

Charles M Beasley Jr  
11/10/99 03:48 PM

To: Norma Kim Ascroft/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly  
cc: John A Krueger/AM/LLY@Lilly  
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

Anna:

Please forward my summary of the post-marketing hyperglycemia data to Norma, she may want to convert it to slide format.

Charles

----- Forwarded by Charles M Beasley Jr/AM/LLY on 11/10/99 03:43 PM -----

Norma Kim Ascroft  
11/10/99 12:10 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, Lawrence Gelbert/AM/LLY@Lilly, Mark L Heiman/AM/LLY@Lilly, J David Leander/AM/LLY@Lilly  
cc: Norma Kim Ascroft/AM/LLY@Lilly  
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

In preparation of the Steering committee meeting on the 23rd, it would be greatly appreciated to forward electronically your 2-4 slides that will be utilized in the overviews to Barbara Whitaker, Sr Asst to Alan Breier (please cc; Norma Ascroft), by November 17, 1999. The acetates will be collated and ready for the presentation on the 23rd.

Thank you and we look forward to seeing you on the 23rd.

----- Forwarded by Norma Kim Ascroft/AM/LLY on 11/10/99 12:04 PM -----

Alan Breier  
11/09/99 05:03 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Thomas F Bumol/AM/LLY@Lilly, Frank Bymaster/AM/LLY@Lilly, Jose F Caro/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, Richard D DiMarchi/AM/LLY@Lilly, H Christian Fibiger/AM/LLY@Lilly, Dong-Jing Fu/AM/LLY@Lilly, Lawrence Gelbert/AM/LLY@Lilly, Brian Grinnell/AM/LLY@Lilly, Mark L Heiman/AM/LLY@Lilly, Richard Deane Hockett/AM/LLY@Lilly, J David Leander/AM/LLY@Lilly, Karena Meehan/AM/LLY@Lilly, Edmundo Muniz/AM/LLY@Lilly, Steven M Paul/AM/LLY@Lilly, Gregory S Probst/AM/LLY@Lilly, Eric Ravussin/AM/LLY@Lilly, Paul R Rosteck Jr/AM/LLY@Lilly, Gary D Tollefson/AM/LLY@Lilly, Louis Vignati/AM/LLY@Lilly  
cc: Norma Kim Ascroft/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, John C Lechleiter/AM/LLY@Lilly, August M Watanabe/AM/LLY@Lilly  
Subject: Executive Steering Committee for Olanzapine-associated Weight Changes and Hyperglycemia

Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule. In addition, it could be argued that Eli Lilly, with its strengths in neuroscience, metabolism, endocrinology and diabetology is better positioned than any other institution to elucidate the mechanisms and developed treatments for this side effect. Thus,

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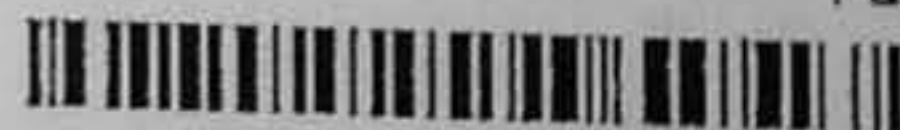
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we have formed a cross-functional action team to meet these challenges. Success of this effort will contribute to securing the future of olanzapine and the financial health of our company, and likely spur the development of next generation antipsychotic drugs (i.e. olanzapine without the weight gain) and drugs for obesity.

A pivotal meeting of the Olanzapine-Associated Weight Changes and Hyperglycemia Cross-Functional Action Team has been placed on your calendars for Tuesday, November 23, 1999, 3:00 PM to 5:00 PM. The purpose of this meeting is for the Executive Steering Committee, comprised of Alan Breier, Jose Caro, Richard DiMarchi, Chris Fibiger, Steve Paul, Greg Probst and Gary Tollefson, to review the ongoing work, future study plans and resource needs and provide guidance for the scope and direction for future activities. The format of the meeting will be 1:15 minutes of presentations followed by a 45 minute closed meeting of the Steering Committee. The agenda is attached.

I want to thank you in advance for joining us to work on this important project and look forward to seeing you on the 23rd.

Alan

 agendaNov23Mtg.doc

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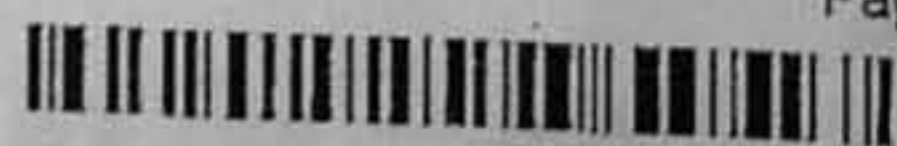
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ZY1 00776091

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Robert W Baker  
10/10/2000 10:19 AM

To: Charles M Beasley Jr/AM/LLY@Lilly  
cc:  
Subject: Re: meeting with endocrinologic consultants


Dear Charles -

thanks. Agree regarding weight gain and we've been shifting in the direction of more acknowledgement and talking about potential interventions. At least within the mania group we're now testing a "sell sheet" with recommendations including that for some patients risk-benefit ratio may favor another drug with less effect on weight. Probably won't be popular internally, but we are exploring it.

From diabetes standpoint, I'm tweaking medical slides to be more cautious in tone, will forward soon for your comment.

Thanks,

R  
Charles M Beasley Jr

 Charles M Beasley Jr  
10/10/2000 10:00 AM

To: Robert W Baker/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

Agree but believe that the emphasis on marketing approach is to acknowledge weight gain and not underplay it while for diabetes to be cautious until we are sure.  
Charles

Robert W Baker

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:

ZY 2224 247

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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 1-2% gain of 40+ kilos into the absolute number based on 5 million patients, the number is 50,000 to 100,000. 100,000 people putting on 90 pounds of weight is a lot.

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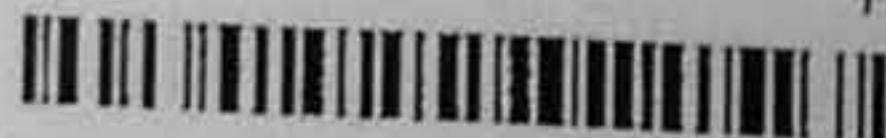
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On the diabetes side, the concern was about the use of categorical analyses. It was not that they necessarily did not believe our findings, but that such analyses can be very easily not believed (subtle difference), a la, Fellow Simeon Taylor and others. 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 tolerance / 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 sufficiently 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-variables (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 their 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 tolerance / diabetes, the message was clear. Don't get too aggressive 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 abnormalities 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 attendees when linked to the Rezulin comparison. Charles did let them know that already we have sent several volumes with all our info to FDA, but I'm not sure that they fully appreciated this.

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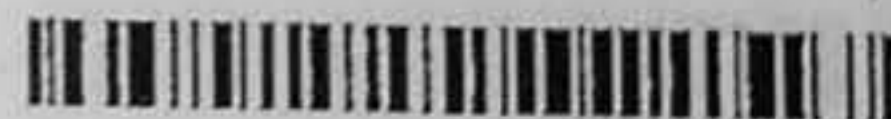
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Thanks,

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 Zyprexa 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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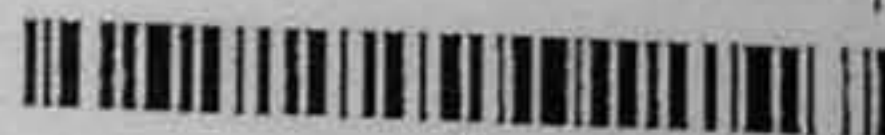
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Robert W Baker  
10/10/2000 02:40 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Braier/AM/LLY@Lilly,  
Patrizia Cavazzoni/AM/LLY@Lilly, Jamie Danenberg/AM/LLY@Lilly,  
John H Holcombe/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY, Bruce  
Kinon/AM/LLY@Lilly, John R Richards/AM/LLY@Lilly  
cc: Thomas M Brodie/AM/LLY@Lilly, James B Gregory/AM/LLY@Lilly,  
Bryan Johnstone/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Michael  
B Murray/AM/LLY@LILLY, Eugene R Thiem/AM/LLY@LILLY, Patrick A  
Toalson/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly  
Subject: Lilly visit from Sam Dagogojack, M.D.

Please consider meeting with Dr. Dagogojack as your schedule permits during a visit to Lilly on Friday December 8. He is an endocrinologist in Jackson, MS with particular interest in diabetes, clamping, and co-morbidity in psychiatric illnesses. The ML in his area, Pat Toalson, has been working to develop this relationship because of Dr. D.'s interests and expertise, but also because he is interested in working with us, and he has relationships with two psychiatrists who are key drivers of concerns about olanzapine and hyperglycemia: He has been a colleague and co-author with John Newcomer MD, he now is located in the same University as Henry Nasrallah, M.D.

The 12/8 visit will be consultative around marketing and sales force handling of current data. However, I will appreciate any time that you can spare to convey your personal activities and especially updating Sam on our data and ongoing plans. He's had several ideas that others may evaluate better than I, and he likely will be interested in pursuing some studies himself should we be interested. It is I know close to ACNP but has been hard to schedule.

This visit is a supplement to other efforts now underway to strengthen relationships with the Lilly Endocrine academic advisory board and consideration of assembling a board including endos to help us in an ongoing way.

Thanks,

Robert

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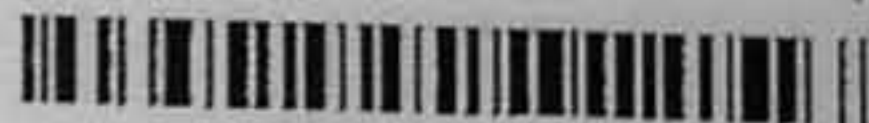
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John H Holcombe  
09/08/2000 09:01 AM

To: Christopher C Bomba/AM/LLY@LILLY, Eugene R  
Thiem/AM/LLY@LILLY  
cc: Robert W Baker/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Suni  
Keeling/AM/LLY@LILLY, Paula T Trzepacz/AM/LLY@Lilly  
Subject: endo consultants

Gene and Chris

I agree with the names Mel Prince gave you, including Richard Rubin. I know the latter quite well. As a psychologist, he wouldn't be one to put in front of a psych audience to talk about diabetes, HOWEVER, it would be very important to have him as a consultant along with the endocrinologists to get his input on how best to proceed with educating psychiatrists about diabetes. He could do that better than anyone. He's written several books on behavior problems in diabetes, he's internationally recognized, and I like Lilly. He has a son with type 1 diabetes...

Just about anyone on our NADAB could serve on an olanzapine board as well, with the exception of Gene Wright and Neil Brooks. I say that because neither is an expert in the pathophysiology of diabetes. Of the board members, in order, that I would suggest are the following:

Bernie Zinman

Richard Bergenstal (David Kendall works with him and we might choose David instead to build relationships..)

James Gavin (doesn't come to many NADAB meetings, but might be interested in the olanzapine issue)

Vivian Fonseca (he is incredibly bright)

Others not on the board, but should be considered are

Helmut Steinberg (spelling?) who's at IU doing the insulin clamp study with olanzapine now

Julio Rosenstock (Dallas), good friend of Lilly and a practical endo.

Ralph DeFronzo (Famous diabetologist, has done significant work on insulin resistance)

Of course we can come up with other names as well. I would suggest 10 or fewer for the board, but how many did you guys have in mind?? Endos LOVE to get involved with ad hoc issues, so I anticipate a good response.

I would be delighted to personally call any of the docs whom we'd like to invite.

I'm working from home today.. Call [Redacted] if you have questions.

John

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