

To: CN=Robert W Baker/OU=AM/O=LLY@Lilly; CN=James B Gregory/OU=AM/O=LLY@Lilly
CC: CN=Michele Sharp/OU=AM/O=LLY@Lilly; CN=Fan Zhang/OU=AM/O=LLY@Lilly; CN=Richard C
Risser/OU=AM/O=LLY@Lilly
Date: 05/03/2001 05:38:03 PM
From: CN=Michele Sharp/OU=AM/O=LLY

Robert and Jim,

I apologize for the poor timing of this e-mail; I am sure that you are extra busy with APA preparations. However, I have finally a peaceful moment at my desk.....I wanted to make both of you aware that the Zyprexa Team will be conducting interim analyses for the Redacted Redacted and the bipolar maintenance registration study (HGHL) this year. Based on the enrollment rates, these interims will likely occur in the August timeframe. As background, these interim analyses are pre-specified in the protocols and the intent of the interim analyses is to terminate the study if results demonstrate overwhelming efficacy or overwhelming ineffectiveness.

The reason for this e-mail is to address a question raised a couple months ago about getting secondary endpoint results in the label. If we believe that from a marketing and/or medical perspective secondary results need to be in the label, then we ideally need to document with the FDA **prior to conducting the interim analyses** which secondary endpoints we will include in our proposed label. However, if we commit to the result, then we must put the result in the label regardless of outcome. Remember that at this point we have been presenting secondary results in our promotional pieces. Of course, our ability to continue this practice could change if DDMAC would find the use of secondary endpoint data violative.

I want to make it clear that the interim analyses will only be looking at the primary endpoint. So, we could take the strategy (with some risk) of documenting with FDA our intent to include secondary results in the label at a later time; however once we "look" at blinded data then the FDA could become suspicious of what other data have we looked at (and not told them), especially if we would submit this secondary result proposal soon after conducting the interim analyses.

I am asking you to partner with me in deciding whether we want to propose secondary endpoints in the label. For your consideration, here are the primary and secondary efficacy measures we are collecting for the 2 studies.

HGGY---Bipolar Depression

Redacted

Secondaries: Redacted

induction of mania (≥ 15 Y-MRS total score)

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HGHL--Bipolar Maintenance

Primary: prevention of relapse into manic or mixed episode after stabilization with open-label olanzapine (measured by increase in Y-MRS total score and HAMD-21 total score) during 12 months of therapy

Secondaries: improvement in Y-MRS total score, Y-MRS non-psychoic items, SADS-C Mania Rating Scale score and 2 subscores, HAMD-21 total score, HAMD-21 mood item, MADRS total score, BPRS total score, PANSS total and positive scores, CGI-BP severity during the 6-12 weeks of open-label olanzapine therapy

improvement in Y-MRS total score, Y-MRS non-psychoic items, SADS-C Mania Rating Scale score and 2 subscores, HAMD-21 total score, HAMD-21 mood item, MADRS total score, BPRS total score, PANSS total and positive scores, CGI-BP severity during 12 months of therapy

Let me know your initial thoughts and if we need to discuss further, I'll schedule a meeting with you after APA.

Thanks,
Michele

PS. Rick and Fan (who I have copied on this message) are the Zyprexa statisticians who are preparing for these interim analyses.

To: CN=Robert W Baker/OU=AM/O=LLY@Lilly; CN=Mauricio F Tohen/OU=AM/O=LLY@Lilly
CC: CN=Richard C Risser/OU=AM/O=LLY@Lilly; CN=Michele Sharp/OU=AM/O=LLY@Lilly
Date: 06/07/2001 05:03:14 PM
From: CN=Michele Sharp/OU=AM/O=LLY
Subject: REVIEW REQUESTED: FDA correspondence letter
Attachments: DRAFT FDA Letter Secondary Endpoint June 01.doc

Mauricio and Robert,

I have attached a draft FDA letter for your review. This correspondence letter is intended to document with FDA our intent to include results from HGGY of a secondary objective (induction to mania) in labeling regardless of outcome. I could especially use your help in paragraph 2 when describing our rationale for wanting to include this information in labeling.

With respect to paragraph 3, I will be discussing this wording with some of my regulatory colleagues and directors. I have written this paragraph as an initial proposal. I do not want the FDA to interpret our proposal as a co-primary objective. However, I also do not want them to interpret these sentences to mean that the final study outcome should necessarily be determined by only the primary objective. I want to give us as much negotiating power as possible if our primary does not quite reach $p < .05$ for both studies. For example one study is very robust on the primary and the second study is close on the primary, but our secondary objectives for response and remission for both studies is robust. Would we not want to try and make the case that we have determined effectiveness?

I would appreciate your comments.

Thanks,
Michele



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