Transcript of FDA Press Conference on Early Communication about an Ongoing Review of Vytorin

FTS-HHS-FDA

Moderator: Susan Cruzan
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Coordinator: Good afternoon and thank you for standing by. At this time, all participants are in a listen-only mode. After the presentation, we will conduct a question and answer session. To ask a question at that time, please press star-1 on your touchtone phone.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now I would like to turn the meeting over to Ms. Susan Cruzan. Ma'am, you may begin.

Susan Cruzan: Thank you. Good afternoon and welcome. My name is Susan Cruzan with the Food and Drug Administration's Office of Public Affairs. This is an FDA teleconference for credentialed media to discuss the agency's early communication about its ongoing review of Vytorin.

With me today are several officials from FDA's Center for Drug Evaluation and Research -- Dr. John Jenkins, Director of the Office of New Drugs; Dr. Mary Parks, Director of the Davison of Metabolism and Endocrine Products; Dr. Robert Temple, Director of the Office of

Medical Policy; and Dr. Eric Coleman, Deputy Director of the Division of Metabolism and Endocrine Products.

Dr. John Jenkins will make brief remarks and then we will move into the question and answer segment for credentialed media only. Reporters will be in a listen-only mode. And I want to point out that the news release announcing the early communications has been sent to reporters on our media list and is posted to FDA's web site at www.fda.gov.

At this time, I will turn the call over to Dr. Jenkins.

Thank you.

John Jenkins: Good afternoon.

We're to discuss the early communication we released today about our ongoing review of the new information about Vytorin and Zetia. And I'm going to refer to them by their trade names for simplicity throughout the conversation.

As you all know, on January 14 of this year, Merck/Schering Plough Pharmaceuticals released the preliminary results of the ENHANCE trial. This trial was designed to evaluate the amount of atherosclerotic plaque in blood vessels in the neck based on images obtained through ultrasound in patients treated with Vytorin, the combination product of ezetimibe plus simvastatin, or simvastatin alone.

The preliminary results of the trial failed to demonstrate a significant difference in the amount of atherosclerotic plaque in the walls of the

carotid arteries despite the fact that the combination arm of Vytorin demonstrated a lower LDL cholesterol compared to the single ingredient simvastatin.

We have not yet received a final study report and at this time can not explain further why the lower levels of LDL cholesterol that was seen in patients treated with Vytorin did not lead to lesser amounts of plaque compared with those patients treated with simvastatin alone.

I wanted to talk a little bit about our basis for approval of cholesterol-lowering drugs. And elevated LDL cholesterol is a very well established risk factor for heart disease and many studies over many years have supported the conclusion that lowering cholesterol levels reduces the risk for a heart attack and stroke.

The LDL cholesterol level is one of the factors that physicians use to monitor and treat individual patients. And it's also the factor that's part of national guidelines for reducing the risk of cardiovascular disease.

It is a validated surrogate endpoint and FDA has treated it as such as the basis for approval of lipid-lowering drugs.

Our approval of lipid-lowering drugs has always been based on a demonstration of lowering of LDL cholesterol. And we have not required for initial approval the demonstration of reduction in risk of cardiovascular events such as heart attack or stroke.

Over the years, however, many of the drugs that've been approved across various classes have completed cardiovascular outcome

studies and have demonstrated a reduction in risk of heart attack or stroke.

Zetia and Vytorin were both approved based on their ability to lower LDL cholesterol. However, they have not been demonstrated to reduce the risk of cardiovascular disease, such as heart attack and stroke.

And that information is clearly documented in the labeling, as it has been for all other lipid-lowering agents until they completed a cardiovascular outcome study.

In the ENHANCE study, there was no significant difference between the number of cardiovascular events between the Vytorin-treated group and the simvastatin-treated group.

However, the ENHANCE study was small and of shorter duration than we would normally expect to see for a cardiovascular outcome study. And you really can't reach any conclusions on cardiovascular risk reductions from the ENHANCE study.

The sponsors do have another study ongoing that's called IMPROVE IT that is looking specifically at the question of cardiovascular risk reduction. And they inform us that they expect that study to be completed in 2011.

At this time, we are reminding physicians and patients that they should carefully consider the available information and data and also the current labeling for Zetia and Vytorin as they make individual treatment decisions for lowering cholesterol and reducing the risk of cardiovascular disease.

Once we receive the final study report from the sponsors, we estimate that may take as much as six months for us to fully evaluate the results of the ENHANCE study.

And we may communicate further with the public after we've completed our review. And we will be considering whether any further action is warranted with regard to Zetia or Vytorin and also whether this study has any impact on our approach to the approval of lipid-lowering drugs.

At this point, we believe it's premature to embark on any systematic changes in how we approve lipid-lowering drugs because we believe there is a long track record of success in the approach that we have followed over the last several decades.

So I'm going to stop there and turn it back to Susan for questions.

Susan Cruzan: (Corey), we can now start taking questions. Thank you.

Coordinator: Thank you.

At this time, we are ready to begin the question and answer session. If you would like to ask a question, please press the star-1 on your touchtone phone. To withdraw your request, you may press star-1. Again, if you would like to ask a question, please press star-1 on your touchtone phone at this time.

One moment please for the first question.

Susan Cruzan: Again, this is for credentialed media only.

((Crosstalk))

Coordinator: Peggy Peck of MedPage Today, you may ask your question.

Peggy Peck: Yes, thank you very much for taking our questions. And I have a question about this ongoing review, actually two questions.

One, how long do you anticipate it will be until you get the full study results? And then once you get that, what I don't understand is why would it take six months to evaluate those data?

John Jenkins: Right.

Well, we don't know exactly when we will receive the full study report from the sponsor. They have estimated that may occur as quickly as a couple of months from now. And when we get the report, we will review it as quickly as we can.

I said it could take up to six months to complete our review. We will be doing comprehensive analyses of the data and it is possible that we will need to go back with to the company with questions or additional analyses that we will be asking them to complete.

You know, the six-month time frame is our usual goal for completing a review of these types of submissions. We may well be done with our review earlier than that, but that's the - kind of the outer limit of what we're expecting it wall take to complete the review.

Peggy Peck: Well, just on follow, I just want to try to understand this. It's my understanding that the trial, the trial has - that it - the data collection was completed almost two years ago.

And are you saying now that you believe that it could be as long as two to three more months before those data are submitted to you and then it would be six months on top of that? So we would really not hear anything until late this year? I just want to understand the timetable.

John Jenkins: It's my understanding that the data from the trial were unblinded in December and the preliminary results were released by the company in January.

When we talk about a full study report that's submitted to the agency, we're talking about thousands of pages of analyses and information. We're not talking about what people are used to seeing in a journal publication.

So this is not a three- or four-page journal article. This is going to be thousands of pages of individual patient information, case report forms, et cetera.

So obviously it takes the sponsor a considerable amount of effort to put together that submission. And so that's why it may take them as much as a couple of months to submit it to us and then that's why it can take us considerable amounts of time to review it because we also have to work this in with all of the other projects we have on our plate at the time it comes in.

So the outer limit we're suggesting would be if we get the report in a couple of months, we would expect we would be done in no more than six months. It may well be sooner than that.

Peggy Peck: Thank you.

Susan Cruzan: Can we have our next question, please.

Coordinator: Shannon Pettypiece of Bloomberg, you may ask your question.

Shannon Pettypiece: Hi.

I guess I'm wondering why has it taken the FDA so long to come out and make a statement about this two weeks after the company put out their statements?

John Jenkins: Well, I'm not sure if I would characterize that as so long. The statement came out on January 14. Today is January 25. We had to have a chance to review the preliminary information.

We have received, I think, more information about the preliminary results of the study than have been released publicly. And we had to discuss amongst ourselves what we wanted to say to the public, develop the documents, and then get them out to the public. So it's actually been a fairly quick turnaround for getting that done.

Susan Cruzan: Thank you. Can we have the next question? And we'll take one question and one follow-up. Thank you.

Coordinator: Kim Dixon of Reuters, you may ask your question.

Kim Dixon: Hi.

How typical is it for a study to end at a certain point in time and then not to be unblinded until I'm not sure if it's a year and a half later, somewhere in that range? Is that typical?

I mean, I know that there are like you say these thousands of pages to go through, but in terms of the timeliness of obviously this has been an issue of (it coming out) and just wondering how typical that is?

John Jenkins: Well, I think first of all you'd have to direct any specific questions about the timing of the, you know, the unblinding of the data to the sponsors since we were not involved in that process.

As a general matter, I would say that after a study is completed, that means after the last patient has visited the clinic and finished the trial period, there is a lot of work that has to go on to collect the information from the study site, to audit that information and to go back and verify results.

And I think in this case, there was a central reading committee to read the ultrasound images, that that is a process that can take some time.

There's also the question, you know, where in the priorities or the other projects the company may have on their plate that they assign their resources to get the necessary work done before they unblinded the data.

So for the specific question, I'd have to refer you back to the company. It's not unusual for it to take quite some time, months or maybe even longer than months to do all of the data cleanup before you're ready to say that the database is ready to be unblinded and analyzed.

Kim Dixon: Okay, so you don't see it as unusual that the gap between when the study was said to be over when the data was unblinded? So months and then a year, more than a year seems like a bit of a difference.

John Jenkins: I think we would have to know more about the reasons for why it took the time from April 2006 from the last patient visited until they unblinded the data.

We don't monitor or regulate that process, so I really can't comment further. But it's not unusual for complicated studies to take considerable amounts of time for data collection, monitoring, auditing, and getting the database ready to be analyzed.

There's a lot of work that has to go into that. And I think this was a study that had a complex endpoint of the ultrasound images that had to go through a reading committee that was blinded.

So again, I would refer you to the company for the timeline of what was happening during that period of time.

Kim Dixon: Okay.

And then what regulatory action are you considering? Or what potential actions are there on the table?

John Jenkins: Well, I think it's premature to speculate. You know, we would have to consider whether we wanted to change the labeling in any way for these products. So I think it's premature until we've looked at the information.

Had this been a positive study showing a reduction in the amount of plaque in the arteries, that might've led to putting this information in the labeling and maybe even a claim for reducing the progression of atherosclerotic disease.

Given that it's a negative study, our main focus is going to be on any new safety concerns and whether that should translate into any labeling that should be added.

I would remind you that the labeling already makes very clear that there are no data to show that these drugs reduce the risk of cardiovascular disease such as heart attack or stroke. That's the same labeling that we put on all of these drugs when they're first approved and before they actually conduct the outcome study.

So that information is already there. And we want to remind physicians and patients that, you know, they can look at that information and decide what products are most appropriate for the individual circumstance.

If the physician wants the certainty of using a product that has outcome data, there's a large number of those products that are available. There are a couple of currently approved products that don't yet have these data. And they can make decisions about which one is right for their patients.

Susan Cruzan: Thank you, Kim.

I do want to remind people that we are allowing one question with one follow-up. Thank you.

Can we have the next question?

Coordinator: Aaron Smith of CNN Money, you may ask your question.

Aaron Smith: Thanks for taking my question.

This is obviously a big deal financially to the companies that produce this drug, also to the patients that are paying for the name brand drug, but I was just wondering what is the chief - why - what is the focus of your study?

Are you trying to find out whether there are safety issues with this drug? Because from what I've seen so far, the ENHANCE study says that Vytorin offers no clinical benefit over Zocor.

John Jenkins: (Unintelligible).

Aaron Smith: But I'm not sure why that would create concerns over safety.

John Jenkins: Well, we want to better understand the results of the trial. You know, the expected outcome was that the LDL would be lower more on Vytorin than it was on Zocor. That was seen.

There was no significant difference seen in the atherosclerotic plaque size. And we'd be interested in looking, how does that compare across subsets of the patients, how did that occur over time.

You should understand that we consider LDL lowering as a well validated surrogate for approval. The intimal-medial thickness or the thickness of the plaque is a much less well-validated surrogate that we use in a much more limited way from a regulatory perspective.

So we don't want to go too far down the path of making decisions about the overall benefit of these products based on this one study of this endpoint. We really would like to see the data from the outcome study.

The other - many of the other drugs approved for lipid lowering have demonstrated, you know, the benefit when they do the outcome study.

So let me turn to see if anyone else here, Dr. Temple or Dr. Parks, want to address that question.

Aaron Smith: Yeah, I guess is there any reason to believe that there's a safety issue with this drug?

John Jenkins: We have not identified any safety issue per se above and beyond what's already in the labeling. The question we're going to be looking to kind of better understand is why did the expected decrease in LDL, which was seen, not translate into a decrease in the amount of plaque in the arteries and then how to interpret that finding.

Dr. Temple may want to comment on that as well.

Robert Temple: Yeah, I do.

(Unintelligible) to think of something like plaque volume or intimal-medial thickness as, oh, a direct measure of what these drugs do. But that may not be the very best measure of what they do.

For example, in the ENHANCE study that we're talking about, over the course of time, the intimal-medial thickness actually got worse, somewhat worse, in the group that got simvastatin.

Well, we know that simvastatin, Zocor, is a drug that has been tested in people with coronary artery disease who've had a heart attack and has a profound reduction in their mortality and in their likelihood of getting another heart attack. So here's a drug that we know works from tangible data. It did not have an effect on this endpoint in this trial.

So a real question is what does that mean? We also know that the benefits of lowering cholesterol from - with statins appear as quickly as four to six months, well before there's a major effect on plaque size.

My explanation for that has always been that they allow the vessel wall to repair itself, the surface to repair itself so that it doesn't attract platelets and cause plaque. We don't really know that. I can't prove that (unintelligible).

The surrogate that really has worked over time turns out to be LDL cholesterol. And you have to go a long way before you rebut that, but we need to look at the data and see what it says.

Susan Cruzan: Thank you.

Can we have our next question?

Coordinator: Anna Matthews of Wall Street Journal, you may ask your question.

Anna Matthews: Two questions -- one, when the company - companies launched this study, did they talk with FDA at all or indicate - work with FDA on the protocol at all or indicate in any way at that stage or any other stage that they intended to potentially seek a label change or labeling claim based on this study? That's question one.

And then two, which I suppose would be my follow-up, given your skepticism of the endpoints used in the ENHANCE study, which you mentioned are less well validated than LDL as a surrogate, why would the result in this study cause you to even think about reevaluating your current approach to drugs that lower LDL cholesterol?

John Jenkins: Well, on the first question, the company did interact with the FDA on the protocol for this study. They are not the first company with a new lipid-lowered drug that has pursued this type of imaging study for looking - using ultrasound to look at the plaque thickness. And we did interact with them on that study.

And in other cases, companies have been able to have labeling language added to the package insert describing the results of the study if it has been positive.

However, even in those situations, they continue to have the labeling that says that the - that there are no data to show that they actually

reduce the risk of heart attack and stroke until they complete the cardiovascular outcome study.

As far as why would the results of this study lead us to reevaluate our paradigm for approving lipid-lowering drugs, we're not saying that it will. We're just saying we need to look at the data carefully. It's an unexpected finding. I think people would've expected the lower LDL would've translated into less plaque thickness.

And we'd like to better understand that and just consider it. At this point, we think it's premature to be discussing or suggesting that the very well-tested paradigm that's stood the test of time for using LDL cholesterol as a valid surrogate should be changed.

And Dr. Temple has a comment as well.

Robert Temple: I just want to add something. This is a sort of public health point. Some of the stories about this have raised some questions about whether people should really worry about their own LDL cholesterol and do anything about it.

The results with statins make it overwhelmingly clear that controlling your LDL cholesterol is really essential, that doing so reduces the rate of heart attack, stroke, and death dramatically. It's very important.

We already know that people tend to stop the statins when they're on them. And I'm very concerned personally that this will lead to people becoming indifferent to this extremely important measurement. It would be as bad for people as not controlling their blood pressure. So I - we're very (unintelligible).

John Jenkins: Yeah, I think - this is Dr. Jenkins again.

I think the point is we think we have to be very cautious and not overreact to this one study. And as there has been a lot of potential overreaction, it could have significant public health consequences if it drives people away from continuing to reduce their risk through lowering their cholesterol.

Susan Cruzan: Okay, could we have our next question, please?

Coordinator: Linda Johnson of Associated Press, you may ask your question.

Linda Johnson: Are you saying that you don't feel that the paradigm that reducing LDL cholesterol reduces risk of heart attack and stroke is in question? And if so, what are the other possible explanations as to why the Vytorin arm didn't have less plaque? Is it possible there's just a maximum amount of plaque reduction you can get out - off of drugs? Or what are the other explanations?

John Jenkins: Well, we're definitely saying it's premature to consider revisiting the paradigm of using LDL cholesterol as the basis for approval. We believe that's a well validated surrogate through many, many studies and many years of data.

I don't think we yet know the explanation for why this study may have proved negative for intimal-medial thickness of the carotid arteries. There are methodologic (sic) issues that could've come into play.

There could be differences in the patients. Even though it was a randomized study, you could have differences in the characteristics of the patients that may have influence.

And sometimes even drugs that we know to be effective, you know, studies turn out to be negative, so even studies that are known - even drugs that are known to work, when you study them, they don't always uniformly demonstrate an effect.

So that's why we need to carefully analyze the data. At the end of that analysis, we still may not be able to explain why this study didn't show the effect - the expected decrease in thickness. We will be wanting to see the cardiovascular outcome study to see how it translates there into the actual reduction of heart attack and stroke.

Linda Johnson: Okay.

And could you say which cholesterol drugs currently are specifically proven to reduce the risk of heart attack and stroke and which ones just have proven LDL reduction?

John Jenkins: Okay.

All of the drugs in the class called statins with the exception of one have the labeling claim for reduction of cardiovascular risk. The only one that doesn't is the most recently approved, Crestor, and they are working to complete their outcome study currently.

I'm going to turn to Dr. Parks for what other classes of drugs carry that claim beyond the statins.

Mary Parks: Yes, the other class of drugs that carries a claim for reduction in cardiovascular disease or risk is niacin. Any other product that does not have any of those - any outcome studies will have a disclaimer that this drug - the (effect of this) drug (are a) reduction in cardiovascular mortality and morbidity has not been established.

Linda Johnson: Okay.

So the statins currently proven would be Lipitor, Zocor, who else?

Mary Parks: Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin will have those claims.

Linda Johnson: Would you possibly say that a little slower?

Mary Parks: Lovastatin…

Linda Johnson: Right.

Mary Parks: …trade name Mevacor, pravastatin, trade name Pravachol, simvastatin, trade name Zocor…

Linda Johnson: Right.

Mary Parks: …fluvastatin, trade name Lescol, atorvastatin, trade name Lipitor.

Linda Johnson: Thank you very much.

Susan Cruzan: Okay, and that was Dr. Mary Parks.

Linda Johnson: Thank you.

Susan Cruzan: (Unintelligible) question, please?

Coordinator: (Rob Foreman) of CBS Early Show, you may ask your question.

(Rob Foreman): Yes, since this came out, there have been, you can call them, speculations, conspiracy theories -- call them what you want. But as FDA officials, I guess you should reinforce your answer to them, the notion Zocor was about to go generic. They came up with a combination of two drugs in order to keep Zocor in play a little longer.

What's the - is there an explanation that contradicts that and what the reason for combining two drugs in this way?

John Jenkins: Well, you know, it's not unusual for companies to look for ways to extend the patent protection or the exclusivity protection for their products. That's not illegal. They demonstrated that when you combine Zetia with Zocor that it was a safe and effective drug. And that's the standard that we use to approve the drugs.

I can't really comment on, you know, the motivation. That's not an unusual phenomenon to extend the life of the product. And sometimes the combinations are actually very beneficial to patients.

And Dr. Temple may want to follow up for a minute as well.

Robert Temple: Well, I don't want to talk about their business practices particularly, but the idea that getting the cholesterol lower by adding a second drug, which is what the combination does, is not crazy.

Epidemiologically how low your cholesterol is matters and there's at least some evidence -- not all we want -- that lowering the cholesterol more with drugs gives you a bigger effect than lowering it less.

The most dramatic demonstration of that was done by a company in a study that was against its interests. This was a study called PROVE IT where Bristol-Myers compared -- Bristol Squibb, I mean -- compared 40 milligrams of Pravachol with 80 milligrams of Lipitor.

They did that because they believed that these drugs work through mechanisms other than LDL cholesterol. What they found, however, was that Lipitor, which had a considerably greater effect on LDL cholesterol -- getting it to about 70 instead of 100 with Pravachol -- had an improved outcome on heart attacks and strokes and things.

So lowering cholesterol more turned out to be quite beneficial.

Man: And just…

Robert Temple: And Zetia, it was - in combination is a way of getting the cholesterol down further. So they may well've thought that it would get the cholesterol down further and that was attractive, probably thought it would help them compete with Lipitor.

John Jenkins: Yeah.

And another point to make is that Zetia is available as a single-ingredient product that either be used alone or in combination with other statins, so it's not as if the combination of Vytorin was forcing people who wanted to use Zetia to use it only with simvastatin. It is available as an individual ingredient.

That business practice is not illegal. They met the standards for approval. And, you know, patients and physicians have the choice of which ones they choose to use.

Susan Cruzan: Thank you.

(Rob Foreman): Thank you.

Susan Cruzan: Do we have another question, please?

Coordinator: Daniel DeNoon of WebMd, you may ask your question.

Daniel DeNoon: Thank you very much. This is a question for Dr. Parks or Dr. Coleman.

Is there anything about the way that Zetia lowers cholesterol that might suggest an answer to this conundrum of why the cholesterol lowering might not be as effective with this particular drug as it is say with the statins?

Mary Parks: Let me just repeat the question so I understand. You want to know whether - is there something about the pharmacologic action of Zetia that might explain the differences…

Daniel DeNoon: Let me be a little bit more…

Mary Parks: …in the efficacy between this drug a statin?

Daniel DeNoon: That's correct.

Is - does the mechanism - Zetia certainly has a mechanism of action that is different than the statins. Is this a clue to a - perhaps to a - some differential in why the cholesterol lowering might've had a different effect than with the statins?

Mary Parks: I think that that would be speculative on my part to try to explain the difference in efficacy based on pharmacologic action. I think that certainly the different mechanism of action has been considered a basis for combining the two products because you typically don't combine two agents that act on the same pathway.

Whether or not reducing cholesterol production in the liver results in greater LDL lowering than inhibiting absorption, that's a possibility. But again, that is speculation.

John Jenkins: But I would add we don't know that there's a difference yet. The study was small. It doesn't give you any outcome data at all of any value. All you know is the effect on the intimal-medial thickness.

((Crosstalk))

John Jenkins: And as I said before, in this study, the drug we know works let the intimal-medial thickness get bigger during the course of the study. So I - there are possible reasons to imagine the difference, but this really doesn't answer that.

Woman: (Unintelligible).

Mary Parks: One other thing I want to add to that, this difference in the intimal-medial thickness, I don't know if it has really reached the public. I know the company has made this known that the difference is 0.0058 millimeters, so that is a very small difference.

Now that is a difference, it was observed, at least from what the company has informed the public. But what that means clinically we don't know.

Susan Cruzan: Okay, thank you.

Can we have the next question, please?

Coordinator: Deborah Kotz of US News and World Report, you may ask your questions.

Deborah Kotz: Yes, hi.

I wanted to find out what post-marketing data requirements the FDA is requiring for companies to file with regards to side effects?

There's been a lot of talk in terms of the incidence of the side effects like the muscle aches and pains as being underestimated in the PDR and nobody actually knows the true incidence.

So I was wondering if the FDA is expecting updates on this from all of the statin manufacturers or from any of the statin manufacturers.

John Jenkins: Well, the companies have an obligation under the regulations to report to us adverse events that are reported to them through something we call the Spontaneous Reporting System.

And they're also required to report to us safety information that they become aware of from any other source, including controlled trials that they may conduct or epidemiology studies that they may conduct.

So that - that's an ongoing requirement for all drugs, not just the statins, and we do that information on an ongoing basis and as necessary make changes to the labeling or add new warnings and communicate that to the public.

Deborah Kotz: But there are no specific phase IV trials that are underway?

John Jenkins: Well, there are lots of post-marketing studies that are underway. The ENHANCE study was a post-marketing study that was also collecting safety information. The (impacted) study is also a post-marketing study that was collecting safety information.

For Zetia, there was one post-marketing study that we asked the company to do at the time of approval. That was to look at the safety and efficacy of the product in different ethnic groups. They did do that study and submitted it to the agency and we consider that commitment to have been fulfilled.

Robert Temple: The huge outcome studies that've been carried out are very good at major events like rhabdomyolysis. I think what people are concerned about is how good they are at minor aches and pains. You know, you'd

have to go out of your way to collect those and that's an interesting question.

Susan Cruzan: Okay, thank you. That was Dr. Jenkins and Dr. Temple. May we have the next question, please.

Coordinator: (Kyle Stud) of Philadelphia Inquirer, you may ask your question.

(Kyle Stud): Yeah, I've certain - I've read a bunch of studies from companies that are tracking doctors' prescribing habits that many doctors are moving away from Zetia and from Vytorin. And I'm talking specifically about studies by IMS and other companies.

And I'm wondering if what - what you think about this trend of are doctors doing the right thing by moving away from the drugs?

John Jenkins: Well, I would say we do not see any reason to change the labeling or the approved indications for either of these drugs based on this study.

As I said earlier, we think it's important for doctors and patients to carefully consider all of the available data on these drugs, as well as the other lipid-lowering drugs, and they can make a decision about which one they think is most appropriate for the individual patient's circumstance.

If a doctor wants assurance that the drug he or she is using has been shown to reduce the risk of cardiovascular disease, there are several choices they can make.

However, they may choose to use Zetia or Vytorin or Crestor for other reasons, including a different side effect profile, possibly the patient didn't tolerate other members of the class, so they want to try a different agent.

So it's really a decision the doctor has to make considering the patient's circumstances and their treatment goals and concerns about adverse reactions.

(Kyle Stud): You know, we just had a major study come out that's saying that a lot of negative studies never make it - never get published. And it was in a different area, but do you have any assurances that there aren't negative studies here that are going unheard or have not seen the light of day yet?

John Jenkins: Well, many of the studies that you're referring to -- that was in depression trials that there was a recent report that many of (the) studies never get published. Those studies were submitted to FDA and were reviewed by FDA.

So we see a lot more studies submitted to us under the regulations and the requirements that never get published. So we're not aware of any studies that would help to address this question that have been completed that haven't yet been reported to us.

Man: We and others have been telling people for decades that about half of all anti-depressant trials fail to beat placebo. It's not a secret. Why the publication comes out that way is for someone else to figure out.

Susan Cruzan: All right, are you done? Thank you.

We can take a few more questions. Can we have the next question, please?

Coordinator: Matthew Harper of Forbes, you may ask your question.

Matthew Harper: Did the companies ever - given - since the last patient was dosed (and) it seems that there were different approaches taken to deal with biologically implausible or missing images.

Did the companies ever amend the protocol for analyzing those images or for changing the main endpoint of this study? And which - I mean, if there are various cuts of the data there, which one is the right one to use for analysis? Is it - I mean, is it kind of the original data that came out? Or is it one of these other cleaned-up versions I guess?

John Jenkins: Well, our expectation for protocols like this, the company specifies in advance what the analysis plan will be and what the primary analysis will be and how that will be conducted. That's the analysis that we focus our primary attention on.

There are circumstances, however, where it's legitimate and valid for a company to have seen trends in the data that's still blinded that lead them to make decisions to change the primary endpoint.

So it's not out of the ordinary or illegal so to speak to make changes in your primary endpoint or the size of your study or how you plan to analyze the data if that's done before you've unblinded the data and you haven't done it in a way that might introduce bias into the analysis.

So I don't know what happened specifically with the analysis of this study. I don't think (unintelligible) submitted any protocol amendments to us that I'm aware of.

Mary Parks: I believe that is so. Eric, do you want to confirm?

Eric Foreman: Yeah, can you hear me?

All: Yes.

Eric Foreman: Yeah, they - we did review their statistical analysis plan with the past year or so, but they never formally proposed a change the primary endpoint. I know that was mentioned in the press, but we never actually received a submission requesting that.

Susan Cruzan: Okay. We have time for one more question. Thank you.

Coordinator: Mike Huckman of CNBC, you may ask your question.

Mike Huckman: Good afternoon.

First of all, thank you, thank you, thank you for using the trade names instead of the scientific, clinical name.

Wanted to first of all get clarification on what was discussed at first, whether the six-month timeline you're mentioning is on top of the couple to three months that you anticipate it'll take to get the full data. And then the…

John Jenkins: Yes.

Mike Huckman: …follow-up question is please, did the companies or either both of them or one of them ask you to do this today?

John Jenkins: The first question is yes, those timelines are sequential. We expect that the company is going to get us the study report - at least their current estimate of when they will get us the study report is within the next couple of months.

And then after that, we expect it to take us no longer than six months. So those are cumulative timelines, two plus six, eight at the outside, assuming the company gets us the study report where they currently expected to.

Neither of the companies asked us to do this early communication today. This is part of our ongoing effort to communicate with the public early when new information comes out about marketed drugs.

We've done a whole series of early communications and public health advisories over the past couple of years. This was something we felt needed to be done because of the, you know, the media attention to this issue and the surprising outcome of the study.

We felt it was important to let the public know what we're planning to do, when they can expect to hear from us again about further analysis of the study, and that we think it's premature to be thinking about changing the paradigm for approval of lipid-lowering drugs based on this study.

Mike Huckman: So again, the companies did or did not ask for this early communication?

John Jenkins: They did not.

Mike Huckman: Did not. Thank you.

John Jenkins: We informed them of our plan to have the release today and to do this call. I think we informed them of that yesterday, which is our standard procedure that we try to give the company a heads up about a day in advance of our communications with the public so that they will be aware and ready to handle the media calls, but also the calls from patients and physicians that may be coming to them asking about the FDA's statements.

Mike Huckman: Thank you.

Susan Cruzan: Thank you. That will conclude our call today.

I do want to remind you that FDA's early communication is posted online. There is a statement and a link to the communication. If you have - for any questions, you can email me at susan.cruzan@fda.hhs.gov. And we will try to get back to you.

Thank you so much. Have a great day.

END