To: CN=Mauricio F Tohen/OU=AM/O=LLY@Lilly
CC: CN=Giedra M Campbell/OU=AM/O=LLY@Lilly; CN=John C Saunders/OU=EMA/O=LLY@Lilly; CN=Richard C Risser/OU=AM/O=LLY@Lilly
Date: 10/16/2002 11:38:37 AM
From: CN=Doug Williamson/OU=AM/O=LLY
Subject: Re: Clinical Summary update

But, surely we want patients to stay on OLZ long-term, so the reversibility of the event is not an advantage?

Doug Williamson MD, MRCPsych
Zyprexa Bipolar Team
317 433-2486
redacted
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(+1) (317) 651-4180

Mauricio F Tohen

10/16/2002 09:49 AM

To: Giedra M Campbell/AM/LLY@Lilly
cc: Doug Williamson/AM/LLY@Lilly, John C Saunders/EMA/LLY@Lilly, Richard C Risser/AM/LLY@Lilly
Subject: Re: Clinical Summary update

I would like to include the FU glycemia issue because it points towards the reversibility of the event

Giedra M Campbell

10/16/2002 08:47 AM

To: John C Saunders/EMA/LLY@Lilly
cc: Richard C Risser/AM/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Doug Williamson/AM/LLY@Lilly
Subject: Re: Clinical Summary update

Hi John--

I sent the last e-mail by accident before finishing it. A few more comments on the comments.....

You asked that the disposition sentence from the Overall Integ Database include the concept that completers did not experience recurrence. I added a phrase to match what was added for HGHL. Let me know if this works for you.

> Of the 1545 patients who received olanzapine in the included studies, 582 (37.7%) completed the last study phase in which they participated without recurrence of a manic, mixed, or depressive episode or discontinuing for any other reason.

Regarding the discussion of the statistically significant difference in glucose mean change for HGFU, I haven't yet heard from Mauricio about how strongly he feels about including it. Both you and Doug have expressed reservations about it. Mauricio, Rick, your thoughts? (Scroll to the older e-mail below for the actual text--note also text highlighted in yellow within that text showing how I might change the existing text according to a request from John to avoid the phrase "driven by.")

I am now working on inputting changes from validators---they found some good stuff!

Call me if you want to discuss anything in particular further!

Thanks,

Giedra

Giedra Campbell
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John C Saunders

10/16/2002 06:00 AM

To: Giedra M Campbell/AM/LLY@Lilly
cc: Susan Forda/EMA/LLY@Lilly, Anne M Goebel NONLILLY/AM/LLY@Lilly, Joanna Nakielny/EMA/LLY@Lilly, Richard C Risser/AM/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Krisann M Van Hoosen/AM/LLY@Lilly, Doug Williamson/AM/LLY@Lilly
Subject: Re: Clinical Summary update

some comments after hasty review

John Saunders
European Regulatory
Phone: 44 (0) 1276-483381

Giedra M Campbell

15/10/2002 18:38

To: Richard C Risser/AM/LLY@Lilly, John C Saunders/EMA/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Doug Williamson/AM/LLY@Lilly
cc: Anne M Goebel NONLILLY/AM/LLY@Lilly, Krisann M Van Hoosen/AM/LLY@Lilly
Subject: Clinical Summary update

Dear John, Mauricio, Rick, and Doug:

The clin summ is moving right along, at least from my end. Formal editing is underway, and I will have results of validation efforts by the end of today.

Can you please send me your thoughts on the e-mail below ASAP, or at least give me an idea of when you *will* get back to me? (Doug, I know you may be unable to get back to me at all, but let me know what you think.) Note that this is scheduled to go to publishing by the end of the day on Thursday, so time is running short!

Thanks,

Giedra

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----- Forwarded by Giedra M Campbell/AM/LLY on 10/15/2002 12:32 PM -----

Giedra M Campbell

10/11/2002 11:17 AM

To: John C Saunders/EMA/LLY@Lilly
cc: Richard C Risser/AM/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Doug Williamson/AM/LLY@Lilly
Subject: Re: clinical summary: yet another version

Hi John--

It was good to talk to you this morning (afternoon!) and hammer out some of the clinical summary issues. Below is a summary of specific issues/areas that I would still like you and the othe reviewers to review (though I would also encourage another complete review from anyone who has the time!), and then after that, under a line, are excerpts from previous e-mails, with ANSWERS to questions that we discussed today, so that other reviewers can see what we covered.

I am also attaching the latest version in case anyone needs it, but if you have already printed yesterday's version to look at, yesterday's should be fine, although there have been some more recent text corrections as detailed below (plus the table numbering has been updated).

Please re-review efficacy key findings (Section 2.1)

Please review the conclusions of each of the efficacy sections: 2.3.5, 2.4.5, and 2.5.5. In particular, please verify that the sentences about FU seem okay, given the less robust results of that study in the protocol-defined analyses.

Please review overall conclusions of efficacy section (2.7).

Section 3.2.1.1: John, here is how I rewrote the HGHL disposition section to try to soften the "only 66 completers" language. New or revised text is shown in green:

Table WS.2.2 (Section 2.3.2) summarizes patient disposition and reasons patients discontinued from the double-blind maintenance period. Three hundred sixty-one patients began double-blind treatment (225 olanzapine, 136 placebo). Patients who experienced recurrence were discontinued from the double-blind maintenance period (and entered into the open-label rescue period), but “recurrence” was not formally captured as a reason for discontinuation for these patients. At the end of the double-blind maintenance period, 66 patients had completed all 12 months of treatment without recurrence of a manic, mixed, or depressive episode or discontinuing for any other reason. A statistically significantly greater percentage of olanzapine-treated patients completed double-blind treatment compared with placebo-treated patients (23.6% vs. 9.6%). The most common reasons for discontinuation in both treatment groups were lack of efficacy, adverse events, and patient decision. Placebo-treated patients were statistically significantly more likely to discontinue due to lack of efficacy than were olanzapine-treated patients. There were no other statistically significant treatment group differences for individual reasons for discontinuation.

Please re-review Sections 3.6.1.1, 3.6.3.2, and 3.6.7 (excerpts below), which discuss d/c due to AE for final disposition vs in any interval. I think the text is pretty clear now (see red highlighting).

3.6.1.1 SAYS: Table WS.3.66 summarizes patient disposition and reasons patients discontinued from the included studies. This table presents each patient's final disposition; ie, disposition in the last phase in which a patient participated. Of the 1545 patients who received olanzapine in the included studies, 582 (37.7%) completed the last study phase in which they participated. Given the long durations of the included studies, this completion rate is relatively high. Only 220 patients (14.2%) discontinued participation in the study as a result of adverse events.

3.6.3.2 SAYS: Table WS.3.71 summarizes patient discontinuations due to adverse events at any point during olanzapine treatment. A total of 230 olanzapine-treated patients (14.9%) discontinued due to adverse events. This is slightly higher than the 220 patients whose final disposition reflected discontinuation due to adverse events because some patients could have discontinued one study phase due to adverse events but then entered a subsequent phase and discontinued for another reason or completed the relevant phase. Two patients discontinued twice due to adverse events....

3.6.7 SAYS: A total of 220 patients (14.2%) discontinued from the study due to adverse events. (the study, not the phase)

Mauricio/Rick/Doug: Please review Section 3.7.1.1: Discussion of stat sig difference in mean change in glucose for the HGFU maintenance period. John and I discussed Mauricio's comment (below, purple) and the resulting text (below, blue), based on analyses in HGFU study report. John is ok with this explanation BUT has reservations about including it, because it operates on the assumption that olz automatically increases glucose. This may be a true assumption, but do we want to present this this way? Does inclusion of this explanation open us up to questions on glucose that we'd rather not bring up? John suggests that if we include it, we need to pass it by Patrizia to check it against the company line on this topic. Mauricio--how strongly do you feel about including an explanation here? (Discussion at ISS online resulted in conclusion to just present the result without explanation.)

As shown in Table WS.3.x, mean changes in nonfasting glucose were small across all databases, with just one statistically significant treatment group difference. In the HGFU database, patients receiving olanzapine plus mood stabilizers (Olz+MS) had a mean increase while patients receiving placebo plus mood stabilizers (Pla+MS) had a mean decrease. .(MT:) Since some patients had received olanzapine during the acute phase, it is possible that the decreace in nonfasting glucose in the Pla+MS was secondary to the olanzapine discontinuation.

As shown in Table WS.3.x, mean changes in nonfasting glucose were small across all databases, with just one statistically significant treatment group difference. In the HGFU database, patients receiving olanzapine plus mood stabilizers (Olz+MS) had a mean increase while patients receiving placebo plus mood stabilizers (Pla+MS) had a mean decrease. Analyses of mean change presented in the HGFU study report demonstrate that this statistically significant difference between groups during the double-blind maintenance period was the result of the effect on glucose of switching treatments following the acute phase: Pla+MS patients who had previously received olanzapine showed a mean decrease of –0.50 mmol/L during the maintenance period while Olz+MS patients who had previously received placebo had a mean increase of 1.11 mmol/L. In contrast, Pla+MS

patients who had previously received placebo had an increase of 0.10 mmol/L during the maintenance period, and Olz+MS patients who had previously received olanzapine had an increase of 0.15 mmol/L.

Section 3.7.3.2: John, I have reworded the text throughout the EPS section to make it CRYSTAL CLEAR when we are talking about incidence of abnormalities based on scales changes vs. when we are talking about incidence of EPS-related MedDRA-coded adverse events. Because the akathisia section is really the only one that was confusing (since the AE term AND the scale-related abnormality are both akathisia), I also added the words "the adverse event" prior to the word "akathisia" wherever appropriate. See below (with changes highlighted in red):

Table WS.3.23 summarizes the incidence of treatment-emergent akathisia, as determined by assessing the proportion of patients with a Barnes Akathisia Scale global score 2 at any double-blind visit from among those with a score <2 at baseline, across study databases. The incidence of treatment-emergent akathisia in olanzapine-treated patients ranged from 0.0% in Study HGHT to 18.4% in Study HGHQ. There were no statistically significant differences in incidence between olanzapine groups and comparator groups.

Treatment-emergent adverse events related to akathisia were assessed within the overall integrated database (WS.X.X). The only adverse events related to akathisia in this database were akathisia (reported by 4.2% of patients), restlessness (3.4%), increased activity (1.1%), and hyperkinetic syndrome (0.2%). The incidence of the adverse event akathisia ranged from 0.5% in the HGHT database to 8.8% in the HGHQ database, and was statistically significantly more common in olanzapine-treated patients than in divalproex- and placebo-treated patients in the HGHQ and HGHL databases, respectively. Only 2 patients in the overall integrated database discontinued due to this adverse event, one from Study HGHQ and one from Study HGFU.

None of the following akathisia-related adverse events were seen in the database: : akathisia aggravated..... [this info was previously included at beginning of 3.7.2]

Please re-read safety conclusions (Section 3.8).

ISSUES JOHN AND I COVERED (Other reviewers--your input in these areas is still welcomed, as appropriate) (John's answers in green):

John, I have noticed that the structure of the introductory section of the efficacy part is different than that presented with the mania submission. In particular, the mania submission presented details of the study designs and objectives prior to presenting the statistical methodology. We essentially present the same information, but we present it later, for each study individually. I just wanted to bring it up and make sure that this structure will be acceptable to CPMP. I could change it if needed, but it would be tedious and involve a lot of renumbering, so if it's needed, I need to know ASAP. JOHN OKAYED STRUCTURE.

along the same lines, I have added a section called "Validation of Endpoints" (Section 2.2.2) because I noticed this section in the template and we didnt' have anything like it. Please take a look and confirm whether it is necessary, and if so, whether the section as written is adequate. I welcome further input! JOHN OKAYED SECTION, with minor changes.

In overall conclusions of efficacy section (2.7). I was unable to find literature to support the placebo bias issue--but it seems self-evident, so I tried to write it up that way. Please have a look and see what you think. Is it important for us to include more than one explanation here? We deleted placebo argument; the population differences are sufficient.

Prolactin details are deleted from HGHL safety conclusions.

Section 3.6.3.5: I have summarized the pregnancies in a single paragraph. John, can you verify that this is what you meant in your comment about this section? Take a look and see what you think. if you want me to put the individual summaries back, I can. JOHN OKAYED PARAGRAPH with one minor change to reflect that abortions were by patient request.

Please verify whether or not HIGH3 analyses should be left in the document. They would be easy to delete. WE DELETED.

Section 3.7.1.2: We left the OID mean change line out of the HbA1c table.

John read and okayed section discussing COSTART/MedDRA conversion.

[attachment "clin summ for rev Oct 11 jcs.doc" has been removed by Giedra M Campbell/AM/LLY]