

# EXHIBIT 20

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**From:** Kitazawa\_Kiyoshi@takeda.co.jp  
**To:** Roebel, Mick (TGRD); Collett, Phillip (TGRD)  
**CC:** George, Michael (TGRD); Moules, Ian (TGRD); Yates, John (TGRD); Wada, Yasuhiko; Kitazawa, Kiyoshi  
**Sent:** 8/8/2005 7:06:54 PM  
**Subject:** RE: Proactive malignancy data and KPNC new data. likely, best and worst case scenarios.

Dear Phil and Mick,

Thank you very much for your extensive thoughts on the possible reactions both from EMEA and FDA. As you understand very well, Actos is the most important product for Takeda and therefore we need to manage this issue very carefully and successfully not to cause any damage for this product globally. In this regards, I very much ask for both of you the extensive and sophisticated works to get the positive outcome just like the best case scenario from each regulatory authorities.

Best regards,

Kiyoshi Kitazawa

-----Original Message-----

From: Roebel Mick/VP Reg Affrs Regulatory Affairs. TGRD.  
Sent: Tuesday, August 09, 2005 7:36 AM  
To: Yates John/President Medical Research & Development. TGRD.; Collett Phillip/European Regulatory Affairs Director.Takeda Europe R&D Centre; Wada Yasuhiko/医薬開発戦略部長  
Cc: George Michael/Managing Director.Takeda Europe R&D Centre; Moules Ian/European Development Director.Takeda Europe R&D Centre; Kitazawa Kiyoshi/取締役 (医薬開発本部長)  
Subject: RE: Proactive malignancy data and KPNC new data. likely, best and worst case scenarios.

As John says, the bladder cancer issue has died down in the US over the last several months. We continue to provide expedited Safety Reports for cases of bladder cancer to the Agency, as agreed in Feb. 2003. For PROactive specifically, we informed FDA in Mar. '04 of a number of cases of bladder cancer from the trial but told them we did not want to break the study blind at that time in order to maintain study integrity. We assured the Agency that the DSMB had approved the continuation of the study. FDA did not question us on this.

#### Best Case Scenario

As in the EU, it's not unlikely that the Metabolism and Endocrinology Div. at FDA will request some sort of labeling change. Best case is that this happens subsequent to our PROactive US submission and data review, and includes relatively benign wording around bladder cancer findings from the study along with "benefits" wording if trial is positive.

#### Worst Case Scenario

It seems pretty unlikely in the US that the FDA would try to remove the drug from the market given the equivocal safety data seen. However, the overall evaluation is, of course, a benefit/risk proposition and if the PROactive "benefit" turns out to be worse than neutral (decrease mortality, other?) this could change. A more likely "worst case scenario" could be for the Agency to ask for an immediate label change incorporating bladder cancer findings, possibly some sort of a "Dear Healthcare Provider" letter to be sent, and posting of pioglitazone on the new "Drug Watch" portion of the FDA Web page. This "Drug Watch" list, accessible to the public, is meant to identify drugs for which FDA is actively evaluating safety signals during a period of uncertainty while FDA and the Sponsor evaluate new, significant safety information. The situation would first be discussed by the new FDA Drug Safety Oversight Board prior to any posting; the company may or may not be involved in these discussions. If pioglitazone were to be posted, I would expect the media to pick this up. The Agency could also ask us to put together some sort of Risk Management plan for the product to minimize any possible bladder cancer risks associated with pioglitazone (ways to identify populations most at risk, only treat populations most benefiting from product, etc).

#### Most Likely Scenario

Depends on overall results of PROactive, but "most likely" is expected to be more like "best case" than like "worst case". Depending on how FDA views our pharmacovigilance plan

(preclinical studies, PROact extension, KPNC study, etc), they may or may not ask for additional work. Labeling changes likely, but hopefully not until after our PROactive US submission to incorporate both benefit and risk elements coming from the trial.

Any questions, let me know.

Mick

-----Original Message-----

From: Yates, John (TGRD)  
Sent: Monday, August 08, 2005 3:49 PM  
To: Collett, Philip (TGRD); Wada, Yasuhiko; Roebel, Mick (TGRD)  
Cc: George, Michael (TGRD); Moules, Ian (TGRD); Kitazawa, Kiyoshi  
Subject: RE: Proactive malignancy data and KPNC new data. likely, best and worst case scenarios.

Phil

Thank you for your thoughtful response. I agree with the different scenarios you have presented.

While the scenarios for the US are similar, this has not been as much of an issue for FDA as it has been in Europe, so we believe the risks are somewhat lower.

John

-----Original Message-----

From: Collett, Philip (TGRD)  
Sent: Monday, August 08, 2005 10:41 AM  
To: Wada, Yasuhiko; Yates, John (TGRD); Roebel, Mick (TGRD)  
Cc: George, Michael (TGRD); Moules, Ian (TGRD); Kitazawa, Kiyoshi  
Subject: RE: Proactive malignancy data and KPNC new data. likely, best and worst case scenarios.

As requested I have attached a word document outlining the likely, best and worst case scenarios. The very worst case is unlikely but I have to consider it. It also depends on the proactive outcome results and how they are interpreted by the European regulators.  
best wishes.

Philip

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-----Original Message-----

From: Wada\_Yasuhiko@takeda.co.jp [mailto:Wada\_Yasuhiko@takeda.co.jp]  
Sent: 08 August 2005 08:01  
To: Collett, Philip (TGRD); Yates, John (TGRD); Roebel, Mick (TGRD)  
Cc: George, Michael (TGRD); Moules, Ian (TGRD); Bhattacharya, Mondira (TGRD); Van Troostenburg, Anne (TGRD); Kitazawa, Kiyoshi; Wada, Yasuhiko  
Subject: RE: Proactive malignancy data and KPNC new data

Dear John, Phil, and Mick ,

As the reports on malignancy to the authorities are of critical importance for Actos, you are requested to pay very very careful attention to this matter by all means.  
To ensure that the interpretation is right to avoid unnecessary arguments against the safety of Actos, you better consult with the outside experts like epidemiologists in prior to your submission to EMEA/FDA. Is it what you are going to do?

Please inform us of your projected schedule upto EMEA/FDA submission, including the dates for the first draft available to TPC, its review by experts, its finalization and the submission

to EMEA and FDA.

On top of that, we need to know the following scenario in terms of responses given by authorities you should predict when you submit the reports to EMEA and FDA from regulatory perspective.

1) Most likely scenario, 2) Best case scenario and 3) Worst case scenario

Phil, please advise us your opinion on the EMEA response. Mick, please advise us on the FDA response.

Thanks for your expertise to cope with this matter.

Best regards,

Yasu

-----Original Message-----

From: Collett Philip/European Regulatory Affairs Director.Takeda Europe R&D Centre

Sent: Friday, August 05, 2005 10:50 PM

To: Yates John/President Medical Research & Development. TGRD.; Wada Yasuhiko/医薬開発戦略部長

Cc: George Michael/Managing Director.Takeda Europe R&D Centre; Moules Ian/European Development Director.Takeda Europe R&D Centre; Roebel Mick/VP Reg Affrs Regulatory Affairs. TGRD.; Bhattacharya, Mondira (TGRD); Van Troostenburg, Anne (TGRD)

Subject: Proactive malignancy data and KPNC new data

Dear Yasu.

This email seeks TPCs agreement on our proposal to inform regulatory authorities in the EU and US regarding the newly available malignancy information from the proactive study and the bladder cancer data from the first cohort of the KPNC study in the US.

This week, myself, Mick Roebel together with a few senior pharmacovigilance personnel were unblinded to the malignancy data from the proactive study. We were also unblinded to the preliminary information from the first cohort of the KPNC study. (Dr Yates obtained agreement from John Dormandy that we could be unblinded to the proactive safety information only.). Yesterday we held a ad hoc safety review videoconference in order to make a preliminary assessment of the significance of this data and also to decide the nature of the regulatory submission that we need to make. The participants were Dr Yates, Dr George, Mr Moules, Dr Collett, Dr Roebel, Dr Bhattacharya, Dr Van Troostenburg, Dr Gerrits and Dr Kupfer.

I understand you have been unblinded to the proactive data. Anne Van Troostenburg is currently drafting a detailed report of the malignancies in the proactive study with emphasis on bladder cancer.

We had site of a preliminary draft of the KPNC report and a later draft will be available next week. Mondira Bhattacharya is liaising with the authors of this report and I will ask her to send you a copy. The preliminary draft reports that pioglitazone patients were not at a significantly increased risk of bladder cancer (adjusted Hazard Ratio=1.19, 95% CI 0.78 to 1.82). The secondary analyses showed some increased hazard ratios in certain subgroups only. For example 12 to 24 months of use but not 24 to 36 months of use. The primary analysis is reassuring but the secondary analysis are not as clear cut but are difficult to interpret.

We consider that we need to report these new information to the regulatory authorities. (In fact in Europe we are committed to reporting the KPNC information within August 2005 and the proactive malignancy data within September 2005). Because of the importance of the bladder issue we should report these new data as soon as they can be worked up and interpreted by the company and by appropriate experts. We propose that a submission should be made to the regulatory authorities within August 2005.

Attached I have proposed a structure for the submission. In essence this is a stand alone overview together with the component reports. The overview is composed of small sections summarising, the new proactive malignancy data, the KPNC data, the actions of the proactive DSMB during the study, expert comments on the new data and a conclusion and company position. I propose to help Dr Van Troostenburg write this overview. We will of course review it within TGRD and then send it to you for the approval of TPC.

As you are aware TPC will need to make a decision as to the reporting of this data to regulatory authorities other than the EMEA and FDA and to partner companies and marketing companies.

I do hope you are able to agree to our proposed reporting activities to the FDA and EMEA.

best wishes

Philip Collett

<<Suggested outline of August pioglitazone regulatory submission document.doc>>

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