

EXHIBIT 10

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalczyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

- 1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
- 2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Could the interaction with age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like? For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Should we get together to chat?

Thanks
Lisa