCH.UCLA.EDU;
Rosemary_Oakes@sbphrd.com
Subject: Comments 329 Manuscript

Hi Sally,

I have reviewed the second draft of the manuscript. It is nicely done but I do have the following comments. Please note that several of the questions raised by the authors have been addressed in the comments from Rosemary Oakes, the SB statistician. These are attached below.

I agree with Rosemary that we must describe the protocol defined "primary variables" and add descriptions for the various "depression related " variables. We may also need to justify some of these endpoint. Clearly clinicians will accept the HAMD and the global evaluations as valid endpoints, but the definition of remission and response require some explanation. I would state that all endpoints were identified in an analytical plan prepared prior to opening the blind.

I suggest we consider additional tables describing the depression efficacy results. The only table shown provides negative results with secondary measures. I also expect reviewers may question the effect size in the HAMD and its clinical meaning, as well as the large placebo response based on remission.

A reviewer may question the adverse events profile for paroxetine. Although most events reported were similar in nature and frequency to that reported in the adult, there were higher number of paroxetine patients who reported "emotional liability" and "hostility". The term "emotional liability" was catch all term for "suicidal ideation and gestures". The hostility term captures behavioral problems, most related to parental and school confrontations. Although the investigators did not feel this was a problems, it may raise a flag if not described.

The text describing Figure 2 is incorrect. I believe it is a "LOCF only" analysis.

My secretary compared the values reported in the tables to the approved Q/C version of the report. Some minor corrections are needed. I will send these via regular mail.

I do not have Dr. Keller's E-mail address, so I will send via regular mail.

Jim

ROSEMARY OAKES
05-Mar-1999 18:03

Sr. Statistician: Biostatistics & Data Sciences - Phase IV DART   UP:
   4-1239D, mail code UP4130   8282-5057, FAX: 8282-4702

To: James P McCafferty
cc:
Subject: PAR329 - Rosemary's comments on manuscript

Jim:

Here are my comments on the PAR329 manuscript:

(1) pg 3, 11: It is not clear from the manuscript which variable was primary for the study. As it reads, the reader might imply there are 8 primary variables. Can we either specify which was primary (as determined by sample size calculcations) or refer to these variables as 'depression-related variables.'

(2) pg 3/4, 11: Please clarify the primary timepoint of interest (i.e., study endpoint--last observation carried forward). It's not too clear to me from these paragraphs.

(3) pg 4, 16, 18: There are questions about statistical significance here. We did not perform statistical tests to compare the reasons for withdrawal. The study was not designed for such tests and we usually try to keep the additional tests performed to a minimum.

(4) pg 11, 15: There were 150 screen failures--so the number of patients screened could be considered as 150+275=425. Keep in mind this is only those patients of whom we have a record on the database.

(5) pg 13/14: In the statistical methods section, please revised the 1st two sentences of the 1st paragraph to the following sentence. (Note, the text represented by the ... can remain the same.)

"Changes from baseline to endpoint in the ... implemented using the general lines models (GLM) procedure of the SAS system with a model including effects for treatment and investigator."

Please add the following text to the end of the 3rd sentence of the paragraph.

"...(CATMOD) of the SAS system with a model including effects for treatment and investigator."

(6) pg 14: I will note that the original sample size calculations called for 300 patients and this was determined apriori. The 275 was a modified number.

(7) We did not compute confidence intervals for the data. Since these are not presented, I would remove reference to them from the text and from Table 4. Also, why does Table 4 not include any of the 8 depression-related variables? I find it odd that only the 'secondary' variables are presented. Without figures or the table, this gives the reader no reference, other than the text, to this data.

(8) Why is there only a graph for % patients in remission? I would suggest that we might want to have graphs for all depression-related efficacy variables.

(9) Due to time constraints, I have not confirmed any numbers with our source tables. I will look as these as I have time. I assume some QC was done to confirm these numbers(?).

Regards,
rosemary.