Nos. 13-1088, 13-1089

IN THE UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

UNITED STATES OF AMERICA ex rel. HELEN GE,

Plaintiff-Appellant,

v.

TAKEDA PHARMACEUTICAL CO.,

Defendant-Appellee.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

BRIEF FOR JACK COOPER AND THE MILLER FIRM, LLC AS AMICUS CURIAE IN SUPPORT OF PLAINTIFF

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INTEREST OF THE MILLER FIRM, LLC AND THE ACTOS PLAINTIFFS IT REPRESENTS

This appeal relates to litigation involving at its core allegations that defendant Takeda Pharmaceutical Company and its affiliates ("Takeda") are liable under the False Claims Act ("FCA"), 31 U.S.C. § 3729, *et seq.*, for their failure to comply with federal statues that require them, as a drug manufacturer to report to the Food and Drug Administration ("FDA") adverse events associated with drugs that they manufacture, market and distribute to the American public. In the decision below, the district court dismissed the relator's complaints on the basis that she had failed to plead her claims with sufficient particularity and to state a claim upon which relief could be granted. In so far as these rulings were based on a lack of evidentiary support, the court was simply mistaken on the standard it imposed and ignored in large part the vast evidence in the public sphere that corroborates Dr. Ge's assertions.

By leave of Court, Jack Cooper and The Miller Firm, LLC as legal representative of hundreds of victims of Takeda's gross violations of federal law, participate as amicus curiae on appeal to provide the Court

with its view of the sufficiency of the factual support that exists in the public realm which supports Dr. Ge's assertions contained in her complaint. In particular, Jack Cooper's case was tried to verdict in April of this year against Takeda in the Superior Court of California for Los Angeles. The case centered on Takeda's manipulation and obfuscation of the risk of bladder cancer from taking Actos; a fact well known to the company. Also at issue was Takeda's improper overstatement of Actos' cardiovascular safety profile.

The Cooper jury awarded Mr. Cooper and his wife $6.5 million. The undersigned firm has similar cases going to trial in August in Maryland, November in Nevada, February 2014 in New Mexico and Pennsylvania, March 2014 in Indiana, April 2014 in Wisconsin, and October 2014 in West Virginia. In addition, the undersigned is prosecuting several hundred cases in consolidated litigation where over 3000 bladder cancer suffers - all victims of Takeda's misrepresentations – are seeking redress.

This brief was authored by The Miller Firm, LLC and was not funded in any way by any outside source or party to this litigation.

STATEMENT OF FACTS

A. Relevant Statutory Provisions

Under the Federal Food, Drug, and Cosmetic Act (FDCA) manufactures of pharmaceutical drugs must receive approval from FDA before a new drug may be sold or marketed in the United States. *See* 21 U.S.C. § 355. To approve the drug, FDA must, *inter alia*, find the new drug to be safe and effective for its intended use. *Id.* As part of their continued obligations to FDA, pharmaceutical companies with approved drugs are also required to continually update and forward reports of adverse events associated with the drug to FDA. *See* 21 C.F.R. §§ 314.80, 314.98(a); *see also* 21 U.S.C. §§355(k), 331(e). Any reported adverse event that is classified as serious or unexpected must be submitted to FDA within 15 calendar days of the receipt of such knowledge. *See* 21 C.F.R. § 314.80(c)(1)(i). Any adverse event that is associated with a known adverse event already identified with the drug in question is submitted to FDA through periodic reports. *See id.* § 314.80(c)(2). Failure to comply with the above regulations can result in serious action by FDA. *See* 21 U.S.C. § 332, 333(a), 355(e).

The False Claims Act, 31 U.S.C. § 3729, *et seq.*, prohibits the submission of false or fraudulent claims for payment to the United States or the making of false statements for the purpose of causing a false claim to be paid. A person that is found to have violated the FCA is liable to the United States for civil penalties and for three times the amount of damages. 31 U.S.C. § 3729(a)(1). Actions based on the FCA may be brought either by the United States itself through the Attorney General or by a private person via a *qui tam* suit. 31 U.S.C. § 3730(a) and (b)(1). If the United States does not intervene, the relator conducts the litigation and any damages recovered are dispersed between the relator and the government. 31 U.S.C. § 3730(d).

B. Procedural Posture

Relator Dr. Helen Ge commenced these actions against her former employer Takeda alleging that it had failed to report or under reported adverse events associated with several different drugs that it manufactured; all in violation of application FDA regulations noted above. *See* Appendix 12, Second Amended Complaint (SAC), Docket # 17, Case

No. 10-11043 (D. Mass); Appendix 128, Second Amended Complaint, Docket # 28, Case No. 11-10343 (D. Mass.). Dr. Ge based her cause of action under the False Claims Act alleging that Takeda had "knowingly caus[ed] to be presented false claims to Government Healthcare Programs" by healthcare providers and states, as well as conspired to defraud the government. *See* Appendix 72-74, Docket # 17, ¶ 161-176, Case No. 10-11043 (citing 31 U.S.C. § 3729(a)(1)(A), (B), (C)).

In the district court, the court granted defendants' motion to dismiss on two bases: that the relator failed to state her claim with the requisite specificity under Rule 9(b) and that the relator had failed to state a claim under Rule 12(b)(6). Addendum 73-74. With respect to the court's Rule 9(b) ruling, it held that the Dr. Ge had failed to state her claim with the requisite specificity because she had "failed to allege the specific details of any claims that were allegedly rendered 'false' as a result" of the alleged fraud on FDA. *See* Addendum 71-72. The court also rejected Dr. Ge's theory that "all of the claims for these particular drugs in the relevant years were rendered false by Takeda's failure to properly report adverse events,"

reasoning that the relator had not made specific factual allegations to support an inference that FDA would have withdrawn approval for the drugs in question. *Id.* at 72.

The relator filed a motion for reconsideration but which was denied. Docket # 48. These appeals followed.

SUMMARY OF ARGUMENT

The court erred in dismissing the relator's complaints, most egregiously in finding a failure to allege in particular the fraud Takeda undertook on FDA and the medical community at large. At the core of relator's complaint is the allegation that Takeda misrepresented the safety profile of Actos by falsifying and manipulating the submission of adverse events reports to FDA and evading needed label changes. This fraud resulted in the publication and dissemination of fraudulent drug labels and allowed Takeda to market Actos without properly disclosing appropriate safety information regarding the significant risks of bladder cancer. As a result Takeda was able to greatly capitalize on the sale of Actos and market the drug as vastly superior to its competitors. The result was a greatly

distorted safety profile presented to patients, physicians and the medical community at large. Litigation involving Takeda, Actos, and its link to bladder cancer has resulted in a wealth of evidence regarding this link, corroborating Dr. Ge's allegations.

Argument

Thus far, over 30 million pages of documents relating to Takeda, Actos and bladder cancer have been produced to plaintiffs in the Actos litigation. The documents examined thus far have resulted in a tremendous trove of evidence establishing that Takeda knew as early as 1999 when Actos went on the market that it had a substantial and significant risk of causing bladder cancer. As a result of recent litigation, some of this information is now within the public sphere and substantially supports Dr. Ge's factual contentions.

I. Dr. Ge's Factual Claims Are Substantially Supported By The Evidence

At the core of Dr. Ge's claims is the factual premise that Takeda conducted a continual and systematic fraudulent misrepresentation regarding the safety profile of Actos. This misrepresentation underlies Dr. Ge's contention that patients and prescribers were well under-informed regarding adverse events that, even according to Takeda's marketing research, would have been extremely important clinical information for FDA and physicians alike; and that but for this fraud, would have made a substantial and material difference in the prescribing habits and use of Actos. However, Takeda choose to market Actos through a policy of downplaying the bladder cancer side effect, artificially promoting CV safety, and instead focusing sales representatives and marketing personnel on selling ever higher volumes of the drug. As a result of Takeda's failure to inform FDA and the medical community at large, U.S. and state governmental entities necessary ended up paying more for Actos prescriptions because of the inadequate, misleading and evasive practices.

The degree to which Takeda undertook to downplay and even outright hide the link between Actos and bladder cancer from FDA, patients and the medical community is exemplified by a series of events in mid-late 2002. At the end of July and into early August of 2002, Takeda personnel were contacted by employees of FDA regarding serious findings they had been informed of regarding the risk of bladder cancer with the use of Actos. Exhibit. 1. According to Dr. Jeri El-Hage, then the Toxicology Team Leader at FDA, she had initiated contact with Takeda so she "could express her concerns and findings regarding the nonclinical data shared with TPNA during the July 31, 2002 conference call [with FDA]." *Id.* In that call, Dr. El-Hage noted that a promoter-model study with pioglitazone had shown that 85% of the animals that took Actos had developed tumors. *Id.* As a result, Dr. El-Hage expressed that "the Division does not feel that the general population is being adequately informed about the possible risk of dual PPARs [Actos being a dual PPAR]." *Id.* She suggested that the package insert for Actos be updated to reflect this association. *Id.* However, as was to be a continual pattern for Takeda, the company vigorously

fought any addition of language to the label that would reflect an association between its key drug and the development of bladder cancer; namely because of the very real evidence it had regarding the impact such information would have on its bottom line.

In 2002, shortly after Takeda was contacted by the FDA regarding the adequacy of information being supplied to the general population regarding the association between bladder cancer and Actos, Takeda secretly conducted a survey to determine whether physicians would continue to prescribe a diabetes medication that carried a warning of bladder cancer similar to that being proposed by FDA. Beginning in October 2002, Takeda began searching for a way to conduct market research on the impact a warning about bladder cancer would have on the sales of Actos, without actually alerting any doctors about the risk of bladder cancer. Exhibit 2. Despite some delay due to Takeda's inability to find a way to conduct market research without "risking public awareness" about bladder cancer, Exhibit 3, Takeda conducted several market research studies on diabetes medications and the inclusion of language related to

bladder cancer. An internal study entitled "Barriers to TZD prescribing" sought to examine how the company could possibly overcome a physician's negative perception of Actos if it included bladder cancer language. Exhibit 4. As part of the survey, Defendants asked doctors to assume that there was a new product which was very similar to Actos, but which required monitoring urine for hematuria. *Id.* While most doctors did not have any concern about monitoring urine in-of-itself, when they were further informed that the monitoring was due to an association of the drug with bladder cancer, interest declined substantially across all physician groups. *Id.* As an example of the dismay physicians had at the prospect of a bladder cancer side effect associated with a type II diabetes drug, one doctor was noted by Takeda to have stated, "[b]ladder tumors? That would change my thinking altogether. I would not be likely to use the product." *Id.* Similarly, another noted that "[i]f there is a risk of bladder tumors, I would definitely not use it." *Id.* In short, Takeda understood very well the impact a warning for bladder cancer would have on physicians prescribing habits - and by extension, its bottom line- as early as the

summer of 2002 when FDA first brought to their attention serious concerns it had regarding the association of Actos with the development of bladder cancer.

Yet, despite FDA's concern over the lack of public awareness regarding the risk of bladder cancer with the use of Actos, Takeda still undertook a policy of downplaying and withholding relevant information from FDA, the medical community and the public at large. In particular, Takeda began to put together an Actos response team to combat any label change regarding bladder cancer. Exhibit 2. As part of this overall strategy of minimization and withholding, Takeda noted in a powerpoint that was circulated amongst several top Takeda employees regarding how the bladder cancer issue had been effectively countered in the EU and its applicability to the current situation it was facing in the U.S. Exhibit 5. Noting that Takeda had had "been in a similar situation" before in Europe when "the Bladder issue was blocking approval", Takeda noted how it eventually succeed in getting approval "despite a very negative regulatory authority". *Id.* Of particular relevance is the last slide which noted that it

was eventually successful in Europe because if stuck to a theory it understood to have serious flaws, "argued against clinical testing" and perhaps most telling "did not 'turn over stones – e.g. Did not undertake database searches'". *Id*. The obvious implication of this slide deck to the individuals at Takeda was that a similar approach would be relevant in combating the FDA's current interest in the bladder cancer issue. This policy of not to "turn over stones" was to remain standard procedure throughout Takeda's marketing of Actos.

From the period of 2002-2005, Takeda continued to implement this policy of not turning over stones despite repeated inquiries from FDA regarding this potential risk of the drug Actos. In 2005, however, two large clinically relevant studies were completed that Takeda was intimately involved with that without a doubt highlighted the substantial risk Actos posed to patients. These two studies were the Proactive study and the first interim analysis of the Kaiser study. Exhibit 6, Exhibit 7. The Kaiser study, a study that was being conducted specifically for the purpose of looking at the risk of bladder cancer, found a statistically significant increased risk of

bladder cancer for those population groups with longer duration of exposure and larger cumulative dosages. Exhibit 7. Based on these results, Takeda personnel sent a series of emails amongst one another regarding the various scenarios this information would have for the company and its product. In particular, Mich Roebel, VP Regulatory Affairs noted that the very worst scenario for the company was that the public be informed about this risk and noted that the best case would involve only a "benign wording around bladder cancer findings" to be added to the label. Exhibit 8. In response, a senior Japanese official for Takeda noted that "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 [sic]". *Id.*

In true form to this overall approach of Takeda in masking the risk of bladder cancer, Takeda likewise resisted every effort by FDA to have Takeda add language to the label regarding the risk of bladder cancer. As an example, a Dr. Misbin at FDA initiated a phone contact with Takeda personnel in the summer of 2006. Exhibit 9. He noted that recent data

"obligates the company to provide a more informative label" regarding the risk of bladder cancer. *Id.* However, Takeda resisted this effort; to which Dr. Misbin noted that while "this teleconference was not initiated to debate the science […] but to revisit the current label and put it into context of **what data are known**." *Id.* (emphasis added). Dr. Misbin remarked that soon more data would be available in 3-4 years and if it further supported a positive finding, "**then questions may arise as to when the label should have changed**." *Id.* (emphasis added). Almost to the year, in 2011 FDA made a public announcement about the potential link between Actos consumption and bladder cancer and required Takeda to update its label to reflect information known to the company years earlier. *See* U.S. Food and Drug Administration, Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer (June 15, 2011) *available at* http://www.fda/gov/Drugs/DrugSafety/ucm259150.htm.

Finally, even as late as 2011 Takeda was still employing a strategy of minimization and diversion regarding the risk of bladder cancer and illustrates the common pattern for Takeda throughout the entire marketing

of Actos since its inception: namely that Takeda was more concerned about its profit margin than the health and wellbeing of the patients consuming its drug. In 2011, even after FDA had required Takeda to update its label and inform the public about the risk of bladder cancer, top employees of Takeda were still instructing marketing and sales personnel: "If no questions/concerns, do not discuss bladder cancer and sell, sell, sell!" Exhibit 10. In short, throughout the marketing of Actos and even to the point where FDA required Takeda to warn the public about the risk of bladder cancer, Takeda was still employing the same strategy of evasion and minimization that had characterized the company since it began marketing Actos.

CONCLUSION

For the forgoing reasons, this Court should find that Dr. Ge's complaints state a sufficient factual basis as her allegations are more than corroborated by publicly available evidence obtained in related litigation involving Actos and the development of bladder cancer.

Respectfully submitted,

/s/ Timothy Litzenburg
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August 2013

CERTIFICATE OF COMPLIANCE WITH FEDERAL RULES OF APPELLATE PROCEDURE 32(a)

I hereby certify that this brief complies with the requirements of Fed. R.App.P. 32(a)(5) and (6) because it has been prepared in the 14-point Palatino Linotype, a proportionally spaced font.

I further certify that this brief complies with the type-volume limitations of Fed.R.App.P. 32(a)(7)(B) and 29(d) because it contains 3,000 words, excluding the part of the brief exempted under Rule 32(a)(7)(B)(iii), according to the count of Microsoft Word.

/s/ Timothy Litzenburg
TIMOTHY LITZENBURG

CERTIFICATE OF SERVICE

I hereby certify that on August 9, 2013 I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the First Circuit using the appellate CM/ECF system. The participants in the case are registered CM?ECF users and service will be accomplished by the appellate CM/ECF system.

/s/ Timothy Litzenburg
TIMOTHY LITZENBURG

EXHIBIT 1

FDA Conference Call: August 13, 2002

FDA Personnel:

Jeri El-Hage, Toxicology Team Leader
Jena Weber, Project Manager

TPNA Personnel:

David Baron, Ph.D., Director, Nonclinical
Janet Haskins, Manager, Regulatory Affairs
Pat Frank, Ph.D., TPNA Consultant

The purpose of this conference call was so that Dr. El-Hage, could express her concerns and findings regarding the nonclinical data shared with TPNA during the July 31, 2002 conference call.

Dr. El-Hage noted that in light of the fact that several compounds that are dual PPAR agonist have discontinued development due to transitional cell tumors in the bladder and kidneys of male and female rats and in male mice, the Division is becoming concerned. She also noted that in follow-up studies, there was no irritation or formation of calculi noted.

Dr. El-Hage then noted that a promoter-model study was conducted by another company in which pioglitazone was given. The study was designed as follows:

- BBN was given to Fisher rats in their drinking water for four-weeks
- Groups are:
  - Pioglitazone 40 mg/kg/day plus BBN
  - Their compound (no dosages given, but Dr. El-Hage noted it was multiple) plus BBN
  - The control group just received the BBN.
- Duruation was 32-weeks
- Results:

- 85% of the animals in the pioglitazone and the other company's compound group had tumor formation. Either group had calculi formation.
- 15% of the animals in the control group had tumor formation, with around 50% of those having calculi formation.

Based on these findings, and the fact that the other dual PPAR agonist have discontinued from development, the Division does not feel that the general population is being adequately informed about the possible risk of dual PPARs. Dr. El-Hage shared with TPNA that before the other dual PPAR agonist discontinued development they were being required to monitor for bladder tumors in their clinical studies. She noted that the Division's internal consultant suggested screening urine for NMP-22, which Dr. El-Hage believes is approved for screen of bladder tumors and is commercial available.

Finally Dr. El-Hage noted that she is trying to bring these findings to the CAC board in mid-September. She will inquire if they feel that the pioglitazone package insert adequately addresses our data and the data that the Divisions has. She suggested that TPNA might consider adding the following sentence to our package insert: "Increase bladder and renal transitional cell tumors were seen in other compounds in the same class of drugs."

EXHIBIT 2

ACTOS FDA Response, Round 2

Action Item List

Item	Person Responsible	Due Date/ Status
Discuss possible impact on market potential	Orlando	Discussed 9/19; Difficult to determine since primary market research not feasible, still trying to ID similar model internally
Set up consulting agreement with Dr. Droller	Kaluzny	DONE
Set up consulting agreement with Dr. Wood	Kaluzny	DONE
Determine feasability of conducting tumor promoter study in PPARα knockout model	Burant/Expert	Telecon held September 23 with Drs. Reddy and Gonzales
Develop strategy to refute FDA PPAR hypothesis	Baron/Durack/ Burant/Nonclinical consultant/Recker/ Perez	Telecon held September 23 with Drs. Reddy and Gonzales
Determine availability of PPARα knockout models	Burant	Telecon held September 23 with Drs. Reddy and Gonzales
Examine GLAI protocol for how Actos and Avandia were discussed regarding PPARα activity	Perez	DONE; PPARα activity not mentioned in protocol
Schedule additional telecon with Dr. Cohen	Kaluzny	DONE; Scheduled for Sept 30 at 2:30pm

Last Update: 10/10/2002 3:46 PM

Item	Person Responsible	Due Date/ Status
Develop design for case-control study	Page	Proposal distributed to team 9/24/02
Identify expert author for NMP22 PMA application	Durack	DONE; No expert document found, but Mark Soloway identified as author of reference article
Contact Mayo Clinic clinical pathologist to determine usage/any limitations/overall utility of NMP22	Orlando	DONE: Dr. Robert Kisabeth at Mayo Clinic identified
Send bladder cancer Medwatch forms to RA	Page	DONE
Alert FDA to 2 additional bladder cancer cases	Haskins	DONE
Notify TCI about 2 additional bladder cancer cases	Ramstack	DONE
Contact Dr. Joe Brigman at Matritech	Baron	DONE: Confirmed that it's an appropriate tool for high-risk patients (i.e., male smokers over 60, employees in chemical industry) but would not consider test an appropriate screening tool for general public, doesn't know of any cases of test being used in that manner

Last Update: 10/10/2002 3:46 PM

Item	Person Responsible	Due Date/ Status
Identify CRO to approach NMP22 manufacturer for additional information	Recker/Perez/Kaluzny	IN PROGRESS: Held initial telecon with CRO (Theradex) on 10/7/02 to clarify questions for Matritech
Obtain information about NMP22 – specificity, sensitivity, limitations, cost	Thom/Burant	IN PROGRESS; Test used infrequently at University of Michigan, who sends test out to Mayo Clinic
Contact Masahiro Miyazaki re: NMP22 approval in Japan	Ramstack	IN PROGRESS: E-mail sent to Masahiro 9/19/02; Additional follow-up at TCI on 10/2/02
Set up teleconference with Dr. Droller to review clinical questions → Clerval phone call 9:30am - send some questions – distribute papers	Kaluzny Droller	IN PROGRESS; Telecon set up for October 15
Contact Dr. Stadler regarding prevention study	Recker	was out → pio in pt w bladder cancer in progress
Contact Dr. Reddy regarding authoring white paper	Baron	

Ingrid
Chris
Chuck
David

Ryan search on Droller lost 3-5 yrs – bladder cancer 96 papers

TZD's & cancer → good to have PPAR & activation
PPAR
JCI
Sprafleron + Gruzzo PNAS

Last Update: 10/10/2002 3:46 PM

EXHIBIT 3

From: Thom, Claire
To: Saito, Katsuhisa; Kashiyae, Masatake; Kitazawa, Kiyoshi
CC: Daly, Rich; Orlando, Dan; Blake, Bill
Sent: 1/30/2003 6:54:04 PM
Subject: FW: Label negotiation strategy

As requested -- the marketing opinion.

Claire

-----Original Message-----
From: Orlando, Dan
Sent: Thursday, January 30, 2003 6:40 PM
To: Thom, Claire
Cc: Daly, Rich; Blake, Bill
Subject: RE: Label negotiation strategy

Claire,

The decision was made that conducting market research on possible label language around bladder cancer would risk public awareness and raise unfounded concerns about Actos therapy. Therefore we don't have a quantitative measure to gauge the impact of the suggested label changes on the sales forecast. Obviously, the more onerous the clinical language the greater the expected impact.

In Marketing's assessment, the opening position with the agreed upon changes to the "Carcinogenesis" section with no clinical statement, will have little to no impact to the '03 sales forecast. In Marketing's assessment any of the proposed changes which imply a clinical connection would have an impact to sales. Any clinical language would likely be used by GSK to differentiate Avandia on safety. It would be relatively easy for the competition to establish seeds of doubt with the Actos PI. Given the lack of published data to defend the clinical impact of pio on bladder cancer, Takeda representatives would have difficulty managing these safety concerns.

Marketing has been involved with and supports the teams assessment of the alternatives and the scenario of negotiation provided below. Marketing hopes, as all do, that the opening position is acceptable to the FDA.

Thanks, do

-----Original Message-----
From: Thom, Claire
Sent: Thursday, January 30, 2003 10:37 AM
To: Orlando, Dan; Blake, Bill
Cc: Daly, Rich
Subject: FW: Label negotiation strategy
Importance: High

Per our conversation - please comment on the marketing implications and marketing involvement in the labeling as requested in the sentence below:
Comments from TPNA marketing responsible person on the possible effect for the sales figures of Actos in the US in each labeling scenario case

I need your response tonight for deliver to Dr. Kitazawa.

Thanks,

Claire

-----Original Message-----
From: Thom, Claire
Sent: Wednesday, January 29, 2003 6:32 PM
To: Kitazawa, Kiyoshi
Cc: Saito, Katsuhisa; Kashiyae, Masatake; Booth, Mark; Hamanaka, Saburo; Daly, Rich; Kuroiwa, Takashi; Hoos, Ingrid
Subject: Label negotiation strategy

Importance: High

Dr. Kitazawa,

As outlined in the January 3rd correspondence between TPNA and FDA, FDA has mandated that TPNA propose nonclinical and clinical label language change to address their concerns regarding the bladder.

As a follow-up to our conversation tonight, here is the strategy TPNA would like to propose for our meeting with the FDA on February 4th as it relates to the label change. Please note that these alternatives (including the possible label language) was developed by a team of people including our attorneys.

Opening position (as outlined in the January 15th submission to the FDA):
-TPNA accepts the deletion of "The relationship of these findings in male rats to humans is unclear." from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label.
-TPNA concludes that neither of these cases (the two cases identified in the phase IV study 506) can be attributed to treatment with ACTOS and that inclusion of this information in the package insert could be misleading.

We intend to maintain this position based on some new information we have received which further supports that neither case can be attributed to ACTOS. The male patient had 3+ hematuria at screening and the history for the female patient revealed nearly annual recurrence, as would be expected given the natural course of bladder cancer. In addition, the biopsy results for this patient may not even be consistent with a diagnosis of malignancy (we are awaiting expert confirmation on the interpretation of the biopsy report).

We are awaiting the medical history on the third bladder cancer patient who was brought to your attention yesterday. Our expectation is that we will receive consent to obtain the medical record tomorrow but it is unclear how long it will take to actually receive the record.

It is our intention during the formal presentation of the meeting to only share the above information with the agency. If the agency finds this position unacceptable we will move to alternative position #1 verbally.

Alternative position #1:
-TPNA accepts the deletion of "The relationship of these findings in male rats to humans is unclear." from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label.
-TPNA would request the Agency allow additional time for TPNA to obtain the full medical history on the third patient and postpone any discussion of a clinical label change until that information is evaluated (we suspect the "additional time" will be 1-2 weeks only).

If the agency finds this position unacceptable we will move to alternative position #2 verbally.

Alternative position #2:
-TPNA accepts the deletion of "The relationship of these findings in male rats to humans is unclear." from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label.
-TPNA accepts the following language to be added to the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label immediately preceding the cytology data section:
"Rare cases of bladder cancer have been reported in patients receiving ACTOS and comparator medications. The relationship between ACTOS and bladder cancer in humans is unknown"

If the agency finds this position unacceptable we will move to alternative position #3 verbally

Alternative position #3:
-TPNA accepts the deletion of "The relationship of these findings in male rats to humans is unclear." from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label.
-TPNA accepts the following language to be added to the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label immediately preceding the cytology data section:
"Rare cases of bladder cancer have been reported in patients receiving ACTOS. The relationship between ACTOS and bladder cancer in humans is unknown"

If the agency finds this position unacceptable we will move to alternative position #4 verbally

Alternative position #4:
-TPNA accepts the deletion of "The relationship of these findings in male rats to humans is unclear." from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label.
-TPNA accepts the following language to be added to the Adverse Reaction subsection of the label immediately preceding

laboratory values section (includes moving urinary cytology language from the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of the label to the Adverse Reactions subsection) :
"Rare cases of bladder cancer have been reported in patients receiving ACTOS. The relationship between ACTOS and bladder cancer in humans is unknown. During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to 1 year in duration, no new cases of bladder tumors were identified, Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%)." Please note that the language starting from "During prospective" and through .... (0.88%)" has been approved since launch.

If the agency finds this position unacceptable or proposes language which in our estimation is unjustified, we will stop negotiates saying we must confer with our parent company.

Please let us know if you have any questions.

Regards,

Claire and Ingird

EXHIBIT 4

From:	Gabanski, Stacy </O=TAKEDA PHARMACEUTICALS AMERICA/OU=HOMEOFFICE/CN=RECIPIENTS/CN=SGABANSKI>
Sent:	12/29/2003 11:50:21 AM
To:	Gabanski, Stacy <sgabanski@tpna.com>; Fric, Nancy <nfric@tpna.com>; Rillo, Julie <jrillo@tpna.com>; Sharpe, Karen <ksharpe@tpna.com>; Loungaphay, Sue <sloungaphay@tpna.com>
Subject:	Updated: Review Barriers to Prescribing Qual Report and Discuss Quant Portion
Location:	Meeting Room 307 - 475
Start:	Fri 1/9/2004 8:30:00 AM
End:	Fri 1/9/2004 9:30:00 AM
Recurrence:	(none)
Meeting Status:	Accepted
Required Attendees:	Gabanski, Stacy; Fric, Nancy; Rillo, Julie; Sharpe, Karen; Loungaphay, Sue
Optional Attendees:	Blocki, Ginny; Dao, Minh; Trokenheim, Jocelyn
Attachments:	Updated: Review Barriers to Prescribing Qual Report and Discuss Quant Portion; Updated: Review Barriers to Prescribing Qual Report and Discuss Quant Portion; Barriers report 12_22_03.ppt

Please bring any questions you may have on the qual report. Sue and I will give a brief overview of the quant research.

12/29/03 - UPDATE: New Date & Time. Julie I know you have a meeting starting at 9am, but this was the only time I could get everyone togther that day.

BLOCKI DEP. EX. NO. 16
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Barriers to TZD Prescribing Qual Report

December 2003

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Overview

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Background, Objectives, and Method

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Background and Objective

- Despite growing evidence that TZDs offer unique, important long-term benefits as well as a proven safety record, many physicians limit their use of this class of oral antidiabetic medications (OADs).
- The objective of this research is to understand key factors that drive high-level prescribing of TZDs as well as identify barriers to use among low writers of TZDs.
  - Specific barriers addressed included:
    - Cost
    - Weight gain
    - Edema
    - Liver safety/liver function testing (LFT)
    - Cardiovascular safety

Method

- A total of 28 in-depth telephone interviews were conducted with endocrinologists and primary care physicians in November 2003.
  - Interviews were approximately 45 minutes in duration.
- The research was conducted in two phases
  - In the initial phase, in-depth telephone interviews were conducted with a total of 11 high TZD prescribers.
    - 4 Primary Care Physicians (PCPs)
    - 7 Endocrinologists (ENDOs)
  - In the second phase, in-depth telephone interviews were conducted with a total of 17 medium-to-low TZD prescribers.
    - 9 PCPs
    - 8 ENDOs

Note to the Reader:
High vs. Low TZD Prescribers

This report presents the findings of low, medium, and high prescribers of TZDs, as defined by a Takeda *list (See slide 73 in Appendix). Subsequently, the report is designed, in part, to elucidate the differences between high and low writers of TZDs.*

Physicians identified as mid-level prescribers attitudinally had responses characteristic of either group.

Thus the attitudes of "high level" TZD prescribers as well as "low level" prescribers might include the responses from the medium-level group.

Caveat

This research is qualitative in nature and is based on a limited sample of primary care physicians and endocrinologists. This information is intended to provide direction to the ACTOS Brand Team but should not be considered projectable to the universe of each audience.

Numerical estimates (including estimates of patient volume, proportions of patients on TZDs,etc.) must be interpreted with special caution.

Executive Summary

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Executive Summary:

Little change seen in treatment patterns

- The type 2 diabetes treatment paradigm has changed little in the past year.
  - With metformin the first-line OAD of choice, followed by add-on TZDs or sulfonylureas, as second line therapy.
  - Some physicians use TZDs as first line.
    - Starting with combination therapy of TZD plus metformin
    - These are typically high writers of TZDs; however, not all higher writers are first-line use advocates
- Treatment goals are also fairly consistent, focusing on hemoglobin A1c levels, lipid, and blood pressure control.
  - High prescribers of TZDs were somewhat more concerned with long-term complications of diabetes as well as endothelial cell function.

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Executive Summary:

Characteristics of high vs. low TZD Rx'ers

- Principally, high writers differ from low writers in that they are:
  - More "sold" on the secondary target organ, lipid, and endothelial benefits of TZDs.
  - Willing to counsel patients on how the benefits outweigh the perceived drawbacks of TZDs.
    - Particularly higher costs/co-pays and weight gain.
    - Whereas low writers were more willing to quickly switch to another OAD class when patients complain about TZD drawbacks.
  - Apt to believe the mechanism of TZDs offers unique benefits in insulin resistance and Metabolic Syndrome.

Executive Summary:

Characteristics of high vs. low TZD Rx'ers

- High writing physicians of TZDs also tend to be:
  - Higher writers of metformin
    - However, they are <u>not</u> more likely to prescribe sulfonyureas
  - More likely to prescribe polypharmacy (related to above)
- Low writers often express that their main focus in OAD prescribing is managing blood glucose.
  - Several mentioned that other agents (e.g., statins, antihypertensives) can cover target organ protection better and more directly than TZDs.

Executive Summary:

Characteristics of high vs. low TZD Rx'ers

- Those physicians claiming to be more knowledgeable about secondary TZD benefits are more likely to be high TZD writers.
- However, low users claim that "there is nothing more that [they] could learn about TZDs that would change [their] prescribing."
  - They prefer to rely instead on their own experience.

Executive Summary:

Overcoming Barriers

- Specific barriers are listed on the next pages.
  - They are in order of importance.
    - e.g., The first listed barrier is more of an issue than those that follow.

Executive Summary:

Overcoming Barriers

Barrier: Cost & Reimbursement

- Cost and reimbursement are the main barriers of TZD prescribing due to the availability of generic metformin.
  - Causing MCOs to mandate the use of metformin first line in many cases.
- Metformin is also seen as quite effective, demonstrating value.
- TZDs are higher priced and, therefore, have higher co-pays.

High writers overcome by…

- Telling patients that the value of target organ, cardiovascular and endothelial benefits of TZDs outweigh the higher cost.
- Considering the benefits of TZDs among insulin resistant patients.
- Using patient-assistance programs and samples.

Executive Summary:

Overcoming Barriers

Barrier: Weight Gain

- Lower writers are more willing to discontinue TZDs when patients complain about weight gain.
  - A few avoid prescribing TZDs for patients they believe might be sensitive to the issue.

High writers overcome by…

- Turning the negative into a positive—the gain may be a result of improved glucose metabolism.
- Again, counseling the patients of the value of the secondary benefits of TZDs—overshadowing the weight gain.
- Not brining up the subject of weight gain unless it manifests in a patient (and the patient complains).

Executive Summary:

Overcoming Barriers

Barrier: Edema

- While an important issue, few patients develop peripheral edema on TZDs or other OADs.
  - Some instances of TZD-related edema were transient.
  - TZDs are only rarely discontinued due to peripheral edema.
- There are no notable differences between the way high vs. low prescribers handle edema.

Physicians overcome by…

- Halving the TZD dose, if they believe the issue is dose-related.
- In a few cases, prescribing a diuretic.
- Confirming that the edema is not CHF related.

Executive Summary:

Overcoming Barriers

Barrier: Liver Safety

- Liver complications is not a notable barrier among physicians in the study…
  - Except for a few patients with prior or active liver disease.
- MDs state liver function tests (LFTs) are not a barrier.

Physicians overcome by…

- Avoiding use among patients with a history of or existing liver disease.
- Realizing that most patients with type 2 require LFTs for other agents as well (e.g., statins).
- Personal experience: None of the physicians reported liver complications associated with ACTOS or Avandia use.

Executive Summary:

Overcoming Barriers

Barrier: CHF

- Congestive heart failure was not seen as a major barrier to writing TZDs.
  - Only a small minority of type 2 patients were reported to have CHF.

Physicians overcome by…

- Avoiding use among patients with CHF.
- Ruling out CHF if edema is present.
  - Testing for ejection fraction (mentioned by only a few respondents)

Executive Summary:

Overcoming Barriers

Barrier: Onset of action

- A perceived slower onset was volunteered as a barrier to first-line use by about one-quarter of respondents.
  - Physicians concerned about this, particularly lower writers, opted to use other OADs first-line (among other rationale).

High writers…

- Typically were less concerned about slower onset; however most higher writers still used TZDs as second-line therapy.
- Sometimes initiate a patient on both a TZD and metformin, particularly if insulin resistant.

Executive Summary:

Recommendations

- Emphasizing to low writers on how to overcome these barriers will be an important step in increasing TZD use.
  - Particularly in weight gain
- Exposing low writers to data on the secondary benefits of TZDs will also be useful.
  - Such as increase target organ protection, lipid benefits, and endothelial benefits

Executive Summary:

Recommendations

- Educating low writers about the benefits of using *multiple* OADs earlier in the treatment sequence for patients with type 2—A metformin + TZD regimen could help with use earlier in the treatment algorithm.
  - High writers are often quicker to move to metformin + TZD polypharmacy than low writers.

Detailed Findings

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Findings: Current Practices and Overall Attitudes

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Current Prescribing Practices

- Prescribing practices of physicians varied, as shown below by percent of patients treating with each category of agent.
- High TZD prescribers wrote more prescriptions for both TZDs and metformin (but not sulfonylureas).
- High TZD prescribers were more likely to have greater numbers of patients on combination therapy than low/medium writers as seen in "total percentage" column below.

	Metformin	Sulfonyl-ureas	TZDs	Other	Insulin	Total Percentage
High TZD Rx'ers	63%	35%	52%	11%	24%	185
Low/Medium TZD Rx'ers	54%	37%	32%	10%	29%	162

N= 28 physicians: 11 high writers; 17 medium/low

Initial Therapy

- Both high and low prescribers of TZDs tend to start patients on metformin, because:
  - Metformin is seen as efficacious and is available in an inexpensive, generic form.
    - Many believe it is effective in the general diabetic population and among those with insulin resistance.
  - TZDs are more expensive, less available on formulary, and thus tend to be used later in the treatment sequence.
  - Metformin is seen as not increasing patient weight.

Efficacy Measures

- Not surprisingly, physicians focus on lab values to measure success of treatment, with an HbA_{1c} at 6.5 or below as a fairly consistent goal.
- Secondarily, physicians look for efficacy in terms of impact on insulin resistance and among patients with Metabolic Syndrome, such as:
  - Lipid lowering
  - Prevention of long-term complications
  - Impact on blood pressure

Importance of Insulin Resistance

- Most physicians reported that the majority of their patients with type 2 have some degree of insulin resistance.
  - Most report 70% or more of their patients as insulin resistant.
    - There are no notable differences between high and low writers in terms of proportion of insulin resistant patients.

Importance of Insulin Resistance

- Perception of efficacy in insulin resistance reveals an important difference between high and low prescribers of TZDs.
  - High TZD prescribers more likely to believe that TZDs offer unique efficacy against insulin resistance.

    "TZDs are first-line for insulin resistance, they treat the main pathophysiology of the disease." High TZD Endo
  - Low TZD writers more likely to believe that metformin and TZDs are equally efficacious in treating insulin resistance.

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Perceptions of Impact on Endothelium

- Most physicians were aware of some relationship between diabetic "control" and endothelial damage.
- High prescribers appear to have a better understanding of the importance of treating insulin resistance and preventing endothelial cell damage.

  "It's critically important to prevent inflammatory damage to endothelial cells. All the complications of diabetes are related to inflammatory cytokines." High TZD PCP

  "I don't know about endothelial cell function. If the sugar can't get into the cell, it's resistant, it's not utilizing sugar well." Low TZD PCP

Findings: Use and Perceptions of TZDs

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Order of Use of TZDs

- Regardless of level of use, most physicians in the study do not use TZDs as 1st line therapy.
  - Among higher TZD writers, about half in the study write TZDs, to any extent, as first-line therapy.
- Most commonly, TZDs are used as first or second *add-on.*
  - Typically added to metformin, although in some cases third to metformin and sulfonylureas.

TZD Candidate Populations

- Nearly all patients with type 2 diabetes are considered, by physicians, to be candidates for TZD therapy, due to:
  - Efficacy in lowering blood glucose.
  - Perceived cardiovascular and target organ benefits (particularly among high writers).
  - Mechanism of action, which helps patients make better use of their own insulin.

TZD Candidate Populations

- While the candidate population is large for TZDs…
  - Patients with Metabolic Syndrome are considered the *most likely* candidates for TZDs, particularly among high writers.
  - Thus, these are patients who tend to be:
    - Insulin resistant
    - Dyslipidemic
    - Obese
      - However, there is a perception that TZDs can increase patient weight to some extent.

TZD Candidate Populations

- Two main factors drove the higher use perceptions in Metabolic Syndrome:
  - A perceived greater efficacy for TZDs among high writers due to the mechanism of action.
  - The need for multiple OADs with this population (e.g., metformin + TZDs in combination).

TZD Candidate Populations

- Low prescribers tend to fall into two "camps":
  - Those who do not perceive, or are uncertain about, any added value of TZDs over metformin.
    - The majority of lower writers in the study

vs.

  - Those who see a broad range of benefits of TZDs, but find cost and/or formulary restrictions greatly limit their prescribing.

Inclusion/Exclusion of Candidates

- In general, however, low TZD writers were more likely to find reasons to *exclude* candidates for TZDs, such as:
  - Cost
  - CHF
  - Edema
  - Weight gain
  - Patients with current or prior hepatic abnormalities
  - Slower onset of action

> *"Can they be well controlled with cheaper drugs with less side effects?"* Low TZD Endo

Inclusion/Exclusion of Candidates

- For many low writers, cost is the *primary* reason that prevents TZD candidates from being treated with a TZD.

  "My patients are on fixed incomes, they have no Rx plan and are on Medicare. There is also a group in the middle that is not old enough to get Medicare." Low TZD Endo

- Both high and low prescribers are more likely to cite tolerability or side effects as a reason for not treating candidates.

  "The others were tried on TZDs and had fluid retention or were contraindicated by CHF or liver disease." High TZD Endo

- In a few cases, patients refused treatment due to safety concerns or perceived risk of weight gain.
  - A few patients expressed concerns on TZDs after negative publicity about Rezulin according to two physicians.

Inclusion/Exclusion of Candidates

- On the other hand, high TZD writers are more likely to cite the benefits of TZDs, such as:
  - Treatment of insulin resistance
  - Improved lipid profile
  - Endothelial benefits
  - No risk of hypoglycemia

Inclusion/Exclusion of Candidates

- Those more apt to use TZDs first line—among high and medium-level writers—are also more likely to perceive unique benefits of TZDs, including:
  - Beta-cell preservation
  - Protection of endothelium
  - Slowing of disease progression

Focus on Primary vs. Secondary Benefits

- Among both high PCP writers and several ENDOs the perceived unique benefits of TZDs are important.

  "It's very important – the patient gets stable and you can expect a sustained response. Sustained response and insulin resistance are related. If you act on the cause…you treat the insulin resistance and protect the pancreas." High TZD PCP

  "TZDs treat the origin of the problem, helping the muscle to use insulin. It's extremely important." Low TZD Endo

- Others are less convinced of unique benefits, and are more focused on the "primary objective"—blood glucose control

  "I understand the theory about long-term effects [with TZDs], but it's not more efficacious [at reaching goal]. Reaching goal is key, it doesn't matter which drug you use…local experts and ADA guidelines start with tight control with metformin, then sulfonylureas, then TZDs." Low TZD PCP

Self-reported TZD Range of Usage

- High writers cite that, ultimately, about 50% – 75% of their patients with type 2 diabetes are prescribed TZD therapy.
- Lower writers self-report that 25% – 40% are prescribed a TZD regimen.

TZD Preference

- About two-thirds of physicians have no preference for ACTOS vs. Avandia.
  - The remaining physicians are evenly divided as to their preference, however, rationale is often related to the drug that is on formulary, availability of samples, and experience with the agent.

Findings:
Other Factors Influencing Perceptions of TZDs

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High TZD Rx'ers More Knowledgeable

- Those more apt to write for TZDs are also more knowledgeable about secondary benefits of the class than their low-user counterparts.
  - Secondary benefits included lipid/cardiovascular benefits, target organ protection, use in insulin resistance, endothelial benefits.
  - In contrast, most low writers have only a passing knowledge of secondary claims and are more skeptical that any benefit would represent a meaningful improvement.
    - A few low writers, however, are more convinced of these claims, but found that the cost of TZDs outweigh the potential benefits.
- *However*, both high and low writers do not believe that there is anything more that they could learn about TZDs that would raise their level of use.

High TZD Rx'ers More Knowledgeable

- This creates a "disconnect" among physicians:
  - More knowledgeable respondents write more TZDs.
  - Less-informed physicians do not believe more TZD education could increase their writing.
- There are a few reasons given for this:
  - Some low writers prefer more personal experience with TZDs over (more) education.
  - For a few physicians, cardiac mortality data and other secondary benefits are still inconclusive.

Impact of Rezulin on TZD Perception

- Almost all physicians used Rezulin in the past.
  - Rezulin offered a novel mechanism of action and a means by which to add another oral agent rather than starting insulin.
  - Despite the later release of data showing liver toxicity concerns, many of the physicians reported excellent experiences with Rezulin.

    "I used Rezulin because the literature was outstanding on efficacy. It was also a new class. My experience was very positive. It had no fluid retention." High TZD Endo

    "We used Rezulin for people with severe insulin resistance. It was more effective than the current TZDs." Low TZD Endo

Impact of Rezulin on TZD Perception

- Following the release of liver toxicity data associated with Rezulin, physicians initially were concerned about safety of "newer" TZDs.
- However, nearly all physicians in the study had concerns about ACTOS and Avandia allayed over time due to:
  - Physicians' own positive personal experience with the newer TZDs.
  - No evidence of TZD-caused liver toxicity among their patients.
  - Publications demonstrating safety and clinical benefits shown for ACTOS and Avandia.

> *"Initially when Rezulin was recalled, everyone was nervous. Over time, we have used TZDs more in combination…I'm happy with combination therapy. The side effect profile is OK. LFTs are not as critical. The combination of literature and experience and indications have opened up use. TZDs are safer than people think."* Low TZD PCP

> *"I have a good feeling about TZDs. It's gotten more positive over time. They work well, so I use them."* Low TZD PCP

Description of TZDs to Colleagues

- When respondents were asked how they would describe TZDs to colleagues many said that they have some benefits and a good safety profile – regardless of their level of use.

  "TZDs are very valuable, they have unique benefits and there's a lack of understanding [among physicians] about their benefits and safety. Also, they don't have time to educate patients if they are not familiar with the drugs, and it's restricted by the HMO. It's a shame that the patient doesn't get the benefit." Low TZD Endo

Description of TZDs to Colleagues

- Reluctance to use TZDs more widely by colleagues (and respondents themselves) is also attributed to:
  - Inexperience
  - Habit

    "I'm just not in the habit of writing them (TZDs). I should use them earlier, studies show that they slow progression of disease and have benefits on lipids." Low TZD PCP
  - Lack of understanding of TZDs unique impact on insulin resistance.

    "Primary care physicians do not know the endothelial benefits of TZDs, so they don't push as hard. Cost is a big deal, but Medicare doesn't stop me from trying to do what's best for the patient." High TZD Endo

Findings: Barriers to Prescribing TZDs

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Barriers to Prescribing: Overall

- Among the barriers addressed in this research…
  - Cost and reimbursement are the most significant barrier to (increased) TZD prescribing.
  - Weight gain is perceived to be a moderate-level barrier.
  - Viewed as minor concerns, particularly relative to OADs as a whole, were:
    - Edema
    - Liver safety
    - Cardiovascular safety
  - Onset of action was volunteered (i.e., unaided) as a barrier to first-line use by about one-forth of respondents

Barriers to Prescribing: Cost and Reimbursement

- Cost is seen as the greatest barrier to (increased) TZD use by most respondents.
  - Particularly low- and medium-level TZD prescribers
- TZDs are considered "expensive" relative to most commonly used OADs.
  - With metformin typically having a much lower co-pay and out-of-pocket cost.

Barriers to Prescribing: Cost and Reimbursement

- Cost is more often seen as barrier by low TZD prescribers.
  - These physicians are more likely to have patients that do not have prescription coverage.
  - Also, many patients with type 2 are on polypharmacy (statins, ACE inhibitors, antihypertensives, and so forth).
    - Coupons, samples and patient assistance programs are used widely by respondents.
    - However, patient assistance programs are claimed to be of limited value since many patients are not poor enough to qualify.
- High TZD writers are more likely to mention the use of samples as a way to offset the high cost.

Barriers to Prescribing: Cost

- Among the insured, high copays can also be a barrier, particularly when many patients with type 2 are taking multiple, expensive medications.
  - Low TZD prescribers are more likely to discontinue the TZD and switch to a cheaper class when patients complain of costs.

    "About one third of patients refuse [a TZD] due to cost, or drop out due to cost – the will even request insulin." Low TZD PCP

- High writers are more likely to counsel patients on TZD benefits in response to complaints about cost.

  "When they complain about the cost, I tell them it's a bargain, considering the benefits of preventing complications and long term cardiovascular disease." High TZD PCP

Barriers to Prescribing: Weight Gain

- Most physicians believ that minor weight gain is common among OADs, except for metformin.
  - Metformin is considered either weight-neutral or has the potential to help the patient lose weight.
  - Commonly reported weight gain with TZDs is in the range of 5 to 10 lbs., with a few higher exceptions.

- Generally, weight gain is seen as more of a patient tolerability issue rather than a medical issue.

  "Weight gain is not an issue for the doctor, but all patients are very concerned. For the ones that follow their diet and exercise, it is not an issue." High TZD Endo

Barriers to Prescribing: Weight Gain

- Some relate the weight gain to edema, while others attribute it to improved glucose metabolism.
- Several high writers turn reports of minor weight gain into a "positive" and evidence of the improved metabolism.
  - But stress the importance of returning back to their "normal" weight through diet and exercise.
  - Several stress to patients that taking OADs are not a "license to eat whatever they want."

Barriers to Prescribing: Weight Gain

- For high writers, weight gain is not perceived as a major issue among most physicians prescribing TZDs.
  - However weight gain has the highest importance *relative to other barriers* for high writers.
    - Cost is relatively less important to this group of physicians.
- Low writers, who are less apt to consider secondary TZD benefits, are more willing to discontinue TZDs and/or switch to other OAD classes if a patient complains about weight gain.
  - A few doctors will avoid TZDs for patients they deem as more sensitive—in anticipation of weight gain complaints.

Barriers to Prescribing: Weight Gain

- Most high writers do not inform their patients about the potential for weight gain when prescribing, but prefer to address the issue if it arises.
  - When it does arise, high writers of TZDs are more likely to educate the patient about the unique, long-term benefits of TZDs—overshadowing the "risk of gaining a few pounds."
- Nearly all physicians are interested in a predictive model as a tool to screen and counsel patients.

Barriers to Prescribing: Edema

- The incidence of edema is seen as lower than patients experiencing weight gain.
- Most respondents report about a 5% incidence of peripheral edema among their patients.
  - The edema was transient among some patients.
- Physicians do not see edema as a significant barrier in prescribing for TZDs or other OADs.
  - However, when edema occurs, physicians sometimes evaluate the patient to rule out the presence of CHF.

Barriers to Prescribing: Edema

- There are no significant differences between high and low TZD prescribers in terms of how they perceive and address edema.
  - Some consider edema to be dose-related and will lower the TZD dose.
  - Only a few are willing to prescribe a diuretic, which is perceived to be effective in about half the cases of edema.
  - Discontinuation of a TZD due to edema is generally rare.
- A predictive model for edema would be welcomed.

Barriers to Prescribing: Liver Safety

- The potential for liver toxicity does not appear to be a major barrier to increased use of TZDs.
- Physicians agree, regardless of TZD user status, that risk of liver dysfunction does not prevent them from using TZDs more widely.
  - Liver toxicity is considered to be very rare.
  - None of the physicians in the study have experienced a serious liver problem with a TZD patient.

    "I have never had a problem with liver safety" High TZD PCP

Barriers to Prescribing: Liver Safety

- Nonetheless, physicians consider TZDs to be contraindicated for patients with prior or active liver disease.
  - Again, representing a minority of patients with type 2.
- Most do not consider periodic LFTs to be a serious inconvenience.
  - Many TZD patients are also on statins which require LFTs also.

    "Liver monitoring is not a disadvantage, we're doing it on everyone anyway." High TZD Endo

Barriers to Prescribing: Cardiovascular Safety

- Most physicians do not see cardiovascular issues as a major barrier to TZD use.
- Nearly all agreed that TZDs are contraindicated for patients with NYHA classes III and IV CHF.
  - For most, this is a small number of patients.

    "I do not have a problem with this, there are very few patients with CHF." Lower user PCP
- A few physicians mentioned that they check ejection fraction when a patient is suspected of having CHF or is significantly at risk—prior to prescribing a TZD.

Barriers to Prescribing: Onset of Action

- Onset of action is also perceived as a barrier to first-line TZD use.
  - Volunteered by about one-fourth of physicians.
- These physicians prefer to use metformin or sulfonylureas to bring blood glucose levels down more rapidly.
  - Versus waiting 4 - 6 weeks to see an effect with a TZD.

Weighted Issues on Rx'ing decisions

- Physicians were asked to spread 100 points across five issues associated with TZDs: weight gain, edema, cost, liver safety and CV safety, in order to understand the extent to which each issue impacts TZD prescribing decisions .
- The table below shows the average points assigned to each issue.

	Weight Gain	Edema	Cost	Liver Safety	CV Safety	TOTAL
High Rx'ers	27	18	20	15	20	100
Low/ Medium Rx'ers	19	15	39	14	13	100

Weighted Issues on Rx'ing Decision

- As shown in the previous table, cost has a much greater impact on the prescribing decision for low prescribers of TZDs than on higher prescribers.
- As noted previously, high prescribers are more influenced by weight gain when considering prescribing a TZD.
  - The highest of the relatively low barriers for this population of physicians.

Findings: Reactions to New Product Profile

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Reactions to New Product Profile

- In a limited number of interviews (n=12), physicians were presented with a profile of a new product and asked for their impressions and likelihood of use.
  - The results will help New Product Planning gauge an impact of hematuria monitoring for bladder tumors.

Reactions to New Product Profile

- The following profile was read to 12 physicians near the end of the interview:

> I would like you to assume that there is a new class of oral antidiabetic agents that is similar to the TZDs or glitazones. I'd like to give you a very brief description of a potential product in this new class and get your reactions to it.
>
> - Efficacy is comparable to TZDs as measured by A1c reduction
> - The incidence of edema is less than TZDs
> - The incidence of weight gain is the same as TZDs but the actual amount of weight gain is less.
> - Periodic urinary monitoring is required to detect hematuria (blood in urine).
>   - (Note to interviewer: If physicians asks, inform them that monitoring is recommended at baseline and then periodically thereafter, e.g. every 6 months)
> - Assume all other aspects of this product are the same as the TZDs. (Note to interviewer: If asked, confirm liver monitoring is required as with the TZDs.)

Reactions to New Product Profile

- 8 of 12 physician initially expressed interest in using the new product.
  - While 4 physicians in 12 were concerned about the underlying problem causing hematuria.

    " I don't like the hematuria part. What kind of problems would it cause with the kidneys?" Low TZD Endo

- Not surprisingly, those reacting positively did so due to the reduction in edema and weight gain incidence.

- Urine monitoring *per se* is not considered a barrier to use by the majority of physicians.
  - Most diabetic patients are having their urine monitored for albumin.
  - There is concern among some, however, as to potential safety issues that required the monitoring.

Reactions to New Product Profile

- Of the 8 physicians who expressed initial interest in using the product despite hematuria, interest declined when a risk of of bladder tumors was introduced.

  "Bladder tumors? That would change my thinking altogether. I would not be likely to use the product." Low TZD PCP

  - Interest declined greatly among 6 of the physicians.
  - Interest declined only slightly for 2 physicians.

- Of the 4 physicians initially concerned with hematuria, the risk of bladder tumors was serious enough that all felt they would not use the product.

  "If there is a risk of bladder tumors, I would definitely not use it." Low TZD Endo

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APPENDIX

Screening Criteria

TZD User Definition

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Screening Criteria

- Respondents were screened to meet the following requirements:
  - Less than 60 years of age
  - Devote greater than 75% of time to clinical practice
  - See the majority of their patients in an office based practice or clinic
  - Treat at least 15 patients with type 2 diabetes (ENDOs) and at least 25 patients with type 2 diabetes (PCPs) in a typical week
  - Write at least 1 prescription for OADs in a typical week
  - Standard security criteria

TZD User Definition

- High TZD User
  30% or more of OAD share is for TZDs
- Medium TZD User
  15% - 29% of OAD share is for TZDs
- Low TZD User
  - Less than 15% of OAD share is for TZDs

EXHIBIT 5

MAA
EU Bladder Issue

Takeda Europe R&D Centre Ltd London

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MAA
EU Bladder Issue

- EU R&D have been in a similar situation.
- The Bladder issue was blocking approval.

"Pioglitazone is a male rat urinary carcinogen and the mechanism is not fully clarified"

We succeeded eventually despite a very negative regulatory authority.

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The European Regulatory Authorities

- Doubted Sam Cohen's hypothesis.
- Asked about other possible mechanisms.
  - Including PPAR α hypothesis.
- Pushed for clinical testing.

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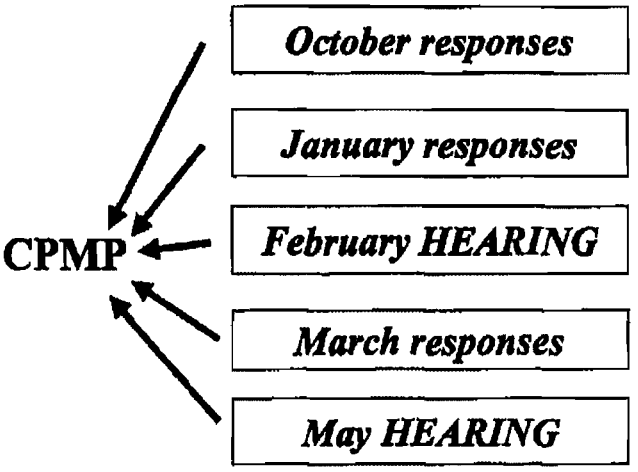
Multiple discussions with CPMP



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CPMP issues -against Sam Cohen hypothesis

- Correlation of tumours and stones is not good.
- Increase in micro crystals is not consistent and not observed at lower dose levels.
- Increase in urine pH is not consistent and not observed at lower dose levels.
- Other mechanisms have not been adequately explored:
  - Local proliferative properties of pioglitazone and metabolites
  - Genotoxicity
  - PPAR α hypothesis

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Correlation of tumours and stones is not good.

- 60% is actually quite a good correlation.
- Calculi dissolve.
- Calculi are lost in tissue processing.
- dissolve in fixative

(S18)May hearing

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Increase in urine pH is not consistent and not observed at lower dose levels.

- pH generally increased.
- The critical factor is a pH greater than 6.5
- pH is only one of the critical factors:
  - Other factors have not all been identified.

(S18)May hearing

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CPMP issues
- proposing PPAR α hypothesis

- Piogltazone has shown affinity for other PPAR activation (which has been associated with cell proliferation).

The role of PPAR in tumourigenic responses should also be explored.

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Piogltazone has shown affinity for other PPAR activation (which has been associated with cell proliferation).

- Pioglitazone does not produce tumours in tissues where PPAR α and γ are most highly expressed.
- Pioglitazone is not tumourigenic in mice or female rats.
- Pioglitazone is neither a peroxisome proliferator nor a hepatocarcinogen.

Study in this receptor field has greatly advanced since our responses

(S9)Jan resp.p26

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CPMP issues
-proposing clinical testing
-Human risk

- How will the company follow up the potential risk of bladder tumours in patients?
- Risk of colorectal neoplasm?

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How will the company follow up the potential risk of bladder tumours in patients?

- Restate the company position (Sam)
- Investigate any malignancies from trials.
- Outcome study data.
- Clinical testing of patients is not helpful.
- Japanese urine clinical study showed nothing.
- A case control study is possible.

(S13)May resp.

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Risk of colorectal neoplasm?

- PPAR γ may inhibit the growth of tumours.
- Glitazones only induce tumours in the genetic context of the APC mutation in mice.

(S10)Jan resp.

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CPMP issues -other issues

- Positive result from the PCNA assay.
- Site of contact genotoxicity could be clarified by a COMET assay.
- Genotoxic potential of metabolite MII has not been investigated.
- Interaction of pioglitazone and metabolites with DNA needs further study.
- Structural activity assessment not definative.

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Positive result from the PCNA assay.

- No correlation between PCNA index and histology.
- PCNA has limitations.
- BrdU is more sensitive and S phase specific.
  - This test was negative

(S9)Jan resp p24

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Site of contact genotoxicity could be clarified by a COMET assay.

- Pioglitazone is not genotoxic.
- COMET assay also positive in apoptosis.
- Assay needs fully validating.

(S9)Jan resp p24

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Genotoxic potential of metabolite MII has not been investigated.

- M II is only present in trace amounts in rat urine.
- M II was present in the in vitro mutagenicity studies.

(S6)Oct resp

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Interaction of pioglitazone and metabolites with DNA needs further study.

- Not genotoxic.
- Urine from pioglitazone treated rats is not genotoxic.
- Structural activity relationship.
  - Not a rodent carcinogen

(S5)Oct resp p13 Takeda Europe R&D Centre Ltd London

Eventual Success: Because of

- **Persistence.**
  - We stuck to Sam Cohen's hypothesis despite many challenges.
- **Argued against clinical testing.**
- **Did not "turn over stones"**
  - eg. Did not undertake database searches.
- **Supported by experts at every opportunity.**

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EXHIBIT 6

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

*John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Korányi, Markku Laakso, Marián Mokáň, Antanas Norkus, Valdis Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Škrha, Ulf Smith, Jan Tatoň, on behalf of the PROactive investigators**

Summary

Background Patients with type 2 diabetes are at high risk of fatal and non-fatal myocardial infarction and stroke. There is indirect evidence that agonists of peroxisome proliferator-activated receptor γ (PPAR γ) could reduce macrovascular complications. Our aim, therefore, was to ascertain whether pioglitazone reduces macrovascular morbidity and mortality in high-risk patients with type 2 diabetes.

Methods We did a prospective, randomised controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease. We recruited patients from primary-care practices and hospitals. We assigned patients to oral pioglitazone titrated from 15 mg to 45 mg (n=2605) or matching placebo (n=2633), to be taken in addition to their glucose-lowering drugs and other medications. Our primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN NCT00174993.

Findings Two patients were lost to follow-up, but were included in analyses. The average time of observation was 34·5 months. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0·90, 95% CI 0·80–1·02, p=0·095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0·84, 0·72–0·98, p=0·027). Overall safety and tolerability was good with no change in the safety profile of pioglitazone identified. 6% (149 of 2065) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups.

Interpretation Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events.

Lancet 2005; 366: 1279–89

See **Comment** page 1241

*Investigators listed at end of paper

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Introduction

Patients with type 2 diabetes are at high risk of fatal and non-fatal macrovascular events. These events are the main reason for their decreased life expectancy, which is about 8 years shorter in a 40-year-old patient newly diagnosed with diabetes than in the general population.[1] There is a two-fold to four-fold increased risk of a macrovascular event in patients with, compared with those without, diabetes.[2,3] Haffner and colleagues[4] noted that the risk of a cardiovascular complication in a patient with diabetes was similar to that of a patient without diabetes who had had a myocardial infarction. In the Heart Protection Study,[5] patients with diabetes and a history of cardiovascular disease at entry had almost a three-fold higher risk of a new cardiovascular event than did those without such a history.

Intensive control of glycaemia decreases microvascular complications, such as retinopathy and nephropathy, but has no great effect on macrovascular complications or all-cause mortality. However, in the UK prospective diabetes study (UKPDS),[6] findings of a retrospective analysis in a subgroup of 342 overweight patients who received metformin showed a significant decrease in cardiovascular disease and total mortality.

Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPAR γ) used to treat type 2 diabetes.[7] The overall pattern of changes induced by pioglitazone suggests a general improvement in various risk factors that might reduce cardiovascular morbidity and mortality. Additionally, pioglitazone reduces the levels of various inflammatory markers, such as highly sensitive C-reactive protein (hsCRP), independently of its effect on glycaemic control.[8]

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Our aim was to ascertain whether pioglitazone reduces cardiovascular morbidity and mortality in patients with type 2 diabetes, and to assess the safety and tolerability of such treatment.

Methods

Patients

The PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) protocol has been described in detail previously.[9] Between May, 2001, and April, 2002, we recruited patients from primary-care practices and diabetic or cardiovascular specialist departments in hospitals to a randomised controlled trial. We included patients with type 2 diabetes who were aged 35–75 years if they had an haemoglobin A_{1c} (HBA_{1c}) concentration greater than the local laboratory equivalent of 6·5% for a Diabetes Control and Complications Trial-traceable assay (DCCT), despite existing treatment with diet alone or with oral glucose-lowering agents with or without insulin. Patients also had to have evidence of extensive macrovascular disease before recruitment, defined by one or more of the following criteria: myocardial infarction or stroke at least 6 months before entry to the trial, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months before recruitment, acute coronary syndrome at least 3 months before recruitment, or objective evidence of coronary artery disease or obstructive arterial disease in the leg. Objective evidence of coronary artery disease was defined as a positive exercise test, angiography showing at least one stenosis of more than 50%, or positive scintigraphy. Obstructive arterial disease of the leg was defined as a previous major amputation or intermittent claudication with an ankle or toe brachial pressure index of less than 0·9.

We excluded patients if they: had type 1 diabetes; were taking only insulin; had planned coronary or peripheral revascularisation; had New York Heart Association class II heart failure or above; had ischaemic ulcers, gangrene, or rest pain in the leg; had had haemodialysis; or had greater than 2·5 times the upper limit of normal concentrations of alanine aminotransferase.

All patients provided written informed consent. The study protocol was approved by local and national ethics committees and regulatory agencies, and was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Procedures

We randomly assigned patients to oral pioglitazone or matching placebo in addition to their existing medication(s) for diabetes. Study medication was assigned via a central interactive voice response system. Allocation of patients to treatment groups was done by the method of randomised permuted blocks within centre. All investigators and study personnel were unaware of treatment assignment for the duration of the study. Only the data and safety monitoring committee saw unblinded data, none of whom had any contact with the study participants. The randomisation sequence was generated by a member of the Statistics Department of Nottingham Clinical Research Limited. Once these lists had been checked, all files were passed on to the interactive voice response system coordinator, who maintained these files securely for the duration of the trial. The original lists were deleted by the Department of Statistics, who had no access to the randomisation code until the study was unblinded. Masking of drugs was achieved by using matching placebo.

If allocated, we gave patients oral pioglitazone 15 mg for the first month, 30 mg for the second month, and 45 mg thereafter to achieve the maximum tolerated dose, according to the licensed dose range for pioglitazone. At any time during the study, the dose of study drug could be adjusted within the same dose range if clinically indicated. Throughout the study, investigators were required to increase all therapy to an optimum, according to the International Diabetes Federation European Region 1999 guidelines.[10] We drew particular attention to the need to reach an HBA_{1c} concentration below the recommended target (<6·5%) and to increase to an optimum lipid-altering, antiplatelet, and antihypertensive therapy.

We saw patients monthly for the first 2 months, then every 2 months for the first year, and thereafter every 3 months until the final visit. We followed-up all patients until the end of the study even if they permanently ceased study medication before the study end. We measured vital signs and bodyweight at every visit. We obtained standard 12-lead electrocardiograms at the beginning of the study, at yearly intervals thereafter, and at the final visit. Two independent reviewers assessed all electrocardiograms for evidence of silent myocardial infarction on behalf of the endpoint adjudication committee. We took blood samples at baseline for central laboratory assessment of concentrations of HBA_{1c}, triglyceride, HDL cholesterol, LDL cholesterol, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and creatinine. Thereafter, we measured HBA_{1c}, fasting lipid, and creatinine concentrations every 6 months, and liver function at every visit in the first year and every 6 months in subsequent years. Urinary albumin concentration was measured locally at the beginning and at the end of the study, using Micral Test strips (Roche Diagnostics, Mannheim, Germany). We identified the presence of retinopathy, nephropathy, and neuropathy from the patients' records. Blood pressure was measured with routine clinical methods.

All samples were measured in a central laboratory that participated in the appropriate national quality-control schemes for all analyses. We measured HDL-cholesterol and LDL-cholesterol concentrations with direct quantitative enzymatic methods, and triglyceride levels with a

glycerol-blanked, enzymatic assay. Methods used to measure concentrations of HDL-cholesterol and triglycerides were accredited by the Centres for Disease Control Lipid Standardisation Program. We undertook all central laboratory methods on automated Hitachi (Tokyo, Japan) P-Modular platforms, using Roche reagents (Roche Diagnostics, Mannheim, Germany), with standards and controls as recommended by the manufacturer. We measured HBA_{1c} concentrations in whole blood with a BIO-RAD-Variant ion exchange high-pressure liquid chromatography analyser (Biorad, Hercules, CA, USA), with standards and controls supplied by the manufacturer. The upper limit of normal for the laboratory was 6·4%.

Our primary endpoint was time from randomisation to: all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle. We diagnosed a non-fatal myocardial infarction if the patient survived more than 24 h from onset of symptoms and, in the absence of percutaneous coronary intervention or coronary artery bypass graft, had at least two of: symptoms suggestive of myocardial infarction (ischaemic chest pain or discomfort) lasting 30 min or longer, electrocardiographic evidence of myocardial infarction, or raised cardiac serum markers; or after percutaneous coronary intervention or coronary artery bypass graft the patient had electrocardiographic evidence of myocardial infarction. Silent myocardial infarction was defined as new Q waves on two contiguous leads or R-wave reduction in the precordial leads without a change in axis deviation. Acute coronary syndrome was noted if the patients received treatment in hospital for ischaemic discomfort at rest that lasted at least 5 min and had electrocardiographic changes or raised cardiac serum markers not sufficiently high to indicate myocardial infarction, or both. Coronary revascularisation was when a patient underwent percutaneous transluminal coronary intervention—eg, angioplasty, stenting, atherectomy, laser ablation—or coronary artery bypass graft. Stroke was defined as acute focal neurological deficit lasting for longer than 24 h or resulting in death within 24 h of the onset of symptoms, which was diagnosed as being due to cerebral lesion of vascular origin but excluding subarachnoid haemorrhage. Major leg amputation included all amputations of the leg above the ankle. Revascularisation in the leg was noted if a patient underwent any of surgical bypass, atherectomy, angioplasty, or thrombolysis.

The prespecified secondary endpoints, in order of priority, were: time to the first event of death from any cause, myocardial infarction (excluding silent myocardial infarction), and stroke (main secondary endpoint in rest of this report); cardiovascular death; and time to individual components of the primary composite endpoint. We classified all fatal events as cardiovascular unless there was a clear non-cardiovascular cause.

We reported all potential endpoints and other serious adverse events to the coordinating centre within 1 working day of becoming aware of the event. We defined serious adverse events as: resulting in death, life-threatening, needing or prolonging in-patient admission, resulting in persistent or significant disability, or needing intervention to prevent any of the above. We elicited non-serious adverse events at every visit. Investigators were required to report, in particular, occurrences of symptoms compatible with hypoglycaemia, heart failure (as judged by the investigator), and oedema in the absence of heart failure, plus any adverse event leading to discontinuation of the study drug.

Monitors reviewed patients' records regularly to ensure that all potential endpoints and other serious adverse events were being reported. All reports of serious adverse event were checked against the patients' clinical notes. An independent panel, working with the endpoint adjudication committee, assessed all potential endpoints and classified them in accord with predefined criteria. The study data and safety monitoring committee supervised the study and assessed

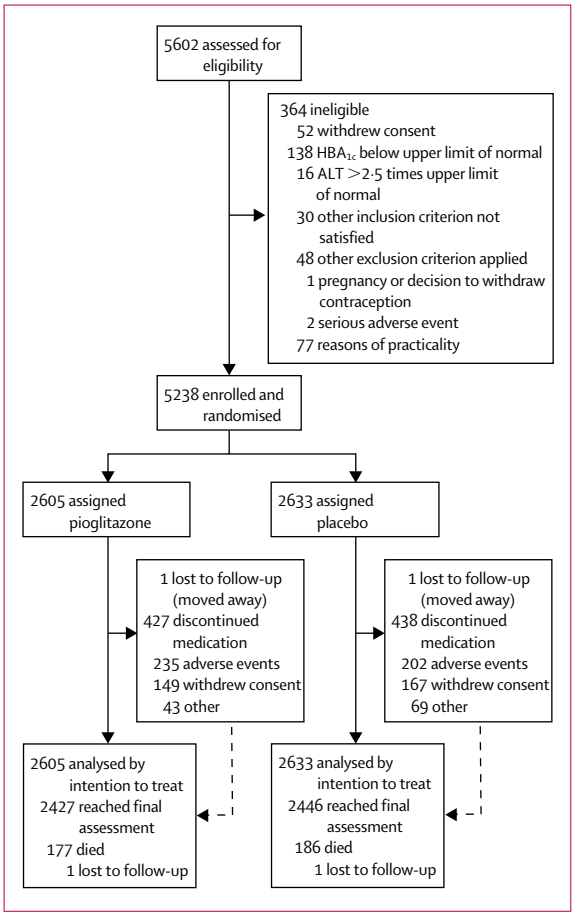

Figure 1: **Trial profile**

	Pioglitazone (n=2605)	Placebo (n=2633)
Patients' characteristics		
Male	1735 (67%)	1728 (66%)
White	2564 (98%)	2600 (99%)
Age (years) (mean, SD)	61·9 (7·6)	61·6 (7·8)
Time since diagnosis of diabetes (years) (median, IQR)	8 (4–13)	8 (4–14)
Body-mass index (kg/m^2) (mean, SD)	30·7 (4·7)	31·0 (4·8)
Blood pressure: systolic/diastolic (mm Hg) (mean, SD)	144 (18)/83 (10)	143 (18)/83 (9)
History of hypertension	1947 (75%)	2005 (76%)
Current smoker	340 (13%)	381 (14%)
Past smoker	1199 (46%)	1159 (44%)
Microvascular disease*	1113 (43%)	1076 (41%)
Blood glucose lowering treatment		
Metformin only	253 (10%)	261 (10%)
Sulphonylureas only	508 (20%)	493 (19%)
Metformin+sulphonylureas	654 (25%)	660 (25%)
Insulin only	5 (<1%)	8 (<1%)
Insulin+metformin	456 (18%)	475 (18%)
Insulin+sulphonylureas	209 (8%)	219 (8%)
Insulin+metformin+sulphonylureas	105 (4%)	107 (4%)
Other combination	306 (12%)	305 (12%)
Diet only	109 (4%)	105 (4%)
Laboratory data		
HBA_{1c} (%) (median (IQR)	7·8 (7·0–8·9)	7·9 (7·1–8·9)
LDL cholesterol (mmol/L) (median, IQR)	2·9 (2·3–3·5)	2·9 (2·3–3·5)
HDL cholesterol (mmol/L) (median, IQR)	1·1 (0·9–1·3)	1·1 (0·9–1·3)
Triglycerides (mmol/L) (median, IQR)	1·8 (1·3–2·6)	1·8 (1·3–2·6)
Creatinine (μmol/L) (median, IQR)	79 (68–92)	79 (68–92·5)
Micral test result		
Negative	1407 (54%)	1428 (54%)
About 20 mg/L	545 (21%)	551 (21%)
About 50 mg/L	357 (14%)	377 (14%)
About 100 mg/L or more	232 (9%)	217 (8%)

Data are number (%) unless otherwise stated. *Retinopathy, nephropathy, neuropathy.

Table 1: **Baseline characteristics**

	Pioglitazone (n=2605)	Placebo (n=2633)
Entry criteria		
Previous myocardial infarction	1230 (47%)	1215 (46%)
Previous stroke	486 (19%)	498 (19%)
Previous percutaneous intervention or coronary artery bypass graft	804 (31%)	807 (31%)
Previous acute coronary syndrome	355 (14%)	360 (14%)
Objective evidence of coronary artery disease	1246 (48%)	1274 (48%)
Symptomatic peripheral arterial obstructive disease	504 (19%)	539 (20%)
Two or more macrovascular disease criteria	1223 (47%)	1278 (49%)
Baseline cardiovascular medications		
β blockers	1423 (55%)	1434 (54%)
Angiotensin-converting enzyme inhibitors	1630 (63%)	1658 (63%)
Angiotensin II antagonists	170 (7%)	184 (7%)
Calcium-channel blockers	892 (34%)	964 (37%)
Nitrates	1018 (39%)	1045 (40%)
Thiazide diuretics	401 (15%)	430 (16%)
Loop diuretics	372 (14%)	378 (14%)
Antiplatelet medications	2221 (85%)	2175 (83%)
Aspirin	1942 (75%)	1888 (72%)
Statins	1108 (43%)	1137 (43%)
Fibrates	264 (10%)	294 (11%)

Data are number (%) unless otherwise stated.

Table 2: **Macrovascular morbidity at study entry and associated medications**

unblinded data to ensure the continued safety of participants throughout.

Nottingham Clinical Research Group acted as a coordinating centre, providing project management, data management, central randomisation services, and statistical analysis. ICON Clinical Research managed and monitored the sites, and did central laboratory measurements.

Statistical analysis

Our planned study sample size of 5000 patients was based on the assumptions of a 6% annual primary event rate in the placebo group, recruitment of patients over 18 months, and a total trial duration of 4 years. A time-to-event analysis was planned, and thus the study had 91% power to detect a 20% reduction in the hazard with a type I error of 0·05. To maintain this power, all patients had to be followed-up until at least 760 patients had one endpoint event or more.

Since the event rate was higher than expected and the enrolment rate was faster than planned, the mean duration of exposure would have been shorter than originally anticipated. Therefore, to ensure sufficient duration of exposure, the protocol was amended in May, 2003, to specify that the trial should continue until the last patient recruited had been followed-up for 30 months and at least 760 patients had had one or more endpoint events.

Two pre-planned interim analyses were done by the data and safety monitoring committee when about half and three-quarters of the target number of endpoints had been reached. We controlled the type I error with the method of Lan and Demets with the O'Brien-Fleming alpha spending function.[11] The final analysis of the primary endpoint thus needed the observed significance level (two-sided) to be less than 0·044 for the treatment difference to be declared significant at the 5% level.

All time-to-event analyses were done by fitting a proportional hazards survival model with treatment as the only covariate. The proportional hazards assumption was tested with the method described by Grambsch and Therneau.[12] Homogeneity of response was examined by testing for interaction in each of 25 prespecified sets of subgroups. We used linear models or logistic regression models for other endpoints, as appropriate. All analyses were by intention to treat.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN NCT00174993.

Role of the funding source

The study was designed by the international steering committee, who also approved the protocol and amendments. The sponsors had two representatives on the international steering committee and the same two were also members of the executive committee. Data analysis, data interpretation, and writing of the report

was done by the executive committee, with contributions from the international steering committee, the data and safety monitoring committee, and the endpoint adjudication committee. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 5238 patients from 321 centres in 19 European countries were randomly assigned to either pioglitazone (n=2605) or placebo (n=2633); 1681 patients were recruited from the community and 3557 from hospitals. All patients commenced study medication and all received their intended treatment. 16% of patients assigned pioglitazone and 17% of those assigned placebo discontinued study medication before death or final visit (figure 1). We completed final visits between November, 2004, and January, 2005. The average time of observation was 34·5 months. Two patients were lost to follow-up. All other patients were followed-up to their final visit or death. The treatment code was broken for three patients (all placebo) during the study for medical or medicolegal reasons.

The two groups were well matched with respect to baseline characteristics (table 1). Mean age overall was 61·8 years, with the median time since diagnosis of diabetes being 8 years. At randomisation, 62% of patients were taking metformin and 62% were taking a sulphonylurea either as monotherapy or in combination for diabetes control. More than 30% of patients were on insulin. Contrary to the study entry criteria, 13 patients (0·2%) had insulin as their only glucose-lowering medication.

Table 2 shows details of macrovascular disease and related concomitant medications taken. Patients had a high level of previous morbidity. We randomised 82 patients (2%) who we subsequently noted did not meet any of the strictly defined criteria for entry based on macrovascular history. Of these, 20 patients did not have any documented evidence of a previous macrovascular event. We included all 82 patients in all intention-to-treat analyses, but assigned them to the so-called absent subgroup for each of the subgroup analyses that related to macrovascular entry criteria.

Throughout, pioglitazone was well tolerated, with 89% (2235 of 2521) of patients reaching the 45 mg dose at the 2-month visit compared with 91% (2293 of 2517) of matching placebo. Thereafter, at least 93% of patients continuing on pioglitazone received the highest dose compared with at least 95% of those on placebo. Compliance in both treatment groups, as defined by more than 75% of tablets used, was greater than 95%.

Figure 2 shows Kaplan-Meier estimates of the proportion of patients reaching an event within the primary composite endpoint by treatment. Fewer patients in the pioglitazone group had at least one event

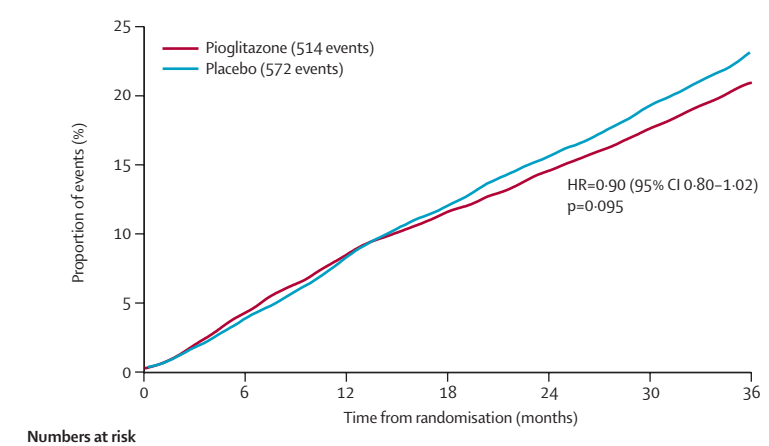

Figure 2: **Kaplan-Meier curve of time to primary endpoint***
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

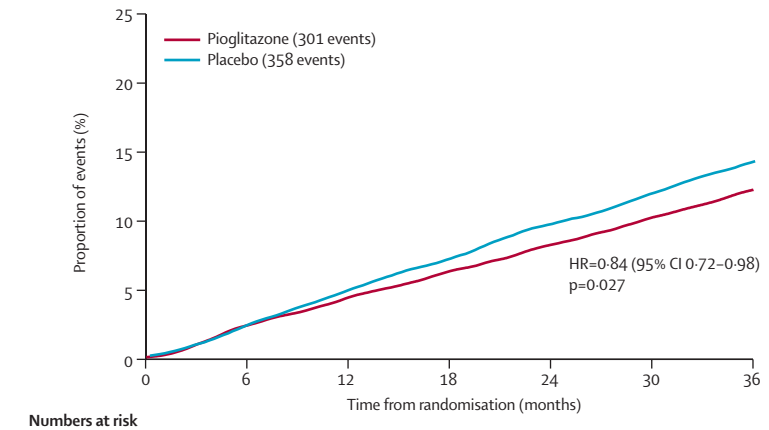

Figure 3: **Kaplan-Meier curve of time to main secondary endpoint***
*Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

	Primary composite endpoint		Main secondary endpoint	
	Pioglitazone (n=2605)	Placebo (n=2633)	Pioglitazone (n=2605)	Placebo (n=2633)
Any endpoint	514	572	301	358
Death	110	122	129	142
Non-fatal MI (excluding silent MI)	85	95	90	116
Silent MI	20	23	NA	NA
Stroke	76	96	82	100
Major leg amputation	9	15	NA	NA
Acute coronary syndrome	42	63	NA	NA
Coronary revascularisation	101	101	NA	NA
Leg revascularisation	71	57	NA	NA

MI=myocardial infarction. NA=not applicable. This table describes the events that make up the primary composite endpoint, so if death is not the first event, it does not appear.

Table 3: **Numbers of first events contributing to the primary composite and main secondary endpoints**

	First events			Total events	
	Pioglitazone (n=2605)	Placebo (n=2633)	HR (95% CI)	Pioglitazone	Placebo
Death	177	186	0·96 (0·78–1·18)	177	186
Non-fatal MI (including silent MI)	119	144	0·83 (0·65–1·06)	131	157
Stroke	86	107	0·81 (0·61–1·07)	92	119
Major leg amputation	26	26	1·01 (0·58–1·73)	28	28
Acute coronary syndrome	56	72	0·78 (0·55–1·11)	65	78
Coronary revascularisation	169	193	0·88 (0·72–1·08)	195	240
Leg revascularisation	80	65	1·25 (0·90–1·73)	115	92
Total	..	..	..	803	900

Data refer to first event of that particular type. MI=myocardial infarction.

Table 4: **Effect of pioglitazone and placebo on each component of the primary endpoint**

than in the placebo group, though this finding was not significant. Figure 3 shows the Kaplan-Meier estimate of the proportion of patients reaching the main secondary endpoint of all-cause mortality, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke. Fewer patients in the pioglitazone than in the placebo group had at least one event. The difference was significant. There was no significant violation of the proportional hazards assumption (p=0·085 for the primary endpoint and p=0·616 for the main secondary endpoint). Table 3 shows the breakdown of event types within the primary and the main secondary endpoints. The four most frequent component endpoints were death, myocardial infarction, stroke, and coronary revascularisation. All are well represented in the primary composite endpoint, and the first three constitute the main secondary endpoint. There were 127 cardiovascular deaths in the group treated with pioglitazone compared with 136 in the placebo group. There were 50 non-cardiovascular deaths in each group.

Table 4 shows the effect of pioglitazone on the first occurrence of each of the individual components of the primary composite endpoint and the total number of events reported. There is consistency of benefit across the endpoints of myocardial infarction, stroke, acute coronary syndrome, and cardiac intervention. The pioglitazone treated patients had 803 events, of which 514 were first events, whereas those on placebo had 900 events, of which 572 were first events.

The statistical analysis plan identified 25 baseline variables for subgroup analysis. Interaction tests within these subgroups did not reveal evidence of heterogeneity. Table 5 shows the results of a multivariate analysis of the association of entry characteristics to the main secondary endpoint. Pioglitazone is associated with an HR of 0·84 even after adjustment for the other factors in this table. An additional 14 factors at baseline—including, blood pressure, duration of diabetes, concentration of triglycerides and HDL cholesterol, and use of metformin and sulphonylurea—were considered but did not contribute significantly to the overall results.

Table 6 shows how the use of concomitant medication changed during the course of the study. With the exception of insulin and metformin use—both of which rose more in the placebo group—use of particular medications rose or fell to a similar extent in patients treated with placebo and pioglitazone.

At entry into the study, two thirds of patients were not receiving insulin (n=3478). Of these patients, 183 of 1741 (11%) in the pioglitazone group and 362 of 1737 (21%) in the placebo group began to use insulin permanently (defined as insulin use for 90 days or more, or insulin use at death or end of study) during the course of the study (figure 4).

As shown in table 7, concentrations of HBA_{1c} and triglycerides decreased, and levels of HDL cholesterol increased, on pioglitazone relative to placebo. Although LDL-cholesterol concentrations increased marginally more on pioglitazone than on placebo, there was a greater decrease in the LDL cholesterol to HDL

	HR (95% CI)	p
Age (year)	1·05 (1·04–1·06)	<0·0001
Previous stroke	1·71 (1·40–2·08)	<0·0001
Current smoker (*vs* never smoker)	1·70 (1·34–2·16)	<0·0001
Past smoker (*vs* never smoker)	1·19 (1·00–1·42)	0·0512
Creatinine >130 μmol/L	1·67 (1·20–2·31)	0·0022
Previous myocardial infarction	1·49 (1·25–1·78)	<0·0001
HBA_{1c} >7.5%	1·48 (1·24–1·76)	<0·0001
Peripheral obstructive artery disease	1·35 (1·10–1·65)	0·0036
Diuretic use	1·33 (1·13–1·57)	0·0007
LDL cholesterol >4 mmol/L (*vs* <3 mmol/L)	1·33 (1·05–1·67)	0·0165
LDL cholesterol 3–4 mmol/L (*vs* <3 mmol/L)	1·22 (1·01–1·46)	0·0357
Insulin use	1·32 (1·12–1·55)	0·0008
Percutaneous coronary intervention or coronary artery bypass graft	0·76 (0·63–0·93)	0·0083
Statin use	0·83 (0·69–1·00)	0·0452
Allocation to pioglitazone	0·84 (0·72–0·98)	0·0309

*Resulting from stepwise selection procedure (other variables considered: sex, body-mass index, duration of diabetes [<5 *vs* 5 to <10 *vs* ≥10 years], use of metformin versus sulphonylureas, combined blood pressure [low risk *vs* high risk], triglycerides [low risk *vs* at risk *vs* high risk], HDL cholesterol [low risk *vs* at risk *vs* high risk], micral test results [positive *vs* negative], previous acute coronary syndrome, evidence of coronary artery disease, photocoagulation therapy, metabolic syndrome [present *vs* absent], use of β blockers, use of angiotensin-converting enzyme inhibitors).

Table 5: **Hazard associated with relevant baseline characteristics* for the main secondary endpoint**

	Pioglitazone		Placebo		p
	Change from baseline	n (%) at final visit	Change from baseline	n (%) at final visit	
Insulin	2·7%	866 (35·9%)	12·4%	1124 (46·4%)	<0·0001
Metformin	−3·1%	1404 (58·1%)	1·8%	1543 (63·6%)	0·0001
Sulphonylureas	−9·0%	1286 (53·3%)	−9·6%	1265 (52·2%)	0·449
Thiazide diuretics	3·1%	447 (18·5%)	3·9%	490 (20·2%)	0·135
Loop diuretics	7·7%	531 (22·0%)	5·4%	479 (19·8%)	0·056
Antiplatelet medications	2·9%	2129 (88·2%)	5·1%	2126 (87·7%)	0·603
Aspirin	1·7%	1841 (76·2%)	2·2%	1793 (73·9%)	0·065
Statins	12·5%	1329 (55·0%)	12·3%	1346 (55·5%)	0·740
Fibrates	−1·5%	207 (8·6%)	−1·1%	245 (10·1%)	0·067

Table 6: **Change in proportion of patients using concomitant medications**

cholesterol ratio. Changes in microalbuminuria were similar in the two groups. Blood pressure was reduced slightly, but significantly (p=0·03), more in the pioglitazone treated group than in the placebo treated group (median change in systolic blood pressure 3 mm Hg *vs* 0 mm Hg).

Table 8 summarises the incidence of serious adverse events that arose in more than 1% of patients. There were fewer serious adverse events in the pioglitazone group than in the placebo group, this difference indicating both the lower incidence of endpoint events and fewer other serious events. Table 9 shows the reporting rates of heart failure in the study. Despite the increase in reported heart failure in the pioglitazone group, the number of deaths from heart failure was similar in each group. Furthermore, 903 patients reported oedema without heart failure (562 pioglitazone, 341 placebo). Symptoms compatible with hypoglycaemia arose in 726 (28%) patients on pioglitazone and 528 (20%) on placebo, (p<0·0001) whereas hypoglycaemia that resulted in admission to hospital arose in 19 and 11 patients, respectively (p=0·14). Slightly more patients in the placebo group needed to be admitted for management of their diabetes. Overall, fewer patients who received pioglitazone were admitted to hospital than those on placebo (1145 [44%] *vs* 1217 [46%]). There was no difference in the overall incidence of malignant neoplasms. There were some imbalances in the incidence of individual tumours. There were more bladder tumours (14 *vs* six) and fewer cases of breast cancer (three *vs* 11) reported in the pioglitazone group compared with placebo. We noted no cases of acute liver toxicity, although there was a small reduction (median 5%, IQR –27 to 20) in the alanine aminotransferase levels in the pioglitazone group compared with a small increase (8%, –17 to 38) in the placebo group. Increases of alanine aminotransferase to more than three times the upper limit of normal at any time during the study arose in 20 pioglitazone-treated and 33 placebo-treated patients. Creatinine values remained constant in both groups throughout the study. There was a 3·6 kg increase in mean bodyweight (range –30 to 29) in the pioglitazone group and a 0·4 kg decrease (–36 to 33) in the placebo group (p<0·0001).

Discussion

Our findings show that pioglitazone non-significantly reduces the risk of the composite primary endpoint—death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg. The pre-defined main secondary endpoint—all-cause mortality, myocardial infarction, or stroke—was also reduced, significantly, in the pioglitazone group. Kaplan-Meier estimates indicate that allocation of 1000 patients to pioglitazone would avoid 21 first myocardial infarctions,

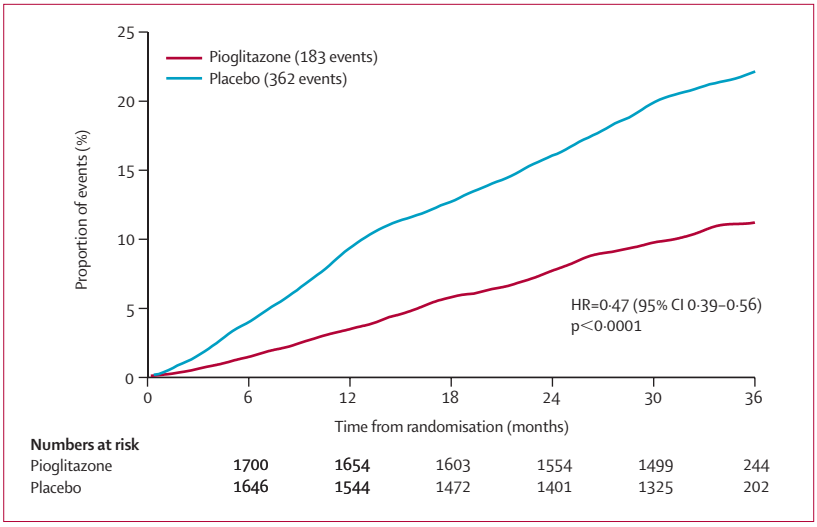

Figure 4: **Kaplan-Meier curve of time to permanent insulin use**

	Pioglitazone	Placebo	p
HBA_{1c} (% absolute change)	−0·8 (−1·6 to −0·1)	−0·3 (−1·1 to 0·4)	<0·0001
Triglycerides (% change)	−11·4 (−34·4 to 18·3)	1·8 (−23·7 to 33·9)	<0·0001
LDL cholesterol (% change)	7·2 (−11·2 to 27·6)	4·9 (−13·9 to 23·8)	0·003
HDL cholesterol (% change)	19·0 (6·6 to 33·3)	10·1 (−1·7 to 21·4)	<0·0001
LDL/HDL (% change)	−9·5 (−27·3 to 10·1)	−4·2 (−21·7 to 15·8)	<0·0001
Micral test results (baseline to final visit)			
Improved (number, %)	492 of 2218 (22%)	451 of 2225 (20%)	0·286
Worsened (number, %)	555 of 2218 (25%)	563 of 2225 (25%)	

Data are median (IQR) unless otherwise stated.

Table 7: **Change in laboratory data from baseline to final visit**

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any serious adverse event	2720	1204 (46%)	2978	1275 (48%)	0·110
Endpoint events*	602	389 (15%)	686	434 (16%)	0·123
Non-endpoint events	2118	1079 (41%)	2292	1150 (44%)	0·099
Most common events (excluding endpoints)†					
Angina pectoris	107	89 (3%)	145	122 (5%)	0·025
Hospital admission for diabetes control	57	55 (2%)	99	91 (3%)	0·003
Accident	53	51 (2%)	50	49 (2%)	0·798
Atrial fibrillation	47	42 (2%)	60	51 (2%)	0·374
Pneumonia	57	53 (2%)	37	35 (1%)	0·047
Transient ischaemic attack	39	34 (1%)	42	39 (2%)	0·587
Neoplasms	118	112 (4%)	117	113 (4%)	
Malignant‡	103	97 (4%)	103	99 (4%)	
Colon/rectal	..	16 (1%)	..	15 (1%)	0·834
Lung	..	15 (1%)	..	12 (1%)	0·544
Bladder	..	14 (1%)	..	6 (<1%)	0·069
Bladder (after exclusion)§	..	6 (<1%)	..	3 (<1%)	0·309
Haematological	..	6 (<1%)	..	10 (<1%)	0·327
Breast	..	3 (<1%)	..	11 (<1%)	0·034
Other	..	47 (2%)	..	46 (2%)	0·876

*Does not include silent myocardial infarctions or events resulting in death. †Events reported by more than 1% of patients, excluding heart failure (see table 9). ‡Some patients had more than one tumour type. §Cases remaining after blinded review, see main text for details.

Table 8: **Serious adverse event summary**

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any report of heart failure*	417	281 (11%)	302	198 (8%)	<0·0001
Heart failure not needing hospital admission*	160	132 (5%)	117	90 (3%)	0·003
Heart failure needing hospital admission*	209	149 (6%)	153	108 (4%)	0·007
Fatal heart failure†	25	25 (1%)	22	22 (1%)	0·634

*Not adjudicated. †Adjudicated cause of death.

Table 9: **Reports of heart failure**

strokes, or deaths over 3 years. In other words, 48 patients would need to be treated for 3 years to avoid one first major cardiovascular event. This finding, however, might be an underestimate of the benefit of pioglitazone, since events subsequent to the initial one are also reduced. It is noteworthy that this improvement in outcome arose on top of normal medical care, which included glucose-lowering, antiplatelet, antihypertensive, and lipid-altering therapies. Furthermore, the improvement was seen in a group of particularly ill patients who we selected on the basis of a macrovascular history.

When the protocol was devised, we thought that the need for amputation, or cardiac or leg revascularisation, was likely to indicate macrovascular deterioration and would respond to therapy in a similar way to stroke and myocardial infarction. This hypothesis did not prove correct in the case of cardiac and leg revascularisation, perhaps because these endpoints are in part determined by the decision to intervene being based on local surgical or medical practice. All three outcomes of the main secondary endpoint were improved. The number of patients reporting an event that are discounted by moving from the primary to the principal secondary endpoint is the same (213, 214) in each group.

Glycaemic control was better in the pioglitazone group than in the placebo group, despite an increased use of metformin and insulin in the placebo group; dyslipidaemia improved without any difference in the use of lipid-altering agents. There was a small increase in LDL-cholesterol concentrations in the pioglitazone group, but the ratio of LDL cholesterol to HDL cholesterol improved more than on placebo. The increase in LDL-cholesterol concentrations could be related to a change in the distribution of LDL particles. Total LDL particles are reduced with pioglitazone.[13] Therefore, the increase in concentrations of LDL cholesterol might not be considered adverse.

How pioglitazone improved cardiovascular outcome in our patients is unclear. The pioglitazone-treated group had a better metabolic profile in terms of glucose, HDL cholesterol, and triglyceride concentrations, and a better blood-pressure profile at the end of the study than at the beginning. The improvement in glycaemic control arose despite the fact that investigators were urged to adhere to the 1999 International Diabetes Federation guidelines and targets for the management of their patients and could alter background medication. Indeed, this requirement explains in part the increased use of insulin and metformin in the placebo group. The improvement in concentrations of triglycerides and HDL cholesterol are also of significant magnitude, and might have contributed to the outcome. The difference in LDL-cholesterol concentrations between the groups is unlikely to be of clinical significance. Although small, the difference in blood pressure between the groups might, however, have contributed to the outcome. Reaven[14] has proposed that insulin resistance is the link between hyperglycaemia, dyslipidaemia, hypertension, and macrovascular disease. Thiazolidinediones, such as pioglitazone, improve insulin sensitivity through their effect on the PPAR γ receptor. This mechanism could be the link between treatment and reduced risk of macrovascular disease in patients with diabetes, but further work is needed to confirm this notion.

We also noted a reduced need to start taking insulin while on pioglitazone compared with placebo. The hazard reduction of 50% could indicate that doctors treating patients in the control group, who were unable to prescribe pioglitazone, used insulin instead to try to improve glycaemic control. Alternatively, pioglitazone might reduce the concentration of glucose in the blood to below a threshold at which insulin would be used. Finally, as previously suggested, pioglitazone could have a specific β-cell sparing effect, manifest in other clinical studies by a reduction of circulating insulin,[15] and in animal studies by regranulation of the β cell.[16]

We believe our results are generalisable to all patients with type 2 diabetes. We recruited patients from 19 countries in Europe; both from primary-care and secondary-care settings. Individuals were at high risk of macrovascular events by virtue of the entry criteria, which required evidence of macrovascular disease. Furthermore, patients were on a wide range of glucose-lowering medications, including insulin. The beneficial effects of pioglitazone are apparent in patients who take insulin as well as in those who do not, and are independent of the use of other oral glucose-lowering treatments. Our results should also be applicable to patients who have not had a macrovascular event, since virtually all patients with type 2 diabetes develop atherosclerotic disease and there is a two-fold to four-fold increased risk in those with, compared to those without, diabetes. Since our subgroup analyses did not reveal any great heterogeneity across the 25 variable categories (a total of 56 subgroups), the overall estimate of efficacy provides the best estimate of effect for all subgroups.

The results of the Universities Group Diabetes Programme[17] and UKPDS[18] indicated no clear improvements in cardiovascular outcomes after an intensive

blood glucose-lowering regimen in patients newly diagnosed with type 2 diabetes. Findings of a subsequent analysis[6] of patients in UKPDS who were obese and who took metformin as the main treatment for their diabetes rather than conventional, non-intensive therapy, showed a significant improvement in macrovascular outcomes. However, in obese patients given metformin as an adjunct to sulphonylurea there was a non-significant, increase in cardiovascular events.

Compared with placebo, we noted no excess deaths in the pioglitazone group, and identified no liver toxicity. Slightly fewer patients in the pioglitazone group reported non-endpoint serious adverse events than in the placebo group. Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of oedema and heart failure, though mortality due to heart failure did not differ between groups. The increased reporting of heart failure in the pioglitazone group might, at least in part, indicate a diagnostic bias because of the increased oedema in the pioglitazone group. It is noteworthy that heart failure was not a centrally adjudicated event. The adverse-event profile was otherwise unremarkable.

The data and safety monitoring committee reviewed the 20 bladder cases with external experts (S Cohen, University of Nebraska Medical Center, and D Phillips, UK Institute of Cancer Research) before the study was unblinded. The experts considered that the 11 tumours that occurred within 1 year of randomisation (eight pioglitazone, three placebo) could not plausibly be related to treatment. After unblinding, there remained nine cases: six and three cases in the pioglitazone and placebo groups, respectively. Of these, four and two cases had known risk factors in their history (smoking, exposure to potential carcinogens, family history, previous tumour, urinary tract infection). Taking into account the timeframe of these cases and the potential confounding factors, it is improbable that the imbalance is related to pioglitazone treatment.

In summary, in patients with type 2 diabetes who are at high cardiovascular risk, pioglitazone improves cardiovascular outcome, and reduces the need to add insulin to glucose-lowering regimens compared with placebo.

Contributors

All authors helped to devise the study protocol, reviewed the full data, and commented on the draft manuscript. J A Dormandy (Study Chairman) chaired the Protocol and Executive Committee and participated in writing all drafts of the manuscript. D J A Eckland initiated the study, chaired the Operations Committee, and contributed to all drafts of the final manuscript. I K Moules chaired the Operations Committee and contributed to all drafts of the final manuscript. A M Skene was responsible for project and data management and statistical analyses. M H Tan contributed to all drafts of the final manuscript. B Charbonnel, E Erdmann, and M Massi-Benedetti were members of the Executive Committee supervising the day-to-day running of the study and writing the initial, working, and final draft of the manuscript. P J Lefèbvre chaired the Data and Safety Monitoring Committee and was primarily responsible for drafting the safety section of the manuscript. G D Murray gave independent statistical advice and contributed to the final manuscript. E Standl, R Wilcox, and L Wilhelmsen served on the Data and Safety Monitoring Committee and contributed to the safety and other sections of the final manuscript. J Betteridge, K Birkeland, B Charbonnel, A Golay, R J Heine, L Korányi, M Laakso, M Massi-Benedetti, M Mokáň, A Norkus, V Pirags, T Podar, A Scheen, W Scherbaum, G Schernthaner, O Schmitz, J Škrha, U Smith, and J Tatoň were members of the International Steering Committee, helped devise the study protocol, and supervised the study in their respective countries, and contributed to drafts of the final manuscript.

Conflict of interest statement

J A Dormandy, B Charbonnel, E Erdmann, M Massi-Benedetti, E Standl, R G Wilcox, L Wilhelmsen, J Betteridge, K Birkeland, A Golay, R J Heine, L Korányi, M Laakso, M Mokáň, A Norkus, V Pirags, T Podar, A Scheen, W Scherbaum, G Schernthaner, O Schmitz, J Škrha, U Smith, and J Tatoň have served as consultants to, and received travel expenses and payments for speaking at meetings from, Takeda. D J A Eckland was an employee of, and has served as a consultant to Takeda. I K Moules works for Takeda. M H Tan works for Eli Lilly and Company. A M Skene is the Managing Director of Nottingham Clinical Research Group, which was contracted by Takeda. The University of Liège (International Diabetes Federation account) was compensated for the work done by P J Lefèbvre as chairman of the data and safety monitoring committee. The independent statistical group located at the University of Edinburgh Medical School was compensated for the work done by G D Murray, statistician and Director of the independent statistical group.

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EXHIBIT 7

Appendix D Kaiser Permanente Northern California Database—First Interim Nested Case-Control Report (submitted 30 November 2006; IND 33,729)

PIOGLITAZONE

KPNC Database Study of Pioglitazone and Bladder Cancer in Patients With Diabetes

Interim Analyses of the Case-Control Study

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Overview

Introduction

This document reports the interim results of the nested case-control study performed within the overall cohort of diabetic patients in the Kaiser Permanente Northern California (KPNC) database. Briefly, this database contains clinical information on a large cohort of type-2 diabetic patients served in a managed care setting and is being utilized for a series of Takeda-sponsored pharmacoepidemiological cohort and nested case-control studies evaluating whether or not exposure to pioglitazone is associated with the development of bladder cancer. This series of investigations were designed with input from regulatory authorities in the US and EU as part of the Risk Management program that was developed because of a non-clinical, rodent, finding. These non-clinical findings of bladder tumors in male, but not female rats, has been postulated to be due to the effect of urinary precipitation in this species. Similar findings have been observed with other PPAR agonists. A recent study of the investigational PPAR, muraglitazar, found that such tumors could be prevented with urinary acidification, which decreases the potential for formation of precipitates. A similar rat study is currently being conducted by Takeda using pioglitazone.

The results of the first interim analysis of the cohort study were submitted to regulators in August 2005. The current report describes the first interim report of the nested case-control study.

The approved protocol for the nested case-control study specified that the first interim analysis would be conducted when 248 cases and controls had been identified and had completed the questionnaires regarding additional potential confounding variables. However in order to meet the timelines outlined in the protocol, the first interim analysis of the nested case-control study was conducted when only 173 cases as well as 173 controls had completed study procedures. The rationale for a nested case-control study was that exposure to important confounders for development of bladder cancer (i.e., qualitative and quantitative smoking history, race, occupational exposure to potential bladder carcinogens) among the KPNC diabetic cohort could not be ascertained from the computerized database and would need to be collected retrospectively using study questionnaires. The details of the

protocol, study tools and methodology for selection of controls and cases are outlined in the attached protocol and study report.

KPNC first interim nested case control report

In the current nested case-control study, all cases of bladder cancer identified in the cohort study, were compared to a random sample of subjects without bladder cancer from the cohort; cases and control were matched in a 1:1 ratio based on gender, age (±2.5 years), and time of entry into the diabetes registry to index date (± 6 months). Selection of controls was performed using the incidence density sampling with the date of the matched case patient's first diagnosis with bladder cancer serving as the index date for the control. The majority of the case-control patients were recruited prospectively, however, to augment the sample size, patients diagnosed between 2002 - 2003 (therefore retrospectively identified) were included in this first analysis as well. In the original protocol it was estimated that based on annual rates of diagnosis of bladder cancer within a diabetic cohort in general, approximately 250 patients would have been recruited by early 2006. However, the study was initiated later than planned to allow for a thorough review by the respective regulatory agencies. As a result, even though 242 patients from the original cohort were diagnosed with bladder cancer between October 1, 2002 and January 31, 2006, irrespective of exposure, the number of cases (and 1:1 matched controls) that completed all study procedures, included in this analysis is 173. Of the 173 case subjects, 117 (68%) were diagnosed prior to January 1, 2005.

The primary outcome of the current interim nested case-control analysis was the odds of prior exposure to pioglitazone in the diabetic patients that developed bladder cancer (i.e., cases) relative to the odds of prior exposure to pioglitazone in matched diabetic controls. The results of the primary outcome do not indicate a causal association between bladder cancer and exposure to pioglitazone; the unadjusted Odds Ratio (OR) was 1.3, 95% CI: 0.6 - 1.3. After adjusting for multiple pre-determined and important confounders and biases (i.e., frequency of urinary tract infection, baseline glycosylated haemoglobin concentration, race/ethnicity, smoking status, occupational exposure and other categories of diabetes medications) in a conditional logistic regression model, the point estimate decreased further to 1.0,

95% CI: 0.3 - 3.2 - implying further that bladder cancer patients were not more likely than matched control subjects to have been treated with pioglitazone.

Of note, none of the other categories of anti-diabetic medications were associated with an increased risk of bladder cancer either, although sulfonylureas showed a trend towards an increased risk that was close to statistical significance (Table 1).

Table 1. Association between diabetes medication use and bladder cancer

Medication	Unadjusted* odds ratio	95% confidence interval	Adjusted** odds ratio	95% confidence interval
Pioglitazone	1.3	0.6-3.0	1.0	0.3-3.2
Other TZDs	1.9	0.5-7.1	1.8	0.4-8.5
Metformin	0.9	0.6-1.5	0.8	0.4-1.5
Insulin	0.8	0.4-1.5	0.7	0.3-1.6
Sulfonylureas	1.9	0.9-3.5	2.0	0.9-4.7

* Adjusted only for the matching variables and other categories of diabetes medications
** Adjusted for matching variables, race/ethnicity, smoking status, glycosylated hemoglobin concentration (with an interaction term for new diagnosis of diabetes at the time of entry into the cohort), and number of prior urinary tract infections

Although the sample size is still small at this stage of the analysis, as per approved protocol, a secondary analysis was performed to examine the relationship between the OR for bladder cancer and the cumulative dose and duration of exposure to pioglitazone. Especially, because of the aforementioned sample size limitation at this stage, but, also due to the fact that the primary analysis before and after adjustment for confounding variables showed no trend, this analysis is exploratory only. In this secondary analysis, shown in Table 3 of the report, using the unadjusted OR, there was a non-significant trend among those exposed to pioglitazone starting at least 1.6 years ago (OR: 2.6, 95% CI: 0.9 - 7.2), having total duration of therapy for at least 1.1 years (OR: 2.7, 95% CI: 1.0 - 7.6) or having a cumulative dose of more than 10,500 mg of pioglitazone (OR 2.2, 95% CI: 0.8 - 6.4). Due to the very small number of case and control patients in this secondary analysis, the only adjustments that were feasible involved adjusting for a single confounder at a time in stead of controlling for these confounding variables simultaneously in a multi-variate analysis.

None of these adjustments had a substantial impact on the unadjusted OR. Of note, adjusting for important markers of disease severity showed a declining trend of the OR, suggesting that the unadjusted secondary analysis is confounded by severity.
In addition, only 3 patients (2 case subjects and one control subject) had exposure to pioglitazone exceeding 4 years. Since even the most potent carcinogens tend to have very long latency periods (1, 2), it seems very unlikely that the observed differences in duration of very short (<1.1 years) vs. short (1.1 to 4 years) exposure represents anything other than a chance finding. Besides misclassification, chance is also the most likely explanation for why shorter duration of sulfonylurea exposure (<4.71 years) was associated with a higher, borderline statistically significant, odds ratio (OR: 1.7, 95% CI: 1.0 - 2.8) than longer term exposure (OR: 1.3, 95% CI: 0.7 - 2.4).

It should also be noted from table 6 of the report that if all *participants*, *refusers* and *non-participants for other reasons* are considered, 26 of the 242 bladder cancer cases (10.7%) had prior exposure to pioglitazone compared to 35 of the 386 controls (9.1%). Thus, in addition to the adjusted primary analysis showing an odds ratio of 1.0, 95% CI: 0.3 - 3.2, consideration of all patients initially intended to be included in the study, fails to demonstrate a higher exposure of bladder cancer cases to pioglitazone than is observed among diabetic control patients.

In summary, the initial results of the primary analysis of this interim nested case-control study provide reassurance that pioglitazone use is not associated with a greater risk of developing bladder cancer compared to diabetic patients not exposed to pioglitazone. Although in the secondary analysis, more cases than controls appeared to have longer durations of exposure to pioglitazone, all but three subjects had less than 4 years of exposure, which represents too short an interval to anticipate that these differences could be explained by other than chance alone. In the subsequent report using the nested case-control approach (currently expected by mid 2009), the primary and secondary analyses will generate more robust results with some patients expected to have longer overall exposure to pioglitazone.

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KPNC Database Study of Pioglitazone and Bladder Cancer in Patients With Diabetes

Specialist Review of the July 25, 2006 Report on the Interim Analyses of the Case-Control Study Through January 31, 2006

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Safety in Knowing

July 26, 2006

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Dear Dr. Gerrits,

Thank you for asking me to review the interim report, **The Risk of Bladder Cancer Among Diabetic Patients Treated with Pioglitazone: Interim Analyses of the Case-Control Study Through January 31, 2006** dated July 12, 2006. This study is being conducted by researchers from the University of Pennsylvania and Kaiser Permanente Division of Research and, as noted on the cover page, also generated this report. The study is being undertaken in response to animal studies suggesting a possible increased risk of bladder cancer.

General Impression: This study is being undertaken by a very credible team of researchers using the patient population of Kaiser Permanente using standard observational study designs, validation procedures, and methodology. This report is being submitted 1 year after the previous interim report (August 2005) which is referred to in the Introduction. Apparently, because of insights gained during the design phase of the study, the researchers planned a nested case-control study to address the paucity of data on potential confounders in the existing electronic medical data. These data were collected on all cases (bladder cancer) and a random sample of controls. This document reports the interim findings from the case-control study.

Comment:
The methods described in this document are sound and appropriate. The document itself presents a balanced report of the study to date including a strong discussion of the strengths and limitations of both the study design and the interpretation of the interim results. My main concern is the potential for any reader of this document, because it presents 'data' and results, to jump to premature conclusions despite the best efforts of the authors. It is important to remember, as these researchers state many times, that this is a planned ***interim*** analysis of an ongoing study. Interim analyses, which really evolved out of the clinical trials world as an attempt to identify early safety or efficacy issues to reduce the risk of potential harm or relatively reduced benefit to subsequent subjects, have found their way into many observational study efforts, often with the same goal in mind. It is critically important to keep in mind the purpose of such analyses and to respect the common concerns among scientists of the tendency to over interpret observed treatment differences in studies subjected to repeated significance testing. This concern is borne out of (unadjusted) repeated significance testing of accumulating data increasing the

Safety in Knowing

overall significance level beyond the pre-specified nominal significance level. These concerns are raised in a number of key regulatory documents, including ICH guidelines, as well as the statistical literature.

Of import in the current document is the reporting of both primary and secondary analyses. As noted by the authors, the primary analyses (adjusted) clearly show no trend or signal of an association for pioglitazone (Table 2). However, Table 3 presents univariate Odds Ratios (lack of sample size prevents multivariate adjustment) with some suggestion of a duration effect of pioglitazone use. Because this is not an overwhelmingly significant and consistent finding, and because of the lack of sample size to appropriately control for multiple potential confounders in a multivariable model, the researchers are appropriately careful to caution against over-interpreting these results because of these issues and because they arose in secondary analyses. They also mention the finding in the primary analysis of sulfonylurea exposure (and other TZDs) have strong odds ratios in the multivariate analyses.

Overall, this report provides a very balanced and appropriate report of a well-designed study program. My cautions articulated above are intended to underscore the issues of over-interpretation and emphasis of interim results of secondary analyses identified by the authors in their discussion. The current report does not present a compelling ethical or scientific reason to alter the study itself or to suggest a confirmatory result.

Please feel free to contact me should you have any questions about my comments in this note.

Sincerely

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The Risk of Bladder Cancer Among Diabetic Patients Treated with Pioglitazone: Interim Analyses of the Case-Control Study Through January 31, 2006

July 25, 2006

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Introduction

In August 2005, we provided an interim analysis of an ongoing cohort study comparing the risk of bladder cancer among patients with type 2 diabetes mellitus treated with pioglitazone compared to those not receiving this medication (Appendix A, B, and C). During the design stage of this study, we recognized that data on several potential confounders would be incomplete in the electronic records. In particular, we anticipated that the electronic data would be incomplete or missing for race/ethnicity, smoking history, duration of diabetes, and occupational exposures. To account for the deficiencies in the electronic data, we planned a case-control study nested within the study cohort to collect these additional data on the patients with bladder cancer and a random sample of patients without bladder cancer. An interim analysis of this case-control study was planned *a priori*, the results of which are reported in this document.

Methods

Source cohort

The cohort that gave rise to this case-control study is described in detail in the report from October 2005 (Appendix A). Briefly, the source population was identified from the diabetes registry, which was first constructed in 1993. Patients were eligible for the study cohort if they met any of the following criteria: 1) as of January 1, 1997 they had been diagnosed with diabetes mellitus, were age 40 or older and were members of Kaiser Permanente, 2) they had been diagnosed with diabetes mellitus, reached age 40 between January 1, 1997 and December 31, 2002 and were Kaiser Permanente members on their 40th birthday, or 3) had diabetes mellitus and were age 40 or older when they

joined Kaiser Permanente between January 1, 1997 and December 31, 2002. From this cohort of 207,389 we then excluded 806 patients with a diagnosis of bladder cancer prior to entry in the cohort or within 6 months of joining Kaiser Permanente in order to avoid misclassification of prevalent bladder cancers as incident diagnoses. Likewise, patients without prescription benefits at the time of entry into the cohort (n=6,674) or those with a gap of more than four months in prescription or membership benefits and the gap started within the first four months of entering the cohort (n=6,782) were excluded. This resulted in 193,127 eligible men and women with diabetes mellitus.

Follow-up started on the first date that the inclusion criteria were met. Follow-up for the cohort was censored when any of the following occurred: 1) a gap of greater than 4 months in either membership or prescription benefits, 2) a new diagnosis of bladder cancer, or 3) death from any cause.

Identification of case and control subjects

From the source cohort, we identified all incident diagnoses of bladder cancer using the Kaiser Permanente cancer registry for the period from October 1, 2002 to January 31, 2006. These patients were selected as potential case subjects.

For the purpose of this report, case patients who were diagnosed before the start of interviewing in January 2005 (October 2002-December 2004) are referred to as prevalent cases; patients diagnosed between January 2005 and January 2006 are referred to as incident cases.

For each case subject, one control subject was randomly selected after matching on sex, age (± 2.5 years), and time from entry into the diabetes registry to index date (± 6

months). In addition, each control subject could not have been diagnosed with bladder cancer or have been censored from the cohort for other reasons as of the date of first diagnosis with bladder cancer of the matched case subject.

When a control subject could not be reached for interview (see below) or refused to participate, additional control subjects were selected until a matched control could be enrolled. A minimum of 15 attempts was made to reach all control subjects before determining that the subject was unreachable.

Data collection

The available electronic data were utilized in the nested case-control study as was described in the cohort study. The additional data for the case-control study were collected through telephone interviews using a standardized questionnaire administered by trained interviewers. The questionnaire was administered using computer-assisted telephone interviews (CATI) with direct data entry by interviewer. For a small number of case subjects who were unable to complete the full interview (n=21), a shorter interview was completed by a proxy. When the case subject data was collected via a proxy interview, the matched control subject also completed the shorter proxy version of the survey.

Prior to contacting case and control subjects for the interview, permission was obtained from the treating physician. In addition, all subjects were sent a letter with opportunity to opt out of the study by return of a pre-addressed and stamped postcard. The first interviews were completed in January 2005. For this interim analysis, the last interview was completed in May 2006.

Exposure data

For the case-control study, the date that the case subject was first diagnosed with bladder cancer served as the reference date for both the case subject and for the matched control.

The primary exposure variable was use of pioglitazone. All medication exposure data were based on the computerized pharmacy records. Our primary definition of pioglitazone exposure in the case-control study was identical to that in the cohort study. Specifically, to be considered ever exposed, a patient had to fill two prescriptions for pioglitazone within a six-month period during the observation time (i.e. between the entry in the cohort and the reference date). The same definition was employed for all other categories of diabetes medications. Diabetes medications were categorized as pioglitazone, other thiazolidinediones (TZDs), metformin, sulfonylureas, insulin, and other (e.g., miglitol and acarbose). In addition, indicator variables were created separately for patients who had not received any diabetes medication prescriptions and for those who received at least one prescription but had not met the definition of exposure (i.e., did not fill two prescriptions for the same medication within a 6-month period). Each of these was considered as a separate variable. Due to the numerous combinations of diabetes medications that are used by patients within the cohort and the absence of an *a priori* hypothesis that certain combinations would be more or less harmful, we did not attempt to create variables to describe the different combinations (e.g., sulfonylurea plus pioglitazone).

All potential confounders based on electronic data were measured prior to entry into the cohort using the same methods described in the cohort study. For data collected from the telephone interview (duration of diabetes, smoking, use of indwelling catheters, frequency of urinary tract infections, and occupational exposures), we used exposure data up to the reference date. In the nested case-control study, smoking was categorized according to total pack-years consumed prior to the reference date. Cigar and/or pipe smoking among non-cigarette smokers were combined as a dichotomous variable for having ever smoked 1 or more cigars or pipes per week for six months or longer. Duration of diabetes was categorized as less than 5 years, 6 to 10 years, more than 10 years, and unknown. Previous and/or current employment in professions associated with bladder cancer was treated as dichotomous variables. Previous urinary tract infection was categorized as none, one to two prior infections, or more than two prior infections.

Statistical analyses

Categorical variables were described with counts and percentages. Continuous variables were described with medians and interquartile ranges. Fisher's exact test was used to compare proportions between patients who participated and those who did not participate in the case-control study. To assess the association between pioglitazone and bladder cancer, we used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Potential confounders were first tested by examining the effect that adjusting for the variable had on the unadjusted OR for the association of pioglitazone and bladder cancer. Any variable resulting in a 10% or greater change in the unadjusted OR was selected for inclusion in the final multivariable model.[1] Cigarette

smoking and race/ethnicity were always included in the adjusted model because of their known strong association with bladder cancer risk. In addition, the following other categories of diabetes medications were also forced into all models: insulin, sulfonylurea, metformin, and other TZDs. Because there were very few patients with exposure to other oral hypoglycemic drugs (e.g., miglitol and acarbose) and very few patients who had filled an occasional prescription for a diabetes drug, but did not meet our definitions of exposure, we repeated the primary analyses excluding patients with these exposures. The results were similar to that of the primary analyses (data not shown).

Secondary analyses

Descriptive statistics were provided for the duration of exposure, recentness of first exposure, and cumulative dose of pioglitazone among cases and controls. For each of these, we created categorical variables that were dichotomized according to the median level of exposure among the control subjects. Because of the relatively small number of subjects in each exposure level, we only performed adjusted analyses including one potential confounder at a time. Additionally, the categories of the confounder variables were collapsed as follows to reduce the degrees of freedom: race/ethnicity - non-Hispanic white vs. other; smoking - more than 40 pack-years, 20 to 40 pack-years, and less than 20 pack-years (including non-smokers and missing); glycosylated hemoglobin – 8% or higher, less than 8%, and missing; urinary tract infections – one or more, none, and missing; diabetes duration – 10 years or less, more than 10 years, and missing; socioeconomic status based on annual household income - $40,000 or less, more than $40,000 and missing; renal function at entry into the cohort – normal creatinine

concentration, elevated creatinine concentration, and missing; occupational exposures as a driver, painter, or hair dresser/barber. Sensitivity analyses examine the influence of the decision to include those with missing smoking data with those who smoked less than 20 pack-years by repeating the analyses including these patients in the group with more than 40 pack-years of smoking. Cumulative duration of exposure was measured by counting the number of days between prescriptions. If the next prescription was filled within 30 days of the expected end date of the previous prescription, we assumed that therapy was uninterrupted. However, if there were no refills within the 30 days after the expected end date of the previous prescription, we assumed a gap in therapy starting 30 days after the date that the previous prescription should have ended.

Cumulative dose of pioglitazone was calculated in a similar fashion. For any prescription that was completed prior to an event date, the total prescribed dose (i.e., number of pills in the prescription multiplied by the dose of the pills) was assumed to have been consumed. For prescriptions that were still active on the index date, the total consumed dose was reduced to reflect the proportion of pills expected to have been consumed by that date.

In an exploratory analysis we combined pioglitazone and other TZDs to further assess duration of therapy and time since initiation of therapy. Variables for time since initiation of any TZD therapy and duration of TZD therapy were dichotomized at the median of the exposed control patients. For these exploratory analyses, odds ratios were calculated relative to no TZD exposure.

In additional exploratory analyses, we examined the association of bladder cancer with long and short duration of metformin and sulfonylurea use in unadjusted analyses.

We decided *a* priori to test for an interaction between duration of sulfonylurea use and whether the patient was newly diagnosed with diabetes at the time of entering the Diabetes Registry. This decision was based on the fact that sulfonylureas have been available for decades and that there may have been substantial amounts of unaccounted use in the database, particularly among patients who had diabetes mellitus prior to entering the cohort. Because there was no evidence of a statistical interaction, we did not include this in the final analyses.

Results

Between October 1, 2002 and January 31, 2006 there were 242 patients from the source cohort with no gap of greater than 4 months in either membership or prescription benefits identified with bladder cancer. A total of 173 case subjects (72%) completed the interview, of which 117 (68%) were diagnosed prior to January 1, 2005. The reasons for exclusion or non-participation are summarized in Figure 1. Each of the case subjects that completed the interview was ultimately matched to one control. Of the 173 controls included on this analysis 81 (47%) were the first control selected. The full version of the interview was completed by 152 (87.9%) of the case and control pairs.

As expected, the case subjects were well matched to the control subjects with regards to age and sex (Table 1). Likewise, as expected, the case subjects were more likely than controls to have a history of heavy smoking (26% vs. 16%) and to have participated in occupations associated with bladder cancer (38% vs. 31%). The bladder cancer patients were more likely to be non-Hispanic white (69% vs. 53%). There were

more case subjects than control subjects with greater than 10 years duration of diabetes (37% vs. 32%).

Bladder cancer patients were not more likely than control subjects to have been treated with pioglitazone (OR=1.3, 95% CI 0.6 – 3.0). Using the methods described above for variable selection, frequency of urinary tract infection, baseline glycosylated hemoglobin concentration (including the interaction for measurement at the time of newly entering the diabetes registry), race/ethnicity, smoking status, and other categories of diabetes medications were included in the final multivariable model. After adjusting for these confounders, the odds ratio for the association between pioglitazone exposure and bladder cancer was 1.0 (95% CI 0.3 to 3.2). Similarly, none of the other categories of diabetes medications were significantly associated with bladder cancer risk, although the odds ratio for sulfonylureas was 2.0 (95% CI 0.9 – 4.7) and for other TZDs the odds ratio was 1.8 (95% CI 0.4 – 8.5) (Table 2).

In secondary analyses, we examined the association between bladder cancer incidence and increasing levels of pioglitazone exposure (Table 3). For each of the exposure variables, there was a trend toward a larger odds ratio in the high exposure category. However, none of these reached statistical significance when adjusted only for the matching variables. When we adjusted individually for potential confounders, pioglitazone use for 1.1 years or longer was significantly associated with bladder cancer risk when adjusted for either race/ethnicity (OR=3.0, 95% CI 1.1-8.6), prior urinary tract infection (OR=3.2, 95% CI 1.1-9.4), or occupational exposures (OR=3.1, 95% CI 1.1-8.7). However, adjustment for baseline glycosylated hemoglobin concentration or diabetes duration resulted in a smaller odds ratio than the unadjusted analyses (unadjusted

OR=2.7, 95% CI 1.0-7.6; adjusted for glycosylated hemoglobin concentration OR=2.4, 95% CI 0.8-6.7, adjusted for diabetes duration OR=2.5, 95% CI 0.9-7.1). Table 4 provides further details of the duration of use of pioglitazone among study subjects.

Sensitivity analyses where those subjects with missing smoking data were included in the group with more than 40 pack-years of tobacco use resulted in nearly identical results for the association of bladder cancer with short-term and long-term pioglitazone use (data not shown).

Other TZD use was more common among those patients with long-term pioglitazone use. Among the case subjects, 29% of patients who had taken pioglitazone for at least 1.1 years had previously taken another TZD, compared to 0% of those with short-term pioglitazone use and 1% of those with no pioglitazone use. Similar results were observed among the controls, with 13% of patients who had taken pioglitazone for at least 1.1 years having previously taken another TZD, compared to 0% of those with short term pioglitazone use and 2% of those with no pioglitazone use. In exploratory analyses, we combined pioglitazone and other TZDs to further assess duration of therapy and time since initiation of therapy. The relative odds for initiation of TZD therapy at least 1.85 years prior was not significantly greater among patients with bladder cancer than controls (OR=1.8, 95% CI 0.8-4.4). For total duration of therapy, the relative odds for duration of therapy of at least 1.1 years was not significantly greater among patients with bladder cancer than controls (OR=2.6, 95% CI 0.9-7.2).

To explore whether there was a systematic bias in our analyses focusing on duration of use, we examined the association of bladder cancer with long-term use of metformin and sulfonylurea (Table 5). In unadjusted analyses, there was no evidence of

an association between short- (<2.52 years) or long-term (≥2.52 years) metformin use and bladder cancer risk (short-term OR 1.0, 95% CI 0.6 – 1.7; long-term OR 1.0, 95% CI 0.5 – 1.7). Likewise, for sulfonylureas, we did not observe a significant association between short- or long-term use and the risk of bladder cancer and there was no significant interaction according to the time of new diagnosis with diabetes. However, the unadjusted odds ratio for short-term sulfonylurea use (<4.71 years) approached statistical significance (odds ratio 1.7, 95% CI 1.0 – 2.8). The relative odds of long-term sulfonylurea use (≥4.71 years) was 1.3 (95% CI 0.7 – 2.4).

To understand how non-participation may have influenced the results, we compared characteristics and exposures among participants and non-participants (Table 6). Among cases, 21 of 173 (12%) of participants were exposed to pioglitazone compared to 5 of 69 (7%) case non-participants (p=0.36). For controls, 15 of 173 (9%) of participants were exposed to pioglitazone compared to 20 of 213 (9%) non-participants (p=0.86).

Discussion

This study was conducted in response to animal studies suggesting a possible increased risk of bladder cancer with pioglitazone exposure. This association was observed in male rats, but not in female rats or in mice of either sex.[2] The same phenomenon has been observed with a related compound, muraglitizar. One hypothesis for the increased incidence of bladder cancer observed in male rats relates to increased urinary crystal formation, a non-genotoxic stimulus for bladder cancer formation in rats. In fact, in further experiments, acidification of the urine, which decreases urinary crystal

formation, prevented the increased incidence of bladder cancer in male rats treated with muraglitizar. (Advisory Committee Briefing Document, Pargluva™ 09 Sept 2005) However, in the absence of controlled studies in humans, it is not possible to know with certainty whether pioglitazone therapy could increase or decrease the risk of bladder cancer in humans.

We have previously reported the results of preliminary analysis of the electronic data from Kaiser Permanente (the cohort study), where we did not observe a significant association between bladder cancer incidence and pioglitazone exposure (or exposure to any other class of diabetes medications). However, in our secondary analyses of the cohort study, certain subgroups of pioglitazone treated patients had a higher incidence of bladder cancer than diabetic patients who had not received this therapy. Specifically, patients who started therapy 18 to 36 months prior, who had between 12 and 24 months of cumulative therapy, and/or who had between 7000 mg and 18,000 mg of cumulative dose had significantly higher incidence rates of bladder cancer.

This nested case-control study was planned to account for potential confounder variables that are incompletely recorded in the electronic data. Using the nested case-control design, we were able to gather information on race/ethnicity, smoking status, duration of diabetes and other potential confounders directly from the patient, thereby allowing us to adjust for these potential confounders in our primary analysis. The nested case-control study confirmed that there was no evidence of an association between pioglitazone use and bladder cancer risk when we examined any exposure to pioglitazone. After adjusting for confounders, the odds ratio for the association between pioglitazone exposure and bladder cancer was 1.0 (95% CI 0.3 to 3.2).

However, in secondary analyses we again observed a suggestion of a possible increased risk with longer use, greater cumulative dose and less recent initiation of therapy, although many of these analyses were not statistically significant. For several reasons, we again caution against drawing strong conclusions regarding the possible cumulative dose and duration response relationship with bladder cancer risk. Importantly, this is a preliminary analysis and our current sample size contained relatively few long-term users of pioglitazone. Among cases and controls combined, there were only three patients with more than four years of exposure. Thus, the estimates obtained in the secondary analyses are less precise than our primary analyses (i.e., have wider 95% confidence intervals). Because of the relatively small number of long-term users of pioglitazone, we were only able to adjust for one variable at a time. Although this resulted in some analyses of duration of therapy reaching statistical significance, adjusting for other variables resulted in reduction of the odds ratio relative to the unadjusted analyses. It is not possible to know what the results would be with simultaneous adjustment for multiple confounders, due to the limited sample size in this preliminary analysis. Of course, multivariable analyses are planned in the future when the sample sizes are sufficient for these models.

We also caution against placing too much emphasis on the secondary analyses, since the primary analyses were negative. Furthermore, the presence of a detectable increased risk of bladder cancer with such a short duration of use is not consistent with current hypotheses regarding the etiology of bladder cancer. Other known risk factors for bladder cancer, such as tobacco use and occupational exposures, are believed to have very long latency periods.[3, 4] Although bladder tumors are thought to occur more rapidly

after exposure to cyclophosphamide than to aromatic amines, there is generally a long latency time (mean 8.5 years in one study[5]) between cyclophosphamide exposure and cancer.[4, 5]

Selection or detection bias are also potential problems. We stated in the original proposal that any associations seen in these earliest analyses, and particularly using the "prevalent" cases, could well reflect a selection or detection bias, given the long lag time expected in the development of bladder cancer. In our analyses, four of the eight cases with the greatest pioglitazone exposure were prevalent cases (i.e., diagnosed before January 2005).

Another reason to caution against over interpretation of the dose and duration analyses relates to the totality of the available data. In our cohort analysis, we observed a significantly increased risk of bladder cancer in patients with intermediate duration of exposure and cumulative dose; the group with the longest duration of exposure and greatest cumulative dose had somewhat lower and non-significantly elevated relative risks. In this nested case-control study, we dichotomized exposure duration and cumulative dose. The exposure level in our long duration and high cumulative dose categories overlapped with the intermediate duration of exposure and cumulative dose categories in the cohort study. Thus, at this point, these data from the nested case-control study do not dramatically increase the evidence base beyond what was known when the first cohort analysis was completed. Finally, to our knowledge, the only other controlled data on the relative risk of bladder cancer among patients treated with pioglitazone comes from the Proactive study, where there was a non-significant excess of bladder cancers among patients treated with pioglitazone (14 vs 6).[6] However, in that study average

follow-up time was 34.5 months, yet much of the excess in bladder cancer incidence occurred in the first year of follow-up (eight pioglitazone vs. three placebo).[6] Thus, while we observed no increased risk of bladder cancer with short term pioglitazone exposure in our cohort or case-control analyses, in the clinical trial, a greater relative risk was observed with less than one year exposure than with more than one year of exposure. The inconsistencies between these results are another reason to caution against over interpretation of these preliminary results on cumulative dose and duration.

Those patients with the longest pioglitazone use are also the patients who were most likely to have used other TZDs in the past (usually troglitazone). Thus, some of the observed association could be partly or completely due to prior troglitazone or rosiglitazone use, as was possibly suggested by the odds ratio of 1.8 for other TZDs in the primary analyses. However, the estimated odds ratio for other TZDs in this study was based on only a small number of users, and thus the confidence intervals are very wide and include unity, in fact extending to 0.4 (i.e., the 95% CI was 0.4-8.5). Not surprisingly, when we repeated analyses of duration and time since initiation of therapy using the combined exposure of any TZD (i.e., pioglitazone or other TZDs), the results were generally similar to that of our analyses examining pioglitazone exclusively. This was to be expected since the proportion of patients with pioglitazone exposure was much larger than that with other TZD exposure.

It is important to consider the possibility of recall bias in our case-control analyses. For most of the data, we still relied on the electronic records, such that recall bias would not be an issue. However, for other variables, such as smoking, race/ethnicity, diabetes duration, and frequency of urinary tract infection, we relied on patient recall.

Although we limited our case selection to patients with a relatively recent diagnosis of bladder cancer, those patients diagnosed prior to January 2005 (prevalent cases) were asked to think back much further about their exposures than were patients diagnosed after the start of interviewing (incident cases). Whether any difference in recall influenced our primary results is unknown. However, we stated a priori that we would have greater confidence in our data from those patients who were diagnosed after January 1, 2005 for this reason. Unfortunately, we do not yet have sufficient numbers of patients to allow for meaningful analyses based solely on incident case subjects and their matched controls. Of course, with additional follow-up, we will only be recruiting incident case subjects, and this will become less of a problem.

Nonetheless, for several reasons, we do not believe that recall bias substantially influenced these preliminary results. Race/ethnicity, one of the important confounders, does not change over time and would be easily recalled by patients. Smoking history may be more difficult to recall, although we observed the expected dose response relationship between cumulative smoking history and bladder cancer risk.[3] Thus, there does not appear to be substantial recall bias related to smoking history. The number of urinary tract infections was a confounder in our primary analyses. We did not observe greater numbers of urinary tract infections among our case patients as has been seen by other investigators.[7, 8] Why this was observed is unknown, but it could be a chance observation, could be unique to patients with diabetes who have an increased risk for infection, or due to incomplete adjustment for factors that confound the association between urinary tract infection frequency and bladder cancer risk. Finally, our measurement of dose and

duration of pioglitazone exposure came from the electronic data, and as such is not subject to recall bias.

Bias from non-participation must also be considered in any ad hoc case-control studies. We have achieved very high participation rates among case subjects, although our control participation rates were somewhat lower. This was partly due to greater physician refusal or physician failure to respond, but also due to greater difficulty in recruiting controls after physician permission was granted. To assess the potential impact of non-participation, we have compared the non-participants to the participants using data available in the electronic files. Our primary exposure definition for pioglitazone was slightly less common among case non-participants than among case participants (7% vs. 12%), but this was not statistically significant. Most reassuring is that among the controls, where we had higher non-participation rates, the prevalence of pioglitazone exposure among the participants and non-participants was nearly identical. Thus, it seems unlikely that non-participation has resulted in a meaningful impact on the results.

Finally, we considered the possibility that there was a systematic bias resulting from the methods used to measure cumulative dose and duration of exposure. Similar to pioglitazone, in our primary analyses we did not observe an association between metformin and bladder cancer (adjusted OR 0.8). However, the relative odds of exposure to sulfonylureas was 2.0 and was nearly statistically significant (95% CI 0.9-4.7). Of course there is no a priori hypothesis that sulfonylurea or metformin exposure is related to the risk of bladder cancer. In secondary analyses focusing on sulfonylureas and metformin, we did not see higher relative odds among patients with longer duration of use. This suggests that the dose and duration relationships observed with pioglitazone are

unlikely to be due to a systemic bias resulting from our study design, although they could still be due to chance or incomplete adjustment for confounding. In addition, it is notable that many of the patients may have had sulfonylurea exposure prior to entry into the cohort. As such, our estimate of duration of sulfonylurea use is potentially less accurate than our estimates of the duration of pioglitazone and metformin use. Whether such misclassification of sulfonylurea duration may have biased these results is unknown. This could be an important consideration since exposure to sulfonylureas for less than 4.71 years was nearly significantly associated with bladder cancer incidence while longer use was not.

In conclusion, we have not observed a significant association between pioglitazone use and bladder cancer in this preliminary analysis of our case-control study. Similar to our cohort analysis, we have observed a trend toward an association between pioglitazone use and bladder cancer among those patients with longer period since starting use and with greater cumulative pioglitazone exposure. However, we are not yet able to draw any conclusions regarding a potential dose or duration response between pioglitazone use and bladder cancer risk as our sample size to date has precluded adjustment for multiple potential confounders. Importantly, with continued time, our sample size will increase substantially, allowing for more precise estimation of the association and clarification of whether or not a dose or duration response truly exists. As planned in our protocol, the next cohort analysis will be completed in late 2007 and the next case-control analysis will be completed in 2009.

Figure 1. Source of the final study population

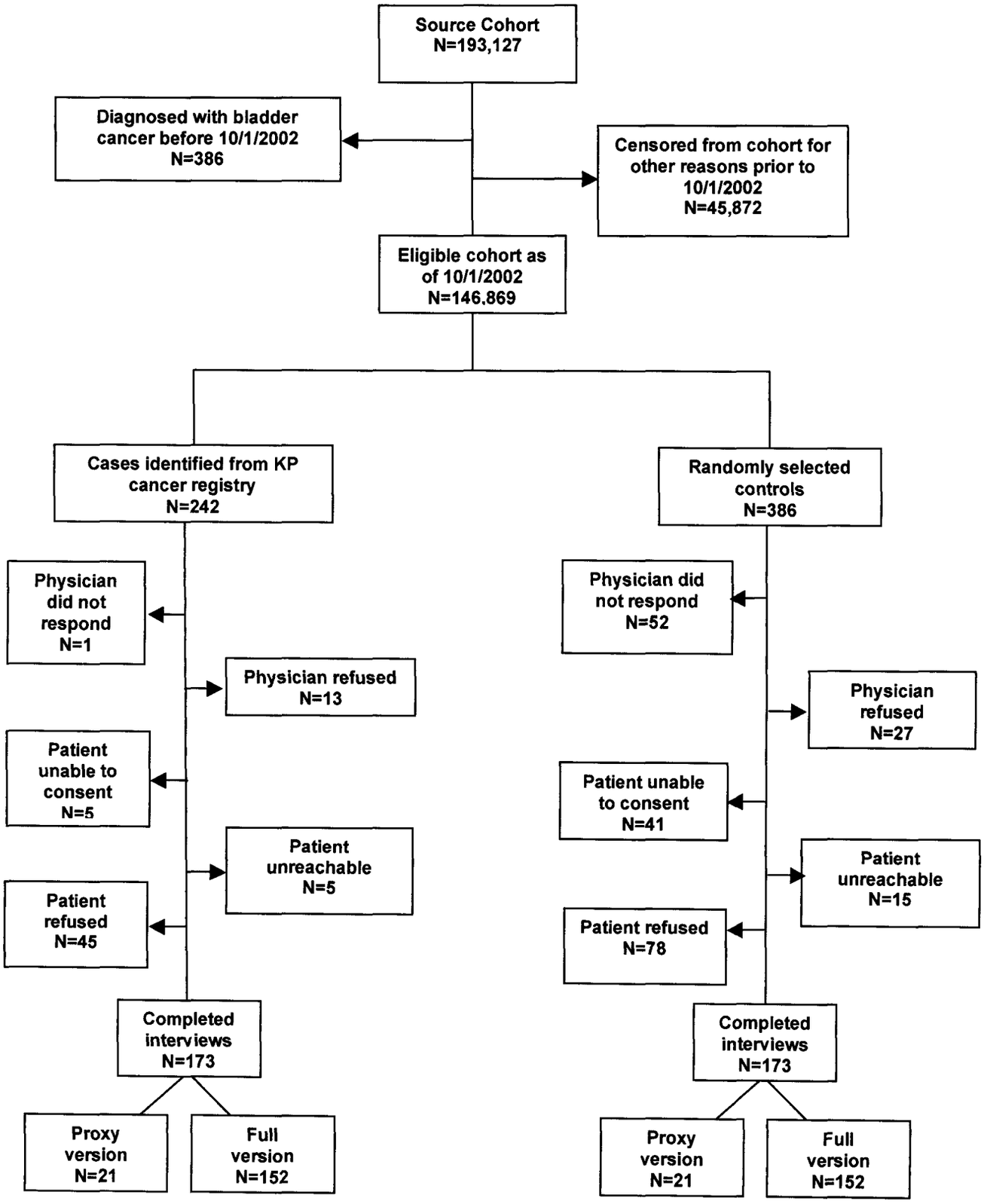

Table 1. Characteristics of the case and control subjects

	Cases (n=173)	Controls (n=173)
Age at reference date		
40-59 years	12 (6.9%)	11 (6.4%)
60-69 years	52 (30.1%)	46 (26.6%)
70-79 years	73 (42.2%)	80 (46.2%)
80 years and older	36 (20.8%)	36 (20.8%)
Female sex	35 (20.2%)	35 (20.2%)
Time in registry		
0-5 years	88 (50.9%)	86 (49.7%)
6-10 years	47 (27.2%)	49 (28.3%)
More than 10 years	38 (22.0%)	38 (22.0%)
Race/ethnicity		
Non-Hispanic White	120 (69.4%)	92 (53.2%)
Black or African American	9 (5.2%)	21 (12.1%)
Hispanic	12 (6.9%)	26 (15.0%)
Asian or Pacific Islander	5 (2.9%)	16 (9.2%)
Other	27 (15.6%)	18 (10.4%)
Cigarette smoking history		
Never smoked	63 (36.4%)	73 (42.2%)
20 or fewer pack-years	30 (17.3%)	41 (23.7%)
21-40 pack-years	30 (17.3%)	28 (16.2%)
>40 pack-years	45 (26.0%)	28 (16.2%)
Missing	5 (2.9%)	3 (1.7%)
Pipe or Cigar Smoker		
No	123 (71.1%)	119 (68.8%)
Yes	27 (15.6%)	35 (20.2%)
Missing	23 (13.3%)	19 (11.0%)
Renal function		
Normal creatinine	139 (80.3%)	134 (77.5%)
Elevated creatinine*	13 (7.5%)	15 (8.7%)
Missing	21 (12.1%)	24 (13.9%)
Urinary tract infections		
None	114 (65.9%)	119 (68.8%)
1-2	23 (13.3%)	13 (7.5%)
3+	8 (4.6%)	19 (11.0%)
Missing	28 (16.2%)	22 (12.7%)
Urinary incontinence		
No	134 (77.5%)	118 (68.2%)
Yes	18 (10.4%)	36 (20.8%)
Missing	21 (12.1%)	19 (11.0%)

Table 1 - Continued

	Cases (n=173)	Controls (n=173)
Catheter use		
No	133 (76.9%)	139 (80.3)
Yes	19 (11.0%)	14 (8.1%)
Missing	21 (12.1%)	20 (11.6%)
Manufacturing industry	54 (31.2%)	39 (22.5%)
High risk occupation[†]	66 (38.2%)	53 (30.6%)
Congestive heart failure	12 (6.9%)	8 (4.6%)
Annual household income		
<$40,000	71 (41.0%)	78 (45.1%)
$40,000-$74,000	67 (38.7%)	50 (28.9%)
≥ $75,000	24 (13.9%)	28 (16.2%)
Missing	11 (6.4%)	17 (9.8%)
Baseline HbA1c		
< 7%	70 (40.5%)	69 (39.9%)
7-7.9%	21 (12.1%)	33 (19.1%)
8-8.9%	20 (11.6%)	12 (6.9%)
≥ 9%	36 (20.8%)	30 (17.3%)
Missing	26 (15.0%)	29 (16.8%)
Newly diagnosed with DM at entry into the cohort.	105 (60.7%)	109 (63.0%)
Diabetes duration		
0-5 years	43 (24.9%)	46 (26.6%)
6-10 years	35 (20.2%)	45 (26.0%)
>10 years	64 (37.0%)	55 (31.8%)
Missing	31 (17.9%)	27 (15.6%)
Ever took pioglitazone prior to reference date	21 (12.1%)	15 (8.7%)
Ever took other TZD prior to reference date	7 (4.0%)	4 (2.3%)
Ever took any TZD prior to reference date	23 (13.3%)	18 (10.4%)
Ever took metformin prior to reference date	72 (41.6%)	73 (42.2%)
Ever took sulfonylureas prior to reference date	104 (60.1%)	88 (50.9%)
Ever took insulin prior to reference date	31 (17.9%)	41 (23.7%)
Ever took other OHA prior to reference date	2 (1.2%)	4 (2.3%)
Never took any DM drugs prior to reference date	43 (24.9%)	42 (24.3%)
None of the above	4 (2.3%)	8 (4.6%)

Table 1 - Continued

	Cases (n=173)	**Controls (n=173)**
Recentness of starting pioglitazone		
Non-user	152 (87.9%)	158 (91.3%)
Use <1.6 years ago	5 (2.9%)	7 (4.0%)
Use ≥1.6 years ago	16 (9.2%)	8 (4.6%)
Total duration of pioglitazone use		
None	152 (87.9%)	158 (91.3%)
< 1.10 years	4 (2.3%)	7 (4.0%)
≥1.10 years	17 (9.8%)	8 (4.6%)
Total dose of pioglitazone		
None	152 (87.9%)	158 (91.3%)
<10,500 mg.	7 (4.0%)	7 (4.0%)
≥10,500 mg.	14 (8.1%)	8 (4.6%)
Recentness of starting any TZD		
Non-user	150 (86.7%)	155 (89.6%)
<1.85 years	7 (4.0%)	9 (5.2%)
≥1.85 years	16 (9.2%)	9 (5.2%)
Total duration of any TZD		
None	150 (86.7%)	155 (89.6%)
<1.17 years	6 (3.5%)	9 (5.2%)
≥1.17 years	17 (9.8%)	9 (5.2%)

*Creatinine ≥1.4 for women and ≥1.5 for men

† High risk occupation is defined as painter, driver or hairdresser.

Table 2. Association between diabetes medication use and bladder cancer

Medication	**Unadjusted* odds ratio**	**95% confidence interval**	**Adjusted** odds ratio**	**95% confidence interval**
Pioglitazone	1.3	0.6-3.0	1.0	0.3-3.2
Other TZDs	1.9	0.5-7.1	1.8	0.4-8.5
Metformin	0.9	0.6-1.5	0.8	0.4-1.5
Insulin	0.8	0.4-1.5	0.7	0.3-1.6
Sulfonylureas	1.9	0.9-3.5	2.0	0.9-4.7

* Adjusted only for the matching variables and other categories of diabetes medications
** Adjusted for matching variables, race/ethnicity, smoking status, glycosylated hemoglobin concentration (with an interaction term for new diagnosis of diabetes at the time of entry into the cohort), and number of prior urinary tract infections

Table 3. Patterns of pioglitazone exposure among cases and controls

	Cases (n)	Controls (n)	Unadjusted OR (95% CI)	Model A OR (95% CI)	Model B OR (95% CI)	Model C OR (95% CI)	Model D OR (95% CI)
Ever exposed	21	15	1.3 (0.6-3.0)				
Time since starting pioglitazone							
No pioglitazone use	152	158	--	--	--	--	--
Less than 1.6 years	5	7	0.8 (0.2-2.4)	0.8 (0.2-2.5)	0.8 (0.3-2.6)	0.7 (0.2-2.3)	0.9 (0.3-3.3)
1.6 years or longer	16	8	2.6 (0.9-7.2)	2.5 (0.9-7.3)	2.4 (0.8-6.8)	2.2 (0.8-6.4)	2.6 (0.9-7.4)
Duration of therapy							
No pioglitazone use	152	158	--	--	--	--	--
Less than 1.1 years	4	7	0.6 (0.2-2.1)	0.5 (0.1-1.9)	0.6 (0.2-2.3)	0.6 (0.2-1.9)	0.7 (0.2-2.4)
1.1 years or longer	17	8	2.7 (1.0-7.6)	3.0 (1.1-8.6)	2.6 (0.9-7.4)	2.4 (0.8-6.7)	3.2 (1.1-9.4)
Cumulative dose							
No pioglitazone use	152	158	--	--	--	--	--
1-10,500 mg	7	7	1.1 (0.4-3.0)	1.0 (0.3-2.9)	1.0 (0.3-2.9)	0.9 (0.3-2.7)	1.2 (0.4-3.4)
More than 10,500 mg	14	8	2.2 (0.8-6.4)	2.3 (0.8-6.9)	2.3 (0.8-6.7)	2.0 (0.7-5.7)	2.7 (0.9-8.1)

Model A – Adjusted for race/ethnicity (non-Hispanic white and other)
Model B – Adjusted for smoking [more than 40 pack-years, 20 to 40 pack-years, and less than 20 pack years (including non-smokers and missing)]
Model C – Adjusted for glycosylated hemoglobin (8% or higher, less than 8%, and missing)
Model D – Adjusted for urinary tract infection (one or more, none, and missing)
Model E – Adjusted for diabetes duration (<10 years, 10 years or greater and missing)
Model F – Adjusted for socioeconomic status (annual household income - $40,000 or less, more than $40,000 and missing)
Model G – Adjusted for renal insufficiency (normal creatinine concentration, elevated creatinine concentration [Creatinine ≥1.4 for women and ≥1.5 for men], and missing)
Model H – Adjusted for occupational exposure (never vs. ever worked as a driver, painter, or hair dresser/barber)

Table 3 (continued). Patterns of pioglitazone exposure among cases and controls

	Model E OR (95% CI)	Model F OR (95% CI)	Model G OR (95% CI)	Model H OR (95% CI)	Multivariable adjusted OR
Ever exposed					1.0 (0.3 to 3.2)
Time since starting pioglitazone					
No pioglitazone use	--	--	--	--	--
Less than 1.6 years	0.8 (0.2-2.5)	0.7 (0.2-2.2)	0.8 (0.2-2.4)	0.8 (0.2-2.4)	Not yet available
1.6 years or longer	2.4 (0.8-6.8)	2.7 (1.0-7.7)	2.5 (0.9-7.1)	2.7 (1.0-7.8)	Not yet available
Duration of therapy					
No pioglitazone use	--	--	--	--	--
Less than 1.1 years	0.6 (0.2-2.2)	0.6 (0.2-2.1)	0.6 (0.2-2.1)	0.6 (0.2-2.0)	Not yet available
1.1 years or longer	2.5 (0.9-7.1)	2.7 (1.0-7.6)	2.8 (1.0-7.7)	3.1 (1.1-8.7)	Not yet available
Cumulative dose					
No pioglitazone use	--	--	--	--	--
1-10,500 mg	1.1 (0.4-3.3)	1.1 (0.4-3.2)	1.1 (0.4-3.1)	1.1 (0.4-3.1)	Not yet available
More than 10,500 mg	1.9 (0.7-5.7)	2.1 (0.7-6.0)	2.2 (0.7-6.3)	2.4 (0.8-6.8)	Not yet available

Model A – Adjusted for race/ethnicity (non-Hispanic white and other)
Model B – Adjusted for smoking [more than 40 pack-years, 20 to 40 pack-years, and less than 20 pack years (including non-smokers and missing)]
Model C – Adjusted for glycosylated hemoglobin (8% or higher, less than 8%, and missing)
Model D – Adjusted for urinary tract infection (one or more, none, and missing)
Model E – Adjusted for diabetes duration (<10 years, 10 years or greater and missing)
Model F – Adjusted for socioeconomic status (annual household income - $40,000 or less, more than $40,000 and missing)
Model G – Adjusted for renal insufficiency (normal creatinine concentration, elevated creatinine concentration [Creatinine ≥1.4 for women and ≥1.5 for men], and missing)
Model H – Adjusted for occupational exposure (never vs. ever worked as a driver, painter, or hair dresser/barber)

Table 4. Duration of pioglitazone use among case and control subjects

Pioglitazone use	**Case subjects (n=173)**	**Control subjects (n=173)**
Unexposed	152	158
< 1 year	4	6
1 - <2 years	6	6
2 - <3years	4	1
3 - <4 years	5	1
4 - <5 years	1	1
5+ years	1	0

Table 5. Association of bladder cancer with sulfonylurea medications and metformin

	Sulfonylurea Odds Ratio (95% CI)	**Metformin Odds ratio (95% CI)**
Short duration exposure*	1.7 (1.0 – 2.8)	1.0 (0.6 – 1.7)
Long duration exposure#	1.3 (0.7 – 2.4)	1.0 (0.5 – 1.7)

* Sulfonylurea use less than 4.71 years; metformin use less than 2.52 years

Sulfonylurea use 4.71 years or longer; metformin use 2.52 years or longer

Table 6. Comparison of respondents and non-respondents

	Case participant (n=173)	Case refuser (n=45)	Case non-participant for other reason (n=24)	Control participant (n=173)	Control refuser (n=78)	Control non-participant for other reason (n=135)
Age at reference date (%)						
40-59	12 (6.9)	4 (8.9)	2 (8.3)	11 (6.4)	2 (2.6)	4 (3.0)
60-69	52 (30.1)	9 (20.0)	5 (20.8)	46 (26.6)	20 (25.6)	30 (22.2)
70-79	73 (42.2)	24 (53.3)	9 (37.5)	80 (46.2)	33 (42.3)	64 (47.4)
80+	36 (20.8)	8 (17.8)	8 (33.3)	36 (20.8)	23 (29.5)	37 (27.4)
Sex (Female)	35 (20.2)	7 (15.6)	4 (16.7)	35 (20.2)	22 (28.2)	40 (29.6)
Congestive heart failure (%)	12 (6.9)	6 (13.3)	1 (4.2)	8 (4.6)	4 (5.1)	3 (2.2)
Elevated creatinine* (%)	13 (7.5)	5 (11.1)	3 (12.5)	15 (8.7)	5 (6.4)	15 (11.1)
Prevalent case (%)	117 (67.6)	31 (68.9)	17 (70.8)	117 (67.6)	64 (82.1)	96 (71.1)
Pioglitazone (%)	21 (12.1)	1 (2.2)	4 (16.7)	15 (8.7)	9 (11.5)	11 (8.1)
Other TZDs (%)	7 (4.0)	0 (0.0)	2 (8.3)	4 (2.3)	4 (5.1)	2 (1.5)
Metformin (%)	72 (41.6)	17 (37.8)	8 (33.3)	73 (42.2)	23 (29.5)	59 (43.7)
Sulfonylurea (%)	104 (60.1)	22 (48.9)	14 (58.3)	88 (50.9)	36 (46.2)	75 (55.6)
Insulin (%)	31 (17.9)	7 (15.6)	10 (41.7)	41 (23.7)	9 (11.5)	18 (13.3)
No diabetes medications (%)	43 (24.9)	10 (22.2)	3 (12.5)	42 (24.3)	29 (37.2)	31 (23.0)

*Creatinine ≥1.4 for women and ≥1.5 for men

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EXHIBIT 8

From: Kitazawa_Kiyoshi@takeda.co.jp
To: Roebel, Mick (TGRD); Collett, Philip (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 Philip/European Regulatory Affairs Director.Takeda Europe R&D Centre; Wada Yasuhiko/医薬開発開発戦略部長
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 uncertainity 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 note 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, PROactive 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

-----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 personel 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 paticipants 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 liasing 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 incresed 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 componant 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 Troosenburg 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 action to the FDA and EMEA.

best wishes

Philip Collett

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

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EXHIBIT 9

CONTACT REPORT FORM - FDA

Originator Name: Mary Jo Pritza **Teleconference:** **Dr. Alfonso Perez** **Dr. Stuart Kupfer** **Dr. Mondira Bhattacharya**	**Date of Contact: June 19, 2006** **Time of Contact: 9 AM**
Contact Person: Dr. Robert Misbin, Medical Officer; Ms Jena Weber, Project Manager — **Contact: 301-796-1306**	
Contact Person's Division: ODE II DMEDP	
Subject: Bladder Safety Summary	**Contact Initiated by:** ☐ TGRD ☒ FDA ☐ Other_____
Compound: ACTOS ☐ **IND #** ☒ **NDA #** 21-073	**Protocol No:** **Primary Issue:** **ACTOS labeling change**

Discussion

The teleconference was initiated by the Agency (Dr. Misbin) who after reading Takeda's bladder safety submission dated 31 August 2005; and 1 June 2006, asked that Takeda consider updating the current ACTOS (and ACTOPLUS MET) based on these new findings. Dr. Misbin stressed that the current package insert presents data in carcinogenicity/mutagenicity subsection from the registration trials which is now out of date since new information has been made available. According to Dr. Misbin, recent data, specifically from PROactive which appears in the public domain, obligates the company to provide a more informative label. He suggests that the revision could be simple, and is not implying to advance language into a warning or precaution. Takeda pointed out that interim data from a nested-case control study will be reported next month which will add to the current understanding of the relationship of ACTOS and bladder cancer. Since the Epidemiology study was on-going Takeda stated that changes to the label would be premature. Dr. Misbin noted that this teleconference was not initiated to debate the science, although "clinical study data trumps epidemiology data", but to revisit the current label and put it into context of what data are known. He added that information in the package insert can always change and that "in 3-4 years" more definitive information may become available on the relationship which could support or negate findings. He cautioned that if in the future the findings support a positive relationship and the label has not been updated in the interim when data are known, then questions may arise as to when the label should have changed. In addition, he advised that Takeda has an action pending on the Duetact NDA and this language will need to be included as part of his review of the new product's labeling. Takeda acknowledged his comment and summarized that the expectation is to evaluate all data and propose language in context of the current ACTOS database. Dr. Misbin concurred with Takeda's assessment. Takeda asked if an additional teleconference would be advisable. The Agency stated that it would not be necessary. Takeda thanked the Agency for their time and concluded the call.

Dr. Bhattacharya DEP. EX. NO. 44
FOR I.D., AS OF 1-10-13 pv

Follow-up Needed:
Submit propose language as labeling supplement

Originator's Signature: [signature]

Date: 6/29/07

Circulate to:

- ☒ VP Regulatory Affairs: L Roebel
- ☒ Correspondence File
- ☐ CMC:
- ☒ Clinical:
- ☐ Non-clinical:
- ☒ Project Mgmt:
- ☐ Regulatory Affairs:
- ☒ Safety:
- ☐ Marketing:
- ☒ President
- ☐ Other: IP.

EXHIBIT 10

DOCUMENT PRODUCED IN NATIVE FORMAT

Sales Force Verbatim

- A verbatim (same as field sales) has been developed to help you address questions/objections within the exhibit.
- Please wait for HCPs to ask the question before using the verbatim. If no questions/concerns, do not discuss bladder cancer and sell, sell, sell!
- If the question the HCP is asking is beyond your scope of reference or off-label, you can offer to:
  - Escort them to Medical Information
  - Submit a Written PIR
  - 1 (877) Takeda 7