Robert W Baker
10/10/2000 09:00 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc: Paul Berg/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly
Subject: Re: meeting with endocrinologic consultants

Dear Charles:

Actually I think that our "takes" are about the same on this - they were quite concerned about the weight issue and due to that or perhaps due to misunderstandings, they were looking for reasons to not believe our analysis. I agree that they would feel more comfortable with the analysis if we can secondarily address mean changes, or adverse effects on glycemia as you've phrased it. I would add that they are quite keen on seeing what happens to the subjects we've excluded (history of diabetes and/or baseline glucose>140). If there is anything I can do to be helpful, let me know.

Regarding the marketing side, I agree that we heard a sentiment (though not sure it is unanimous) that we should not aggressively defend ourselves; in fact I thought we were getting suggestions to more vocally tell clinicians that olanzapine may well have a diabetes problem, based again largely on weight issues. To me, this reinforces the need to take an appropriately cautious tone with our findings. On the other hand, data are data and I do not feel impelled to state the case more negatively than it appears to us; our competitors are handling that quite nicely. I do think that what to say pending more "proof" is a key area for medical and marketing discussion.

I appreciate your help with this and second your suggestion that any additional resources will be a small price to pay for the molecule.

Best,

Robert
Charles M Beasley Jr

Charles M Beasley Jr
10/10/2000 08:33 AM

To: Alan Breier/AM/LLY@Lilly
cc: Robert W Baker/AM/LLY@Lilly, Paul Berg/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly

Subject: Re: meeting with endocrinologic consultants

I have a somewhat different take and believe that a number of individuals in attendance did not understand what was being said. We should talk. There is the marketing approach and then the scientific analyses approach. There are 2 issues -- weight gain and hyperglycemia.

These guys were really concerned about the weight gain, not only because of a diabetes risk but all the other potential health risks. They initially thought it might simply be a response to improvement in schizophrenia with a few outliers (a rather naive view, but they ain't shrinks). When they understood that this is seen in non-psychotic "normals" and animals on fixed diets (less concern with animals) and that olanzapine is the worst offender, other than clozapine, they advocated a different marketing strategy than we are taking. They believe we should "aggressively face the issue" and work with physicians to address methods of reducing weight gain. Although we did not get into details, they seemed more interested in psychosocial and behavioral approaches than pharmacologic. There does not seem much to say about scientific analyses of weight gain, we know it's a weighty problem. When you translate

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On the diabetes side, the concern was about the use of categorical analyses. It was not that they necessarily did not believe our findings, but that such analyses can be very easily not believed (subtle difference), a la, Fellow Simeon Taylor and others. The issue is the arbitrary nature of any categorical analysis with respect to cut points defining a case. This is especially pertinent to our situation where diabetologists don't really like defining diabetes based on random glucoses (in spite of the info on the ADA web site). The meeting helped me appreciate the difference between 2 questions: 1) What is the rate of development of impaired glucose tollerance / diabetes associated with olanzapine relative to other agents (including placebo)? and 2) Does olanzapine adversely affect glycemia relative to other agents? We've been attempting to address the first question. It is probably the more clinically relevant question. I believe we have been doing a good job at addressing it with our methodology. The problem is the arbitrary nature of the cut points and the potential for big shifts depending on those cut points and the fact that we chose the cut points (not really, they came from ADA web site). They specifically referred to the data as being "tortured". The last time I heard this reference was in the context of the suicide analyses but there it was a positive reference. The data there had been tortured but had not surrendered. I believe another factor playing into the skepticism is the magnitude of the number of cases identified in our analyses. On the one hand, the diabetologist, who "know" what a bad glucose is and also "know" the incidence and prevalence of diabetes, probably believe that our cut points are too high (not sufficently sensitive) but on the other hand we find too many cases, even on placebo. Life is difficult when you can't have it both ways.

The group (especially 3 individuals) would feel much more comfortable with an analysis addressing the second question. They want the continuous data (using all data) analyzed over time co-varying for both static (diabetic diagnosis, baseline obesity, etc.) and dynamic co-variates (weight gain, alteration in hypoglycemic dose). Similar to David Allison, 1 or 2 would be happy to take all our data and perform the correct analyses, like we don't have competent statisticians. I will e-mail 2, one US based and the other a Brit, to get there thoughts on methodology. From my crude misunderstanding of methods, these would probably be complex analyses. I will say that I believe we should have a full time, dedicated, sophisticated, statistical resource that does nothing but hyperglycemia, no meetings, no surveys, zilch, until we have completely tortured the data. This would be a small price to pay for this molecule.

With regard to the marketing side of this issue of impaired glucose tollerance / diabetes, the message was clear. Don't get too agressive about denial, blaming it on schizophrenia, or claiming no worse than other agents until we are sure of the facts and sure that we can convince regulators and academicians. W-L with Resulin was the example. Sounds exactly like what Dan Casey was saying.

Charles

---------- Forwarded by Charles M Beasley Jr/AM/LLY on 10/10/2000 07:40 AM ----------

Robert W Baker

10/09/2000 03:42 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly
cc: Christopher C Bomba/AM/LLY@LILLY, Patrizia Cavazzoni/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY

Subject: Re: meeting with endocrinologic consultants

FYI. My take was that this board of academic endocrinologists was impressed enough by magnitude of weight gain and number of reports in the spontaneous adverse event database that they were predisposed toward skepticism to any analysis that did not find higher hyperglycemia rates on olanzapine than comparators.

Charles - do you think it appropriate to look at secondary analysis that does not exclude baseline abnormals and another looking at mean changes in glucose?

Alan - I believe that what Tom is referring to as "not the way Lilly typically does business" are suggestions to more vocally assert that olanzapine may have a problem on the glucose issue and, rather than moving forward with our analyses, turning all info over to an independent board for review, conclusions, and dissemination. Neither strikes me as the appropriate step, but this alarmed the Lilly

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Thanks,

R

---------- Forwarded by Robert W Baker/AM/LLY on 10/09/2000 03:29 PM ----------

Thomas M Brodie
10/09/2000 03:10 PM

To: Robert W Baker/AM/LLY@Lilly
cc: Eugene R Thiem/AM/LLY@LILLY

Subject: Re: meeting with endocrinologic consultants

Robert.....clearly, this group of Endocrinologists (who spoke up and I would rate those who did speak up as the leaders of the pack) are very concerned with the approach Lilly is taking towards the issue that Zyprexia leads to diabetes. I can only hope that you and all of the team who attended the NADAB meeting are gaining the ear of senior leadership and articulating this finding. Although the boards *recommendation is probably not the way Lilly typically does business, I do believe they made a very* strong point that unless we come clean on this, it could get much more serious than we might anticipate.

Gene, John and I were very glad to provide you with time in front of this group and if you should need additional time at future meetings (next one is Feb. 2001) please let me know. It was great meeting you as well.

Regards,
Tom

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