Facsimile

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To: Tadataka Yamada, MD
SmithKline Beecham
Chairman, Research and Development, Pharmaceuticals

Dear Dr. Yamada:

I wanted to set the record straight regarding all the phone calls and questions I have received regarding one minute of a 25 minute presentation at a CME symposium sponsored by Lilly at which I was asked to present a talk on new therapies in diabetes by Dr. Alain Baron on behalf of Indiana University Office of CME. In case you have not heard, I have signed a statement "To whom it may concern" clarifying my presentation and sent it to James Huang out of respect to your company's "equity interest". In light of the nature of your communication with my chairman, I hope that you will do me the courtesy of reading this letter in its entirety at some point. I know you are busy and thus an "executive summary" is provided in the next to the last paragraph.

First, I want you to know that I went to extraordinary ends to try to understand the class of drugs and the available data prior to my presentation. I reviewed every paper published (and available in our library) on the thiazolidinedione class in humans (and many of the animal studies). I reviewed all the data slides presented at the FDA in the March and April meetings on the class of drugs. I reviewed the abstracts on the human trials at the ADA meeting and the Endocrine Society in detail. I spoke with the principals (investigators and marketing directors) at SB, Takeda and Parke-Davis. (Lilly was out of the loop in this process entirely as they do not primarily hold the pioglitazone data set.) In fact I discussed with James Huang and Elizabeth Rappaport of SB (as well as local and regional SB representatives) my impressions and concerns in the context of upcoming presentations at the Endocrine Society and ADA meetings by phone two weeks before the presentation in question and in person a week later in two separate meetings in San Diego to make sure that I understood the issues. I showed the slides that I had prepared to multiple colleagues and modified them several times over a period of about a week based on their suggestions. The slides that the SB sales representatives who attended this symposium apparently found offensive were made by me at my own expense without any assistance. I did substitute some professionally made data slides provided by Takeda for the ones that I had made on PowerPoint the night before the presentation based purely on aesthetics and not on content. I spent at least 40 hours (nights and weekends) preparing for this one lecture at the ADA meeting. In preparing a talk to be presented at a national meeting of my peers I agonize over how I

can tell them something that they cannot easily find out by reading an abstract or listening to someone else's presentation. People want to hear me (or any other "opinion leader") because of the information digested and assimilated not because I am capable of regurgitating it with excellence. I may over compensate as I do not think that I am a particularly good public speaker. I took the task of making that presentation and the other six presentations (sponsored by the Endocrine Society, Lilly insulin people, Hoechst Marion Roussel all under CME guidelines) that I was asked to make at the ADA and the Endocrine Society very seriously and received good reviews I believe becuase I do try to think ahead of the curve.

Now, I may have not explained the issues at that presentation as well as I could have if I had more time, but that may not be the good news. I would like you to know exactly what my concerns are regarding rosiglitazone as a clinical scientist and my approach as a clinician. On the basis of the increase in LDL concentration seen in the clinical trial program (whether the number we accept as the truth is the 18.6% at 4 mg bid in the package insert or the "average of 12%" now being discussed) one would expect an increase in cardiovascular events. If there had been a decrease in triglycerides or convincing evidence that it is was associated with an increase in particle size or no change in particle number, as is the case with fibrates (and arguably the other thiazolidinediones) it would have been an open question (as raised by many when troglitazone was launched). Based on this reasoning, I believe as a clinical scientist that the null hypothesis should be that rosiglitazone has the potential to increase cardiovascular events. Based on studies with statins and plasmapheresis, changes in LDL concentration can be associated with substantial changes in vascular reactivity and endothelial function over a time course of days to weeks. The increase in cardiovascular deaths and ischemic heart events are the relevant endpoints to be examined in the clinical trial program if one were to look for those kinds of changes in endothelial function. The event rate among all comparators is arguably the most relevant comparison group available from the data presented at the FDA hearing. (The event rate in the period of active comparison in both groups [4-6 months] would have been even better.) I know and fully agree that the effects seen are not even close to statistically significant (as I stated) and not different from effects seen with other anti-diabetic drugs (as I also stated). It may have been imprudent of me to say that they were increased 50% (which they are) instead of presenting the actual numbers and letting people do the math in their head, but I was trying to fit two hours worth of data into twenty minutes. That was a snap decision that I made realizing that I was going over the allotted 25 minutes and I regret that decision as it probably only saved me thirty seconds then and cost me ten hours since. I personally have told my patients in whom I have prescribed rosiglitazone that we will need to treat their LDL to a target of <100 mg/dl and TG < 150 mg/dl (as we recommend and usually do for all patients) and that if they do not have at least a 0.5% reduction of hemoglobin A1c at 4 mg bid, that I would recommend stopping the drug. I strongly believe that the rosiglitazone data set supports this kind of clinical decision making. I believe that caution is required until additional data are available.

Finally, before suggesting what I hope will be the nature of SB and my relationship in the future, I would like to convince you that you will never meet a person who is more open minded and less prone to being "bought" by anyone than I. I have devoted my career to not only increasing my personal understanding of the therapy of diabetes through both research and clinical practice. I am the son of two diabetologists. My father was the first endocrinologist in the state of South Carolina and widely regarded as a consummate academic physician and teacher. My mother has had the same R01 grant for over 40 years and is rumored to have the longest running grant at NIDDK. I have very large shoes to fill and work very hard to fill them. I spend a great deal of time trying to increase public awareness and provider competence in diabetes giving approximately 100 oral presentations a

year. Approximately 60% of those are provided with minimal honoraria (<$100) including many in which I do not even receiving reimbursement for my personal expenses despite substantial personal sacrifice. I do get paid an honorarium of between $500 and $2000 for the other 40 or so talks I give a year. The majority of these presentations are sponsored by CME providers. Some are sponsored directly by the pharmaceutical industry. To my knowledge, I have spoken for every company that markets drugs for diabetes in the U.S. except SB. In fact, I have been offered many times to speak for SB but have only accepted one offer (as I am trying to get my partner who will be the first author on the Jack Gerich rosiglitazone clamp studies to get out on the road more and as she has much greater experience than I do with the drug as a result of her study in Rochester). In fact, in my career I have probably received less personally or for the UNC Diabetes Center from Lilly or Takeda than any other company in the United States. To this date, I am sure that I have received more support from SB than Takeda and Lilly combined. I have been to as many or more consultant meetings for SmithKline than for Lilly or Takeda. I was not upset when my chairman called me into his office to tell me that some in your company perceive me as being "for sale" as he knows me well enough to doubt it. I will take tremendous offense to hear about it from others who know me less well as it is obviously not supported by any reasonable understanding of the facts and arguably libelous.

I assume that you can tell that I am angry. It is not because of what has been said or the implied threats of lawsuits that I have heard from my chairman and James Huang, but because of the amount of time I have spent trying to understand the issues, giving people every opportunity to explain to me why my perceptions are illogical, and then having to spend more hours trying to deal with the consequences of my understanding of the issues. The thing that really ticks me off is that I went through this when troglitazone was launched. I publicly stated on many occasions that I thought it was incredible that there was no LFT monitoring requirement from the FDA, that the drug was associated with weight gain and that it was only going to be modestly effective as monotherapy based on a similar detailed analysis of all available data (and I had more access for troglitazone as I had conducted about 5 trials and written or reviewed two or three papers for them). The same dance that we are now engaged in occurred with Parke-Davis in 1997. It took about a year for the marketing people to get over it and to realize that I was right. Now I am their best friend and I have not changed my belief that they have a lovely drug, warts and all, that can be used safely and effectively with certain stipulations.

I hope a similar process will play out with SB with regards to rosiglitazone. I have offered to everyone that I have spoken to that I am happy to help me (and in that process hopefully SB and others) understand what is going on with regards to the vascular system in the setting of rosiglitazone therapy. There is a bunch of data out there that suggests that there are major differences in the genes activated between the drugs in this class. My strongest of all opinions is that head to head studies need to be done and that they will be done. I am afraid that if SB does not set the agenda in this regard, others will and it will further develop the case that this potential Achilles' heel is in fact a real vulnerability of the drug. There are hints which can be read between the lines of presentations that I have heard at SB consultants' meetings which should raise questions and suggest studies if one were inclined to believe the null hypothesis I propose a few paragraphs above is relevant. I am happy and anxious to continue giving SB and your marketing partner BMS my five cents worth regarding these issues for free. I want a safe thiazolidinedione more than anyone does. To establish rosiglitazone's safety will require studies designed to test the hypothesis and not innuendo and marketing "spin" on data. I am also very afraid that if another drug in this class turns out to have a major issue which was in hindsight preventable, the call of people like Michael Stern to hold diabetes/obesity drugs to the

standard of statistically significant outcomes studies with hard endpoints may seem more reasonable to the detriment of us all and our clients/patients.

Executive Summary: I work very hard and am both serious and creative. I may disagree with SB's interpretation of data. I am not for sale. I am anxious to help in any way that I can to establish rosiglitazone as a safe and effective antidiabetic agent with certain stipulations. I cannot change my opinions in the absence of new data or understanding, in large part because I am not for sale. I look forward to working with SB in the future, but will understand and not take offence if I do not. Please call off the dogs. I cannot remain civilized much longer under this kind of heat. Fortunately, I will be out of the country for three weeks on vacation starting on Friday.

I apologize for my lack of brevity in written communication (Fred Sparling has noted that frequently) and thank you for giving me the chance to respond to your company's concerns. Feel free to share this with anyone that you like.

Sincerely,

John B. Buse, MD, PhD, CDE
Associate Professor of Medicine
Director, Diabetes Care Center

Cc: Fred Sparling, Chairman of Medicine, UNC
James Huang, Product Director, SB

Enc: "To whom it may concern" letter