Brecher, Martin

From: Brecher, Martin
Sent: Tuesday, March 20, 2001 8:03 AM
To: Travers, John T
Subject: FW: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

Importance: High

John,
Although the omission of the data beyond 78 weeks in the second paragraph of the results section represents an important flaw, the core message of the publication contains the data out to 4 years.
How is the"message" (ie weight neutral or minimal weight gain) combined with the carrier?
I think the paper supports "minimal weight gain"
Martin

-----Original Message-----
From: Melvin, Karen S
Sent: Tuesday, March 20, 2001 4:58 AM
To: Travers, John T; Brecher, Martin
Subject: RE: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

Martin,
Figures 1 and 2 do include all the data out to 4 years. They use the last recorded weight value.

The attachment below contains the data from the second paragraph of the results section including the time epochs > 78 weeks and contain the patient numbers for your information.

WEIGHT
NFIDENCE INTERV/

Thanks
Karen

From: Brecher, Martin
Sent: 19 March 2001 21:52
To: Travers, John T; Melvin, Karen S
Subject: FW: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

Karen,
Please see John's e-mails in the chain. The key question for me is whether Figures 1 and 2 include all the weight data out to 4 years. Also what were the patient numbers for the time epochs >78 weeks.

John,
If Figures 1 and 2 included all the data out to 4 years, can you support the reprint carrier without a message of weight neutral?
I think this turns in substantial measure on the number of patients after 104 weeks.
Martin

-----Original Message-----
From: Zaal, Judy D
Sent: Monday, March 19, 2001 9:45 AM
To: Brecher, Martin
Subject: FW: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

-----Original Message-----
From: Travers, John T
Sent: Friday, March 16, 2001 1:09 PM
To: Judy Zaal
Subject: FW: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

Judy,

Please forward to Martin Brecher. Thanks

Regards,
John
X67370
302-886-7370

-----Original Message-----
From: Travers John JT
Sent: Friday, March 16, 2001 1:04 PM
To:
Subject: RE: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

Martin,

The mean weight change data beyond 18 months (78 weeks) are, I think, less consistent with a "weight neutrality" story than the data prior to 18 months. I have graphed the data on the attached slide for your review. One note: in the poster and the paper an error was made that is corrected in my graph. In the poster and paper the mean weight gain at 53-78 weeks was given as 1.94 kg. From the data tables provided to me it was actually 2.03 kg. For the following interval (79-104 weeks) the change was 1.94 kg, so I think someone simply and inadvertently misaligned one interval as they transcribed the data. This is only potentially significant in that, with such a misalignment, the next mean weight change that would have been encountered was 3.89 kg. It is the data from 3.89 kg and subsequent which were omitted from the poster and paper.

The ultimate impact on the reprint carrier is that, in the absence of a valid reason for excluding the data beyond 18 months, I can't endorse the reprint/carrier for promotional use as they may not represent a fair and balanced disclosure of the data available to us. This is, I think, compounded by the failure of the paper (and therefore the reprint carrier) to present the incidence of "weight gain" as an adverse event (4.9%) relative to the incidence of "weight loss" as an adverse event (1.9%). These data also suggest to me that the concept of "weight neutrality" are not supported by these data.

I will be interested in tour thoughts as well.

<<File: Mean Weight Changes.ppt>>

Regards,
John
X67370
302-886-7370

-----Original Message-----
From: Brecher, Martin
Sent: Thursday, March 15, 2001 2:46 PM
To: Travers, John T
Subject: RE: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

John,
I don't know the answer to your question and passed it along. How does the answer affect the reprint carrier?
Martin

-----Original Message-----
From: Travers, John T
Sent: Wednesday, March 14, 2001 10:02 AM
To: Brecher, Martin
Subject: RE: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article
Importance: High

Martin,

An additional question has arisen around these weight data. In response to my questions below I received data tables depicting mean weight changes out to 208 weeks (4 years). In the paper, in the 2nd paragraph of the RESULTS section only the data out to 18 months were presented. It appears, however, that subsequent to this, in Figure 1, the mean weight changes by baseline BMI included data beyond 18 months.

Do you know what the thinking was that went into presenting only the 18 month data in the first portion of the RESULTS section? The US business is quite keen on getting this reprint carrier approved quickly, but before I can sign-off on it I need to understand these data a bit better and I am hoping you can help.

Regards,
John
X67370
302-886-7370

-----Original Message-----
From: **Brecher, Martin**
Sent: Friday, March 02, 2001 4:51 PM
To: Travers, John T
Subject: RE: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article

John,
Re point 1:
We stretched to make the weight neutral claim, proposing that since the CI's spanned the 0 line or were below it (weight loss in the obese patients) the data could be interpreted that on average seroquel did not cause weight gain, hence the characterization as weight neutral. Not compelling, but defensible.
Martin

-----Original Message-----
From: Travers, John T
Sent: Thursday, March 01, 2001 2:49 PM
To: Jones, Martin AM (PHMS)
Cc: Brecher, Martin; Rak, Ihor W
Subject: Brecher, Rak, Melvin & Jones Long-Term Seroquel Weight Article
Importance: High

Martin,

I am reviewing a US promotional sales piece for Seroquel around the above article and hope you can answer a few questions for me:

1. In Figure 1 all but one of the 95% Confidence Intervals (CIs) span zero. In the section, EFFECT OF BASELINE BODY MASS INDEX, this is used in support of the concept of Seroquel being "weight-neutral". It would seem to me that these CIs would more likely support the following interpretations:
    a. In the Baseline BMI < 18.5 group, the mean weight change may have been zero. However, the mean change may have just as likely have been as high as a 14.8 kg increase (the approximate upper end of the CI) down to a as low as a 7 kg decrease (the approximate lower end of the CI). In other words, the data would suggest that patients who begin treatment with a BMI of < 18.5 could, on average, gain as much as 32 pounds or lose as much as 15 pounds.
    b. In the Baseline BMI >35 group a statistically significant decrease in weight was observed. In other words, the data would suggest that patients who begin treatment with a BMI of > 35 will, on average, lose weight.
    c. It is unclear to me how these can be reconciled with the concept of "weight neutral". The important aspect of the CI would seem not to be whether or not it spans zero but rather its upper and lower bounds.

2. For the weight changes by time interval (2nd paragraph in the RESULTS section) point estimates are provided for the mean changes. Were 95% Confidence Intervals for these point estimates also calculated? If so, can you provide them? They would seem to be as

important here as in the BMI and dose analyses. If they have not been calculated, could you calculate them?

3. In this paper only mean weight changes are presented (other than the 1 patient who withdrew due to weight gain as an adverse event). In the US label for Seroquel we report a statistically significant dose response for the adverse event of weight gain in the acute trials.
    a. Do you have the incidence of weight gain as an adverse event for this long-term cohort?

4. In the US label we also report a statistically significant drug vs placebo group difference for the variable "weight change of greater than or equal to 7%".
    a. Do you have the incidence of weight gain as defined by a greater than or equal to 7% increase from baseline to endpoint?

We are to review this promotional piece next Tuesday. Any clarification you can provide would be appreciated.

Regards,
John
X67370
302-886-7370