Transcript for Media Availability:
U.S. Food and Drug Administration following the Endocrinologic and Metabolic Drugs Advisory Committee meeting on July 1-2, 2008

Moderator: Susan Cruzan
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3:30 pm CT

Coordinator: Good afternoon and thank you for waiting. All participants will be able to listen only until the question and answer portion of the call. At that time to ask a question please press star 1.

I would like to introduce your speaker for today's call Ms. Susan Cruzan and remind all parties that this call is being recorded. Ma'am you may begin.

Susan Cruzan: Thank you (Grace). Welcome to FDA's Media Availability or Briefing following the Endocrine and Metabolic Drug Advisory Committee on July 1st and 2nd.

Joining us today are Dr. Mary Parks who will give a brief overview. Following her brief overview we will open this up to credentialed media only. Joining us as well for questions and answers from FDA are Dr. John Jenkins, Director of the Office of New Drugs for the Center for Drug Evaluation and Research, Dr. (Curtis Rosebraugh), Director, Office of Drug Evaluation II. Dr. Robert Temple the Director of Office Medical Policy and the Director of the

Office of Direct Evaluation I, Dr. Gerald Dal Pan the Director of the Office of Surveillance and Epidemiology and joining us today also is our Committee Chair, Dr. (Kenneth Burman) who is with the Washington Hospital Center in Washington, D.C.

I will now turn the call over to Dr. Mary Parks for a brief overview and then we will open it up to questions from credentialed media. Thank you.

Mary Parks: Thank you Susan. This is Mary Parks and I'm Director of Division Metabolism and Endocrine Products. In recent years long-term side effects of certain anti-diabetic therapies have raised questions about the adequacy of the clinical development program for the approval of anti-diabetic therapies in patients with type 2 diabetes and I would go so far as there were also questions raised about the surrogacy with a surrogate end point used with approval of this drug, these drugs.

And as follow-up on that there have been calls that perhaps we need to conduct cardiovascular outcome trial because of the side affects or the safety concerns raised were predominantly for increased cardiovascular risk. What was unclear to the agency was what was meant by a call for cardiovascular outcome trial.

Was it to rule out evidence of harm associated with a particular drug? Or was this a call that there was a requirement to show benefit on cardiovascular risk reduction, because up until this point all anti-diabetic therapies have been approved based on the ability to lower blood sugars because there's an expectation that lowering blood sugars in the diabetic population is clinically meaningful.

As a result this advisory committee was convened over a period of two days, first day with guest speakers to provide necessary background information and the second day for deliberations and discussion points and ultimately to answer several very important questions.

I am providing an overall overview of what has come out of this meeting. On the first day it became apparent that hemoglobin A1C, the surrogate for which these drugs are approved and glycemic control is a well-established surrogate based on very strong scientific evidence of microvascular benefit. However, because of the safety concerns particularly in cardiovascular risk and that these therapies are chronic use therapies, it became apparent that additional information may be necessary to better inform physician education about the risk and benefits of these therapies.

Also what came out of the advisory committees were the early findings with really late-breaking news for several critical anti-diabetic therapy or diabetes trials recently presented at the American Diabetes Association scientific meeting just last month. And these trials provided us with some very insightful information on the conduct of these trials and patients with type 2 diabetes, but also gave us information underscore the complexity of the disease process and the complexity of the study design.

With that information ultimately the advisory committee members today were asked a set of four questions and the first one was to discuss how the agency could modify, improve on its current standard of approval for anti-diabetic therapies. The second question was to go into a discussion on the design and conduct of a long-term cardiovascular trial with an anti-diabetic therapy.

And then the third question was really the pivotal question today with some modification to what was originally posed and that was for those drugs or

biologics without such a signal should there be a requirement to conduct a long-term cardiovascular trial or some equivalent measure or method of such, if that should be required and if it is required whether it's required pre-approval or post-approval.

And the following, the last question was if there was a recommendation for such an investigational trial how this could be applied to drugs that are currently on the market as there are no drugs currently on the market that have been established to have macrovascular benefit, nor has there been really good evidence that there's been a lot of harm, cardiovascular harm.

With that I'd like to now open this up to the panel members.

Woman: Does anyone else have any comments before we open it up to questions?

Man: Can you describe the type of studies that the panel prescribed (unintelligible) take the time for anybody (unintelligible)?

Mary Parks: As you heard perhaps earlier or yesterday currently the agency does ask that the companies provide in the Phase 2 and 3 programs at least 2,500 patients exposed to drugs. We also ask that anywhere from about 1,500 patients exposed for at least a year. Now, what was discussed today is an issue of whether or not that is adequate to rule out evidence of cardiovascular risk and whether or not there is anything that can be done to ensure that cardiovascular risk could be ruled out.

Some of the recommendations included what they called a screening trial and there was some discussion with respect to what degree of risk could be ruled out as acceptable. There is also discussion about instead of doing a screening trial, that is one prospective study, --whether or not there could be a combination, I'll use the word pooling but pooling does have its, a particular

meaning from a statistical or a methodological process, but a combination of all the trials in the current clinical development program to look at degree of glycemic control.

Obviously in either case whether it be one single prospective study or looking at the current clinical trial database and how to bolster that would result in a higher number of patients exposed pre-marketing than is currently being asked.

Man/Dr. Temple: There was a lot of discussion about the most important question we asked was whether this is a category of drug that ought to have cardiovascular outcome data at some point. The committee said that they thought it should. There's not a lot of drugs where you need a large-scale cardiovascular outcome data at the time of approval. You can see that people developing non-steroidal anti-inflammatory drugs are getting that kind of data for obvious reasons because there's been nervousness about that. So there's they decided on that.

There was also a lot of discussion of whether you could gain partial reassurance earlier by doing a better (unintelligible) a better job even before this large cardiovascular outcome study and that's one area we heard from. There was a lot of discussion about that and how much to do and whether you could modify what you're doing now or have to do a new kind of study, so there was a lot of discussion, there was a lot of discussion of that.

But to my eye the most important thing was they were saying yeah, you need cardiovascular outcome data maybe just after approval for an anti-diabetic drug because they're intended for long-term use in the (unintelligible).

Woman: And that was Dr. (Temple). Do we have any other comments? This is Dr. (Burman).

(Kenneth Burman): I agree. Thank you. I just wanted to comment specifically to your question. My interpretation with, I'd be glad to be modified is that the size and duration of any studies that would be performed would depend on adverse clinical event trials and might vary accordingly so I think you're giving an exact size and duration is impossible at the present time but it was discussed at the meeting that there were ranges.

Woman: Thank you. Do we have another question.

Woman: Yes. My question (unintelligible) confidence to design as Phase 3 a cardiovascular trial for significant (unintelligible). What is the (unintelligible) and (unintelligible)? [The voting question asked whether FDA should require companies to submit results of a long-term clinical trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. What equivalent evidence are you looking for?]

((Crosstalk))

Mary Parks: I'm going to attempt to answer that question. Yes it was modified and if you were there in the audience you probably note that there was some change up to the slide so I don't have the actual question as it was written.

But what it meant here is that first whether or not one should impose just one single study, a prospective study, there were several members on the panel who suggested alternatives to perhaps providing us some degree of reassurance that risk, an acceptable risk or a rule out of an increase for cardiovascular risk can be performed other than through a one single study. And because of that that's why the question was modified.

Now the alternative could have been a result of just pooling, and again I use the term pooling in quotes of trials that are prospectively planned in such a way that you can adequately combine them to assess cardiovascular risk. Currently that it wouldn't be the case because if you heard from question one we are, companies are not adjudicating for important cardiovascular events and that certainly impairs our ability to detect these events and provide some clarity to these events.

So the alternative here is looking at the current program with respect to clinical trials and glycemic control, perhaps also enrolling more patients at high risk and then combining that to get a sense of risk on cardiovascular disease as opposed to doing a single study in a single patient population to rule out that risk.

Woman: Would you get more from this than what you would get from your standard

Mary Parks: I'm sorry, what was the standard what?

((Crosstalk))

Woman: [safety requirements for integrated safety summary](Unintelligible) on an (ISS) test? So you have to go and indicate the (unintelligible)?

Mary Parks: I think the answer would be yes because currently with the integrated safety summaries these are not trials that are designed to specifically look at cardiovascular risk. So at a minimum these trials would have to be better designed prospectively to evaluate that.

John Jenkins: And this is Dr. Jenkins. Let me add to that as well because the question is if it's modified really came down to asking the question whether a drug that

does not have a signal identified so far in the Phase 2, Phase 3 program should be required to develop data that would allow us to adequately and with comfort assure ourselves that it doesn't have an unacceptable cardiovascular risk.

And the committee didn't specifically define what the unacceptable level of risk would be but they clearly voted that they wanted us to require studies that would give us that assurance although many of them voiced support for the concept that some of that information could be provided before approval as a screening method to rule out a significant increase in unacceptable risk and then after approval they might be able to confirm that.

The way the trial was modified as Dr. Parks said was in response to committee members nervousness that we just focus on one cardiovascular trial versus there may be alternative pathways by which you could achieve an equivalent level of confidence that you've ruled out an unacceptable cardiovascular risk and that's why the question was modified.

But I think the important point was that we heard they wanted us to have greater certainly and assurance before approval about the cardiovascular effects of the drug and that they wanted us to ensure that the question was ultimately answered either before approval or after approval to better understand cardiovascular risk. That's a shift in the expectations of what we're asking for today. It's a higher level of understanding and a higher level of assurance that you've excluded an unacceptable cardiovascular risk.

Man: Okay. Can I give one example of the difference between what we do now and what we might do later? Now typically after a relatively short term study, say a 12-week study, lots of people will be crossed over to the active drug so they'll get long-term data on that drug. The trouble is they get long-term data

on the drug, which is good for rare events but it doesn't really give you any good comparative data.

So this was discussed what they might do instead is continue the two groups that's randomized after a year, year and a half or whatever giving you data that could be informative about relative risk if you had several studies at that time. So the existing database pre-marketing might become more useful for that kind of comparison than it now is.

Woman: Do we have another question?

Woman: (Unintelligible) drugs and how you understood (unintelligible) from (unintelligible) drugs and different drugs on the market(unintelligible)?

Mary Parks: Well even with that question there were some different recommendations there. One particular recommendation was it really perhaps needs to be focused on the newer therapies and not so much on therapies that are already available as generics or older drugs.

There was also, there was also discussion as to looking at what we already have, what information because as you know, as you heard there have been numerous clinical trials already conducted in patients with type 2 diabetes with a lot of these therapies and although they may not have established evidence of benefit those studies may have been sufficient to rule out harm and for those drugs with that kind of data it may not be necessary to go back and look at it.

It really will ultimately require us to look at each individual drug and the amount of evidence that is currently available for those drugs and if we feel

that it's not adequate, it's insufficient then we may have to ask for additional data.

Woman: (Unintelligible).

Man: (Unintelligible). This issue is not (unintelligible) test approved (unintelligible) drugs (unintelligible)?

Gerald Dal Pan: This is Gerald Dal Pan from the Office of Surveillance and Epidemiology. The options are actually limited. One thing you've heard over the last two days is that heart attacks, myocardial infarctions are actually quite common amongst persons with diabetes, somewhere around 2-4% diabetics will have a heart attack per year. That high background rate, it may sound like a low number, 2-4%, it's actually quite high, makes spontaneous reporting through the Med Watch Program or other such surveillance systems really unsuitable for the kind of inferences we want to make about the cardiovascular risk of a drug.

So that type of approach, looking at data from our Adverse Event Reporting System really wouldn't be feasible here because you get individual case histories and all these patients have diabetes, that's why they're on these drugs. Many of them have coexistent high blood pressure, high lipids; you really can't make any inference about the drug. So that's sort of pharmaco-vigilance there.

Other approaches would be to look into administrative databases like one of the advisory committee members mentioned, although the committee didn't really pick up on that, to do what would be called a pharmaco-epidemiological study. These studies are also not without problems. One of the issues just like in clinical trials is validating the outcome or the event of interest.

And just it's important in prospective clinical trial it's also important to validate these events in a administrative database or other such type of epidemiologic study. It doesn't mean it can't be done it's just difficult. It's, those studies are also better for confirming associations than for ruling out associations.

We're currently in the process under (unintelligible) of working on a set of best practices on a guidance document for best practices for durational form of epidemiologic studies using administrative databases for safety questions. We held a public meeting on that I believe it was about two months ago in early may and we'll get starting to get work on that now. Those are pretty much the options we have.

So, while some of these pharmaco-epidemiologic studies may be useful I still think that the clinical trial approach is the best approach here from an ethologic point of view.

Woman: Thank you. (Unintelligible) see if we have any questions from the phone (Grace)? Do we have any questions from the phone?

Coordinator: If you would like to respond please press star 1. One moment please. (Matthew Harper) of Forbes you may ask your question.

(Matthew Harper): I just was hoping for two things, a little more, do you have a sense of whether you felt the panel was, how much leeway the FDA has in designing what this kind of screening study idea would be in terms of, I know you've mentioned it might be a single study, it might be several studies, it might be an interim look at a larger study. I was hoping you could talk a little bit on how much range you see in the tone of the advice and also is this an approach,

this screening approach something that could be applied to other areas where there are safety or advocacy controversies with regard to surrogate endpoints?

Bob Temple: This is Bob Temple. I think the committee at one point or another thought all of those were possibilities. The first, I don't know, a thousand patients in a larger later is possible. Some people thought very much that there ought to be a single long-term study designed early to rule out very large risks and others thought that current practices to be modified enough to give you useful data. I think this is going to take some more data on our part but I think they were all considered reasonably possible.

John Jenkins: And this is John Jenkins to add to that we clearly need to go back and think internally about the advice we heard. I think we clearly heard feedback from the committee that they thought we should have more well-designed studies to address cardiovascular risk before approval and the ability to more clearly understand the potential for risk in the pre-approval database.

If you think about it really what they recommended is this an extension of what we already do with every application with regard to safety? We have to look at what we know from the safety database and whether we think the safety database is adequate to rule out an unacceptable risk given the benefits of the drug and the available therapies.

I think what we heard is the committee recommended that we have more information in the future to better understand the cardiovascular risk and to rule out an unacceptably high risk before approval, so it's an extension of the usual paradigm we apply to these decisions and it is possible that the approach could be applied in other settings you know.

Dr. Temple earlier mentioned the non-steroidal anti-inflammatory drugs where it's very common now because of the history of those drugs and the questions have been raised that they come for approval already having conducted very large studies. Whether this model of a screening approach could apply there, we would have to go back and consider but it's not inconceivable that the model could apply there.

But we really need to go back and think about it in more detail and as Dr. (Burman) said earlier, it's probably going to be to some degree variable depending upon the individual agent in question. We heard the committee discuss today you know, depending upon the benefit that the new agent might be demonstrating that may have an impact on how certain you need to be about ruling unacceptable risk before approval versus after approval and again that's an extension of our usual paradigm. We're much more willing to accept higher levels of risk know or unknown for drugs that have significant benefits over existing therapy.

Woman: Thank you. Do we have any more questions on the phone please?

Coordinator: Once again to respond please press star 1.

Woman: Great. If we don't have questions on the phone I'll move back to the room if we have other questions to be done.

Woman: And I just have a clarification on first like how to be receiving studies would work with candidates and the approval study, would it be, a cardiovascular study, would it be a completely separate phase or an extension of an ongoing Phase 3 study?

John Jenkins: You're looking at me and this is John Jenkins. I'll start answering. I think we heard differing suggestions from you know, the panel. Dr. (Fleming) spoke the most about the concept of the screening study. He did not rule out the possibility that the screening study he was describing could be an integration and a continuation of a Phase 3 trial to demonstrate efficacy, but I think we heard that different models could be used.

We heard that you could have a prospective plan where all of your Phase 3 trials would be done in a way so they could be pulled together at the end to get a cardiovascular risk assessment. We heard ideas of a stand alone cardiovascular safety trial and we heard hybrids of those where some of the Phase 3 trials could be extended longer term.

I even asked a question about in this era where everyone wants to look at adaptive trial designs whether your Phase 3 trial could be looked at for an efficacy analysis at say six or 12 months but then continued on in a long-term fashion and a controlled fashion so that you could do the screening assessment for safety at some point and maybe a final confirmatory assessment for safety at a later point. I think those were all possibilities and I think it's going to depend to some degree upon the sponsor and their desired approach and our assessment of whether it meets our needs to give us the data that was recommended.

Mary, did I cover everything or miss anything...

Mary Parks: I don't know…

John Jenkins: ...that you'd like to add to?

Woman: Do we have another question on the phone? Do we have any more questions on the phone (Grace)?

Coordinator: I have no phone questions ma'am.

Woman: If we have no further questions then we will end teleconferencing and thank you all for participating today.

Coordinator: Thank you for participating in today's conference. You may disconnect at this time.

END