

From: James P McCafferty/DEV/PHRD/SB_PLC
To: SallyL@stimedinfo.com
Subject: RE: Paroxetine adolescent depression study is now finalized
Date: 07/19/1999 15:03:51 (GMT-05:00)

Sally,

I reviewed the latest version of the manuscript and have some comments. Two are minor but one is of some concern.

Minor:

1) The statement that most subjects had a "family history of depression" is based on data in Table 1 that shows that 90% of the patients had a positive family history of "major depression". However, you may recall, that these data were collected using an instrument that asked the parents whether any first degree relative of the patient had shown "signs or symptoms of depression". This is not the same as a diagnosis of major depression. I suggest we remove the term "major" from the table.

2) In the discussion we express the sentiment that future clinical trials with TCAs are unlikely to be conducted because of 1) expired patents and 2) cardiovascular liabilities. Using expired patents as a reason not to conduct a trial seems too commercial, although there is some truth to this. Perhaps we could describe that there is less interest in TCA trials as these are "older therapies", rather than use the patent expiry argument. Or more important than the patent situation, is the consistent finding in clinical trials of little or no benefit with TCAs, once again supported by the results of the present study.

Major.

Safety. It seems incongruous that we state that paroxetine is safe yet report so many SAEs. I know the investigators have not raised an issue, but I fear that the editors will. I am still not sure how to describe these events. I will again review all the SAEs to make myself feel comfortable about what we report in print.

Jim

DR KELLER: PLEASE RETYPE ON YOUR LETTERHEAD

REVISE AS YOU WISH

February 6, 2001

Mina K. Dulcan, MD
Editor
*Journal of the American Academy of
Child and Adolescent Psychiatry*
Children's Memorial Hospital
2300 Children's Plaza, #156
Chicago, Illinois 60614-3394

RE: MANUSCRIPT 2000/1310

Dear Mina:

Thank you for sending the additional Reviewer comments. Enclosed in this package are the following items:

- 1 copy of the manuscript with changes highlighted
- 3 copies of the manuscript without the highlighting
- Response to reviewers' comments
- 1 diskette of the manuscript without highlighting in Word 97.

The figures have not changed, therefore, you should be able to use the EPS file sent previously.

We were able to address each of the Reviewer's suggestions and hope that you find the final version acceptable. I trust that the manuscript now meets your needs and will be accepted for publication.

Thank you for your assistance and for the excellent comments from your Reviewers. I look forward to hearing from you about the publication schedule and timelines for reviewing page proofs.

With best regards,

Martin B. Keller, MD

encl

From: Laden, Sally <SallyL@stimedinfo.com>

To: Barry S Brand/FPL/Pharms/SB_PLC@SB;
Mark E Weihmann/FPL/Pharms/SB_PLC@SB;
Matt R Battin/FPL/Pharms/SB_PLC@SB;
Scott A Sproull/FPL/Pharms/SB_PLC@SB;
Sheila X Hood/FPL/Pharms/SB_PLC@SB;
Steven M Vitale/FPL/Pharms/SB_PLC@SB;
Terri E Smith/FPL/Pharms/SB_PLC@SB

CC: File <File@stimedinfo.com>;
Jim McCafferty <james_p_mccafferty@sbphrd.com>

Subject: RE: PAR 329 - Adolescent Depression Manuscript accepted for publication

Date: 01/11/2001 13:59:24 (GMT-05:00)

cc: 1301 (client)

> Dear Paxil Team:

>

> At long last, the Journal of the American Academy of Child and Adolescent
> Psychiatry has accepted the manuscript entitled "Efficacy of Paroxetine in
> the Treatment of Adolescent Major Depression: A Randomized, Controlled
> Trial". Marty Keller is the lead author along with approximately 20
> other investigators in child psychiatry.

>

The journal hasn't released a publication date yet, but it is likely
that the paper will appear in the March or April issue.

> This news comes in time for Karen Wagner to present the data as 'in press'
> at next week's Forum 2001 meeting, and hopefully it will be published well
> before the APA in May.

>

Thanks and please contact me if you have questions or need
additional information.

Sally K. Laden, MS
Associate Editorial Director
Scientific Therapeutics Information, Inc
505 Morris Ave
Springfield, New Jersey 07081

TEL: (973) 376-5655

FAX: (973) 376-0611

DIRECT TEL: (203) 272-9750

DIRECT FAX: (203) 272-6917

EMAIL: sallyl@stimedinfo.com

PAR008409833

From: Sheila X Hood/FPL/Pharms/SB_PLC
To: SallyL@stimedinfo.com
CC: HOLLY_WHITE@nyc.cohnwolfe.com
Subject: RE: Publication date for Paroxetine Adolescent Depression study (PAR 329)
Date: 03/05/2001 17:00:01 (GMT-05:00)

Hi Sally

Would you please provide both myself and Holly White at Cohn and Wolfe copies of the proofs.

Thanks in advance

Cheers Sheila

----- Forwarded by Sheila X Hood/FPL/Pharms/SB_PLC on 03/05/2001 04:57 PM -----

HOLLY_WHITE%Exchange@yr.com on 03/05/2001 11:41:51 AM
To: Sheila X Hood/FPL/Pharms/SB_PLC@SB
cc:

Subject: RE: Publication date for Paroxetine Adolescent Depression study (PAR 329)

Yes, please. Originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show Paxil was effective in treating adolescent depression, which is not something we want to publicize. However, we should prepare a Q&A and key messages in case reporters do cover this study. The proofs would definitely come in handy.

-----Original Message-----

From: Sheila.X.Hood@sb.com@YRINC
Sent: Wednesday, February 28, 2001 3:37 PM
To: WHITE, HOLLY
Subject: Publication date for Paroxetine Adolescent Depression study (PAR 329)

Hi Holly

Do you want to receive copies of the proofs? Should we do any media around the publication?

Cheers Sheila

----- Forwarded by Sheila X Hood/FPL/Pharms/SB_PLC on 02/28/2001 03:35 PM -----

PAR012140677

"Laden, Sally" <SallyL@stimedinfo.com> on 02/27/2001 01:20:56 PM

To: "Jim McCafferty" <james_p_mccafferty@sbphrd.com>, "Raj Kumar" <rajinder_kumar@sbphrd.com>, "Rocco Zaninelli" <rocco_2_zaninelli@sbphrd.com>, Scott A Sproull/FPL/Pharms/SB_PLC@SB, Matt R Battin/FPL/Pharms/SB_PLC@SB, Terri E Smith/FPL/Pharms/SB_PLC@SB, Shella X Hood/FPL/Pharms/SB_PLC@SB, Steven M Vitale/FPL/Pharms/SB_PLC@SB, Johnny Im/FPL/Pharms/SB_PLC@SB, "Tania Lyons" <tania_lyons@mccann.com>, "Sherri Jaffe" <sherri_jaffe@cohnwolfe.com>
cc: "Romankiewicz, John" <JohnR@stimedinfo.com>, "Phillips, Marion" <MarionP@stimedinfo.com>, "Kistner, Una" <UnaK@stimedinfo.com>, File <File@stimedinfo.com>

Subject: Publication date for Paroxetine Adolescent Depression study (PAR 329)

cc: 1301

Hello Paxil Team:

We learned this morning that the Journal of the American Academy of Child and Adolescent Psychiatry has scheduled a tentative publication date for this manuscript. According to their editorial offices, proofs will be available in mid-May with publication scheduled for August, 2001.

We have offered to help Dr Keller's office proof the galleys in May and could make them available to you then.

Please contact us if you have questions or require additional information.

Sally K. Laden, MS
Associate Editorial Director
Scientific Therapeutics Information, Inc
505 Morris Ave
Springfield, New Jersey 07081

TEL: (973) 376-5655
FAX: (973) 376-0611

DIRECT TEL: (203) 272-9750
DIRECT FAX: (203) 272-6917

EMAIL: sallyl@stimedinfo.com

PAR012140678

From: Sheila X Hood/FPL/Pharms/SB_PLC
To: HOLLY_WHITE@nyc.cohnwolfe.com;
JAFFE, SHERRI <SHERRI_JAFFE@nyc.cohnwolfe.com>
Subject: Re: Paxil adolescent publication
Date: 04/27/2001 12:49:05 (GMT-05:00)

In case I haven't already forwarded, FYI. Cheers Sheila
----- Forwarded by Sheila X Hood/FPL/Pharms/SB_PLC on 04/27/2001 12:40 PM -----

Matt R Battin
04/25/2001 04:52 PM
To: "Laden, Sally" <SallyL@stimedinfo.com>
cc: Scott A Sproull/FPL/Pharms/SB_PLC@SB, Matt R Battin/FPL/Pharms/SB_PLC@SB, Terri
E Smith/FPL/Pharms/SB_PLC@SB, Steven M Vitale/FPL/Pharms/SB_PLC@SB, Sheila X
Hood/FPL/Pharms/SB_PLC@SB, Johnny Im/FPL/Pharms/SB_PLC@SB

Subject: Re: Paxil adolescent publication

Sally,

Because Dr. Keller is a member of our advisory board and an influential KOL we will support his request to purchase 500 reprints.

Terri,
Since this info is off label we won't be able to use in promotion, however, we might be able to work with Traci Lee to have reprints sent out as part of our med query on the use of Paxil in children. Can you follow up with her to see if this is possible?

Sheila,
You may want to give Cohn and Wolfe a heads up on the timing of this for media opportunities.

Thanks,

Matt

"Laden, Sally" <SallyL@stimedinfo.com> on 04/25/2001 10:50:57 AM
To: Scott A Sproull/FPL/Pharms/SB_PLC@SB, Matt R Battin/FPL/Pharms/SB_PLC@SB,
Terri E Smith/FPL/Pharms/SB_PLC@SB, Steven M Vitale/FPL/Pharms/SB_PLC@SB, Sheila X
Hood/FPL/Pharms/SB_PLC@SB, Johnny Im/FPL/Pharms/SB_PLC@SB
cc: "Jim McCafferty" <james_p_mccafferty@sbphrd.com>, "Dodge, Monica"
<MonicaD@stimedinfo.com>, File <File@stimedinfo.com>
Subject: Paxil adolescent publication

cc: 1301

Dear Paxil Marketing Team:

PAR012136791

We have just proofed the page proofs of the paper entitled "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial". The Journal of the American Academy of Child and Adolescent Psychiatry has tentatively scheduled an August, 2001 publication date.

Marty Keller is the corresponding author and will need a supply of reprints. I anticipate that he will need a sizable quantity because of the importance of this paper. Probably in the vicinity of 500 reprints. Dr Keller is wondering if GSK will fund the purchase of these reprints.

I am in touch with the journal about reprint costs, but estimate that a quantity of 500 will run somewhere around \$1500 not including shipping.

So, the questions are:

1. Is GSK willing to fund the purchase of reprints for Dr Keller?
2. Does GSK need a quantity of reprints for their use? If so, how many?

Thanks for your response to this query.

Sincerely,

Sally K. Laden, MS
Associate Editorial Director
Scientific Therapeutics Information, Inc
505 Morris Ave
Springfield, NJ. 07081

DIRECT TEL: (203) 272-9750
DIRECT FAX: (203) 272-6917

TEL: (973) 376-5655
FAX: (973) 376-0611

email: sallyl@stimedinfo.com

From: Ryannd@MSX.UPMC.EDU
To: James P McCafferty
Subject: RE: Comments 329 Manuscript
Date: 03/09/1999 15:46:43 (GMT-05:00)

Marty doesn't have email (still, despite my prompting) but his secretary does and can print stuff from 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 calculations) 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.