Transcript of FDA Second Press Conference on Trasylol

FTS HHS FDA US

Moderator: Peper Long
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Coordinator: I would like to thank all participants for holding all lines will be on listen only until the question and answer portion of today's conference.

I also did want to inform participants today's call is being recorded, if you have objections you may disconnect at this time.

I'd now like to turn the call over to Peper Long, thank you, you may begin.

Peper Long: Thank you, good morning and welcome my name is Peper Long with the Food and Drugs Administrations Office of Public Affairs.

This is a FDA Teleconference for credentialed media only to announce that FDA's request for market suspension of Trasylol a drug used to control bleeding in certain patients undergoing cardiac surgery.

With me today are Dr. John Jenkins, Director of the Office of New Drugs at FDA Center for Drug Evaluation and Research, Dr. Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology at FDA Center for Drug Evaluation and Research, and Dr. Dwaine Reeves, Director of the Office of Medical Imaging and Hematology also at FDA Center for Drug Evaluation and Research.

Dr. Jenkins and Dr. Dal Pan will make brief remarks, and then Dr. Reeves will join them for the question and answer segment which will move into immediately following the remarks.

Reporters will be in a listen only mode until we open up the call for questions. And the news release accompanying this announcement has been sent out to our media list, but it's posted as well on our Website at www.FDA.gov.

I will now turn the call over to Dr. Jenkins thank you.

John Jenkins: Thank you Peper and good morning everyone, as you know we are announcing that Bayer Pharmaceuticals has agreed to suspend marketing of Trasylol in the United States at FDA's request.

Trasylol is a drug that is approved to treat, or to reduce bleeding in patients ongoing a particular type of cardiac surgery known as coronary artery bypass surgery. And in specific surgery where patients are also on cardio pulmonary bypass.

FDA made this request for our marketing suspension to Bayer late last week, and Bayer agreed to that request and is working cooperatively with FDA at this time to implement that suspension.

We planned for a phase out of the product from the marketplace in an orderly way so that there will not be undue harm to patients because there could be drug shortages for the alternatives that are used to treat the same condition.

FDA made this decision after considering further the information from the recently halted Canadian study commonly referred to as BART - B-A-R-T, which was stopped two weeks ago by the Data Safety Monitoring Committee due to an apparent increase in (depth) in patients treated with Trasylol compared to the other two agents that were being studied in that trial.

Over the past couple of weeks FDA has had interactions with the Monitoring Committee and the investigators to attempt to obtain more information about the results from that study.

It became clear to us that it was going to be six weeks or longer before we will receive any additional information, therefore we decided that it was appropriate to suspend marketing in the interim until we can learn more about the specifics of those data.

FDA decided that we could not identify at this time a specific patient population for the benefit of using Trasylol would outweigh the serious risk identified in the BART study.

That said however we understand and recognize that there maybe situations where individual doctors determine that for a particular patient the benefit of Trasylol may outweigh its risk, and therefore FDA is committed to exploring with Bayer options that would allow those doctors to obtain Trasylol under a IND program.

The details of that program have not yet been sorted out, but we are continuing to work with Bayer on that process.

I'll stop there and let Dr. Dal Pan make a few comments about the safety findings before we open it up for questions.

Gerald Dal Pan: Good morning this is Gerald Dal Pan from the Office of Surveillance and Epidemiology.

Trasylol also known as aprotinin injections was approved in 1993 and is currently indicated for prophylactic use to reduce blood loss and blood transfusions in patients who are increased risk for bleeding while undergoing cardiac surgery.

One observational study published in early 2006 suggested that Trasylol use may increase the risk for kidney damage compared to other drugs are used to prevent bleeding. A second observational study published around the same time confirmed the risk of kidney damage.

These two studies led FDA to convene an advisory committee in September of 2006 which focused on kidney damage and certain serious allergic reactions known as hypersensitivity reactions that can occur with Trasylol use.

After that meeting FDA narrowed the indicated use in patients at high risk for bleeding from cardiac surgery or from a cardiac artery bypass grafting surgery, and strengthen the warnings in the label regarding hypersensitivity and kidney damage.

Shortly after the September 2006 Advisory Committee Meeting, FDA learned of another study which Bayer had commissioned that

suggested Trasylol increase the risk for in-house (unintelligible) in cardiac surgery patients.

Another publication February 2007 suggested that Trasylol increased the long term mortality in patients undergoing cardiac surgery who received Trasylol.

This led FDA to convene another advisory committee in September 2007 which focused on the mortality findings.

The committee didn't find the results compelling enough to warrant a withdraw, so the committee recommended more studies where needed, and specifically the committee recommended a randomized controlled trial was needed.

The Canadian study that Dr. Jenkins just referred to the BART Study, was a randomized control trial designed to test the ability of Trasylol to reduce serious bleeding compared to other agents during cardiac surgery.

And the study was halted because Trasylol appeared to increase the risk of death compared to the other two drugs used in that study.

And based on the preliminary findings of this most recent study - the Canadian BART Study, combined with the fact that FDA does not expect to receive study data for at least six weeks and perhaps longer, FDA requested that Bayer suspend Trasylol pending further review of the data. That's it.

Peper Long: All right thank you very much for your remarks, now we'll move into a question and answer session.

I'd like to remind everyone to please limit yourself to one question and one follow-up.

So if we're ready for the first question.

Coordinator: Sure at this time if anyone would like to ask a question you can press star 1, that's star 1 to ask a question.

And our first question comes from (Andrew Bridges) your line is open.

(Andrew Bridges): Hi thank you for taking my question and doing this I guess twice in the day.

In light of the passage of (Padofo) and the obviously strong emphasis there on drug safety, was this withdraw done any differently than you would have done previously and you were able to move more quickly or was anything done differently and if so how?

John Jenkins: Yes this is John Jenkins, I'll start the answer and see if Dr. Dal Pan wants to add.

My brief answer would be no I don't think this was handled any differently that we would handled it previously. And I would point out that I think you're referring to FD Triple AAA or FDAAA the new legislation...

(Andrew Bridges): The new amendment that's exactly...

John Jenkins: ...that (unintelligible) about a month ago. The safety provisions, the new regulatory authority included in that law do not go into effect until March of 2008.

(Andrew Bridges): Oh.

John Jenkins: So really the ability of the FDA to manage safety issues has not been changed yet with the passage of that law.

So I think we - we handled this the way we'd would normally handle drug safety issues as Dr. Dal Pan mentioned we have been to two advisory committee meetings to review the observational data.

And at the most recent advisory committee meeting there was a very strong view expressed that we knew that controlled clinical trials that answer this question.

And at that meeting the BART study was pointed to as just the type of studies that would answer this question.

So the fact that it was stopped early for an adverse finding laid very heavily in our decision to go forward with the request for marketing suspension. Gerald anything you want to add?

Gerald Dal Pan: I think that summarizes it.

(Andrew Bridges): Thank you very much.

Coordinator: Our next question comes from (John Wilkerson) your line is open.

(John Wilkerson): Yes thank you, what - why can't you get the data for the next 6 weeks from the BART Study?

Man: Well the study is being run by a group of investigators in Canada, and we have had contact with them they are in the process of obtaining all the data and looking at it themselves.

We do not have any regulatory authority to require them to provide us any additional data at this point.

We are working with our colleagues that help Canada the Canadian equivalent of FDA to try to obtain the additional data as quickly as possible.

(John Wilkerson): Okay and the second question actually I was going to ask the same question as the AP did.

But, is, can you envision any of the new authorities that you don't yet have that come into effect in March '08. Could you have used any of those new powers in this case had you had them?

Man: Well I think the three main new authorities that are in the FD Triple AAA legislation are the ability to require risk evaluation and mitigation strategies which we formally called risk maps - or risk management plans, the ability to require a specific cross marketing studies, and the ability to require labeling changes.

I don't know that I want to speculate how we might have used any of those authorities differently. We think we proceeded in any orderly way

as we learned about the safety signal as Dr. Dal Pan said in 2006 from the observational studies.

We reviewed those data, presented them to an advisory committee in September of last year once we became aware of additional observational studies that suggested a mortality risk, we reviewed those data in great detail and presented them again to advisory committee this past September.

So I don't think we would have handled things differently under the new authorities, but we don't have those authorities yet so it's hard to speculate and apply them retroactively.

(John Wilkerson): Okay, thanks.

Coordinator: My next question comes from (Susan Edelman) you line is open.

(Susan Edelman): Yes thank you, I wanted to find out how many deaths linked to Trasylol has the FDA been made aware of either through these outside studies or your own adverse incident report.

John Jenkins: Well as far as - this is Dr. Jenkins again...

(Susan Edelman): Mmm-hmm.

John Jenkins: ...as far as the study itself - the BART study we do not have those details at this point.

The only information we were provided were the relative rates of death comparing the three arms of the study which I believe were approximately 1.5 and 1.6 for the rate of reported death.

The other study drugs versus Trasylol I don't know if Dr. Dal Pan wants to address any other parts of that question in regarding adverse event reports.

Gerald Dal Pan: Right so to examine the issue of mortality associated with Trasylol or any kind of agent given during cardiac surgery. Adverse event reports that are in our air system are generally not helpful.

And the reason for that is that mortality did something that does accompany cardiac surgery, there is a mortality rate associated with it and trying to (tease) apart all the different factors that lead to that aren't possible in individual case reports.

In fact when we - the data from the 66,000 person observational study were presented at the advisory committee in September, data collected in a reasonably systematic way.

Even (unintelligible) advisors had trouble assigned (closality) to Trasylol. So it was really...

(Susan Edelman): I just...

Gerald Dal Pan: ...the randomized clinical trial that they were looking for.

(Susan Edelman): Well I need to just find out what - how many deaths are linked to Trasylol as possibly then cause that you have to further investigate. How many deaths have been reported to the FDA?

Gerald Dal Pan: Well we don't have that number right now.

(Susan Edelman): Can you get that for me?

Gerald Dal Pan: Well see what we can do.

(Susan Edelman): Thank you.

John Jenkins: This is Dr. Jenkins, I would also refer you to the transcript and the briefing documents for the Advisory Committee that are available on our Website from the September 2007 meeting.

A lot of the information was presented there and slides both from the FDA the sponsor.

(Susan Edelman): Okay.

Peper Long: Next question.

Coordinator: Once again if anyone would like to ask a question you can press star 1 that is star 1 to ask a question.

Peper Long: May I please ask those reporters asking questions to identify their publication or media outlet.

Coordinator: Okay our next question comes from (Anna Matthews), and once again please state your affiliation.

(Anna Matthews): I'm with the Wall Street Journal, forgive me if this has already been stated or I missed it. But I think Dr. Jenkins you mentioned that the rate of reported deaths for the other two drugs in the BART study was 1.5 and 1.6 I assume I that was - those were percents?

I was wondering what was the rate for Trasylol.

John Jenkins: No, no what I said was that the relative rate of reporting.

(Anna Matthews): Ah.

John Jenkins: ...that we received from the BART investigators was that the rate for the other drugs versus the rate for Trasylol - the ratio was 1.5 for one drug, and 1.6 for the other drug, and those approached statistically significant fee values, but we don't even know which of the other two drugs was Drug A, and which of the other two drugs was Drug B they have not provided us with that information.

So that was not a incidence rate that was relative rate of 1.5 and 1.6.

Gerald Dal Pan: This is Gerald Dal Pan, we don't know the total number of deaths in the BART Study. So we don't know what proportion of patients with Trasylol died, we don't know what proportion of patients with the other agents died.

We know that the ratio of those is approximately 1.5 for each of the two agents.

But we don’t have the level of detail to note the absolute risk.

John Jenkins: And one other follow up I would offer is that Trasylol in the United States is specifically indicated for use in coronary artery bypass surgery in patients who are also receiving cardio pulmonary bypass.

It's our understanding that the BART Study also included patients undergoing valvular cardiac surgery which would not be part of the improved indication for the US labeling.

We don’t know how many of the patients and the risk ratios for patients undergoing bypass surgery versus valve surgery.

So there is a lot of information from the BART Study we would really like to be able to review in greater detail. But it’s clear that we’re not going to have those data for some time.

(Anna Matthews): Can I ask a brief follow up just clarifying?

John Jenkins: Yes.

(Anna Matthews): So, the risk - those relative ratios - just to make sure I’m going to understand them correctly, essentially patients were dying at a 50% higher rate with Trasylol than with Drug A whatever it might have been.

And, a 60% higher rate with Trasylol than for Drug B whatever it might have been, that difference did not achieve the physical significance but came close and we don’t know the absolute risk for any of the three drugs.

John Jenkins: I think that's all correct - Gerald any other comments?

Gerald Dal Pan: I actually thought it was 1.5 for both drugs, but we could check that.

(Anna Matthews): Dr. Jenkins has 1.5 and 1.6.

Gerald Dal Pan: I have 1.5 and...

John Jenkins: Dr. Reeves do you recall?

Dwaine Reeves: 1.5 - right, 1.5 it's 1.5 for both drugs.

(Anna Matthews): Okay.

John Jenkins: Okay my mistake, so 50% increase for the other two drugs versus Trasylol. A perched conventional statistical significance meaning a .05 P Value but they had not achieved that level by the time the study was stopped.

But as you may know the stopping rules for safety in a (unintelligible) analysis of a controlled clinical trial are more conservative than they are for stopping for efficacy.

So approaching traditional .05 is still considered to be a worrisome signal.

(Anna Matthews): And valvular cardiac surgery means valve replacement essentially? Is that - could I describe it as that?

John Jenkins: That would one type of valve surgery there could be others. Again we don't know the you know, the background of what all the surgical procedures were that were included in the BART Study, but one type of valvular surgery would be valve replacement.

(Anna Matthews): Okay, and I'll shut up this is one more question, do you how many of the - I think it was 3,000 patients had been enrolled when they halted the study?

John Jenkins: We do not.

(Anna Matthews): Thank you.

Coordinator: Once again to ask a question press star 1 and our next question comes from (Andrew Bridges) and please state your affiliation sir.

(Andrew Bridges): I'm with the Associated Press, thanks for allowing me a follow up. What degree of coordination was there among the various agencies. I guess the Germans ask that it'd be withdrawn or demanded I guess. You asked to help Canada I guess also wade in as well as others.

Were you able to coordinate with your colleagues abroad or how did this all come about at once.

John Jenkins: Yes this is Dr. Jenkins, we have information sharing agreements with many of the regulatory agencies around the world. And as we were reviewing the results of the BART study in the past couple of weeks we've had frequent communications with them and they've shared information and they're communications with us.

We were aware that the German Regulatory Agency was considering a withdraw - a suspension action toward the middle of last week. I would say though that the FDA decisions to request the marketing suspension was one that we reached independently of the German authorities or any other regulatory agency.

Peper Long: I think we have time for one more question.

Coordinator: Okay once again to ask a question press star 1.

Peper Long: Okay if anybody else has any additional questions you can call me my name is Peper Long I'm with the FDA Office of Public Affairs.

I can be reached at 301-827-0599, or 240-429-9205 thank you very much.

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