it's a question if you have a seronegative six year old in the household do you want to run the risk of transmission to that six year old by an oral route, but I don't have the answer to the risk.

ACTING CHAIRMAN DAUM: Other general comments and questions that pertain to the issues raised by Question 1?

Dr. Snider.

DR. SNIDER: Well, with the state of knowledge that has been imparted to me through the mailings and the presentations, it's not really clear to me what additional studies could be done at this time prior to the proposed clinical trial. I'd be interested in the experts' comments on that.

But I mean, one of the things that I think we were pressing on gets at Question Number 3, which is what is the relevance of any animal models to this whole area, and would that help inform us at all on efficacy and safety issues.

And I suppose one could say, gee, we're convinced that in one sense there may be an animal model, and it would be nice to go back and look at the animal model, but then you get into problems of, you know, how are you going to use the model in the context of this type of vaccine to really evaluate

safety or efficacy for humans.

And it seems to me from what I've heard, all of that is highly speculative and not likely really to, in the end, allow us to be any more confident about taking this step with a Phase 1 trial with 25 people than we really are right now.

With regard to 1(c) though, I think one of the things that needs to be considered is what I alluded to earlier, and that is whether in proceeding with this one wants to proceed with extreme caution and at least say that sex contact should be seropositive; that the individual participants would be only selected if their sex partners were seropositives. That would offer an additional layer of protection to those individuals.

I mean ultimately what I see the next step is the most problematic, and it's really what we're alluding to, and that's the seronegative people. I mean, we're in an environment and proposing to conduct a study where there's a good chance that you won't be infected even when you become an adult in this country.

And to me I think the tougher issues are around any long term adverse effects of infection either with a vaccine strain or with the natural

strain, and we just don't know what the long term consequences are.

I would like to hear that these 25 people are going to be followed up for a long time and contribute to that knowledge base. I didn't hear it, but I would hope that that commitment would be made.

I think the counseling is terribly important. It was alluded to, but I think the counseling of people is terribly important.

One could also consider whether sexual relationships should be -- at least it should be suggested to people that if you are going to have especially a seronegative partner, one option is to not have sexual relations for a period of time that you would predict shedding might occur.

Now, you know, whether people would choose that option or not is an open question, but the issue is whether you put that information out to them. So it's just an example of the kinds of complexities, I think, that surround the counseling issue here, which I think is going to be very tough.

ACTING CHAIRMAN DAUM: Dr. Britt and then Ms. Fisher.

DR. BRITT: No, I think you raised the issue about if you require all partners to be

seropositive. How long will you require that for? I mean I think that's an issue that's probably going to complicate any trial and make it impossible.

ACTING CHAIRMAN DAUM: Okay. Ms. Fisher.

MS. FISHER: My concern is that the statement was made that CMV -- we do not know if CMV encodes other genes involved in long term pathogenic processes, and I would like to respectfully disagree, Dr. Snider, with you regarding the animal studies not being, you know, perhaps useful in that it doesn't seem to me that there has been a really serious attempt to look at non-human primates and whether or not we can do studies there before we proceed to human studies, particularly when you're creating a new virus, a chimera.

It seems that you would want to have something done in non-human primates and to see whether or not you have a genetic change that takes place or other more serious issues.

ACTING CHAIRMAN DAUM: Thank you.

Other general comments -- Dr. Stephens -- before we start being specific here?

DR. STEPHENS: This was a general question that I have for the proposers of the vaccine, and that concerns a statement was made that a single candidate

ultimately would be chosen after a presumed trial in a seronegative population, and I wasn't real clear on how that was going to be determined.

Is that going to be based on shedding or based on immunogenicity or in kind of the long term scheme of things, how are we going to make a decision about these four candidates and to which one you would ultimately propose as a vaccine.

ACTING CHAIRMAN DAUM: Dr. Fast?

DR. FASTs: I'm Pat Fast from Aviron.

That's obviously a very important question, and it's a very difficult question to answer in a really straightforward way. We would want no evidence whatsoever of any side effects of the vaccine because we're looking at such a small number of people, that if you extrapolate to large numbers of people you'd expect something worse to be happening.

Shedding of a vaccine virus, a live virus, is not completely out of the question, but if we had an immunogenic virus that was not likely to be shed, that would obviously create a much simpler situation. However, as you know, polio virus and varicella virus, other viruses are shed to some extent. So shedding isn't a complete show stopper.

And a very vigorous and durable immune

response, I think, is necessary. So we would be looking at the long term responses.

DR. STEPHENS: But obviously the Towne strain is not shed, yet is immunogenic to some degree. Is the difference in immunogenicity between the Towne strain and the presumed chosen chimera the area that would be most focused?

DR. FAST: I think after safety then if we're going to try to select that would be the second area. How long is the neutralizing antibody response? How strong are the T cell responses, and how durable they are?

We think that durability is an extremely key issue here because there's not much use immunizing somebody for a year or two years. They really need to be immune for a long time.

It's not a simple issue as you have obviously determined.

ACTING CHAIRMAN DAUM: We have Dr. Nelson next and Dr. Riddell I see was after that, and I think we'll begin to focus on Question 1.

DR. RIDDELL: I just wanted to make a comment on --

ACTING CHAIRMAN DAUM: Are you deferring?

DR. RIDDELL: He's deferring.

ACTING CHAIRMAN DAUM: He's deferring.

DR. RIDDELL: I just wanted to make a comment on what Dr. Fast raised about the durability to immune response because I think that's likely to be very critical.

One of the characteristics of herpes virus is, like CMV and EBV, is that the T cell responses at least to these viruses are maintained at extraordinarily high levels in healthy infected individuals, and that's probably because these viruses are persistently reactivating, and it actually may be necessary for a live virus vaccine to actually persist in the host and maintain levels of immunity at that level.

So I think one of the things that -- and we know that even with high levels of immunity some people still get reinfected. So I think one of the things that's likely to be required here is not only a virus that induces strong responses in the beginning, but also is able to persist and actually reactivate in the host to maintain those levels long term if it's really going to be effective long term.

ACTING CHAIRMAN DAUM: Thank you, Dr. Riddell.

Dr. Nelson, do you now wish to undefer

(phonetic)?

DR. NELSON: I undeferred.

(Laughter.)

DR. NELSON: I guess, you know, my question kind of pertains to that in some ways in that basically this study is looking at a vaccine challenge of a natural infection, and I guess my question is: what are we going to get from this and what is going to be the rationale for going on to the next studies?

I mean, what was stated was we're going to assure that the candidates are safe and that the virus is attenuated and so on and so forth. We're also going to demonstrate humoral and cellular immunity.

I'm not sure what that's going to really mean because you could be basically just boosting the natural infection and not really looking at the vaccine candidate itself.

So I'm not sure what's going to come from this study itself.

ACTING CHAIRMAN DAUM: The questions that we're asked to deal with today take a natural extension of your comments because the first set that are on the screen for you to look at really deal just with this study, as I understand them at least, and I thank our FDA colleagues for posing them clearly

because these questions I think I understand.

And that is that these questions specifically deal with this study. Should this study go forward, are there concerns specifically about the issues on the screen?

The second issue that we'll be asked also in a systematic way starting like just about now to comment on is the overall approach, these types of live recombinant viruses as vaccines in future studies, which sort of gets at your issue, going beyond this study that's being proposed this morning.

And then the third study, the third question -- excuse me -- has to do with additional preclinical animal and laboratory studies to support future clinical studies.

So having interpreted the questions, I guess, a little bit my way, I'm going to propose that this first set of questions does concern this study and not where we're going after this study is done, but should this study go forward, what are the issues and what are the concerns?

So I'm actually going to go around now and ask people to comment specifically on the questions that are here. I think we'll try to take it all three at once and see how that works, and we'll start with

Dr. Kim.

DR. KIM: I think based on what I heard so far, I think at least in my mind there are some issues that need to be addressed. One, regarding safety, I know I asked this question earlier about staging issues and four weeks was sort of determined based on the study we did Toledo, but chimeric is supposed to be more attenuated. So I'm not sure that four week time period will address issues related with the attenuated viruses compared to Toledo strain.

And then additional study issues, if I understand correctly, that cosmid clones have been pretty much prepared encoding different regions of HCMV, and wonder whether based on some of the earlier presentations and the properties of HCMV on vascular tissues, whether some of the in vitro studies can be done to identify whether out of the four chimeric vaccines some have a more propensity to cause vascular activation compared to others.

So perhaps that may give some limited information on the safety issues. That's all I have to say at this time.

ACTING CHAIRMAN DAUM: Do you think that the available data are sufficient to proceed with this proposed clinical trial?

DR. KIM: Again, I think in order to answer that I raise those issues, and if those issues are somehow addressed, then I would think so. Again, we do not have any alternative, such as animal models, at this time.

ACTING CHAIRMAN DAUM: Dr. Snider?

DR. SNIDER: With regard to 1(a), the data we have, as I understand it, are for the most part extrapolations of data from the Towne and Toledo strains. I mean it's probably the most relevant information we have, and we have some other data from in vitro work that I don't know exactly how to interpret. There's nothing alarming there, but I just don't know whether it has any meaning for human safety or not, and I haven't heard anybody claim that it really does.

But I guess I'm like Dr. Kim. I'm not sure with regard to Answer 1(b) what additional studies relevant to safety that could be done that would boost my confidence in proceeding further, and I'm at a loss, based on the information I have, to know what those studies would be. So I don't know of any studies that I would recommend under 1(b).

And then circling back then to (a), if I don't know any studies that could be done, I have to

say that's the best we can do with regard to I(a), That's the best we can do.

With regard to 1(c), I've already made a number of comments with regard to the precautions that one might conceivably take or at least counsel people about taking as it relates to seropositive sex contacts and so forth.

Of course, that just delays the problem for later on. The more safety precautions you take right now, then you just have to address these issues in some subsequent studies, and it seems to me one might argue that given some of the concerns about or the unknowns, I should say, and concerns about long term effects of CMV infection, that it would be appropriate to proceed very cautiously and do these things step by step.

Look at the four chimeras we have right now in the context of the safest kind of study we could conduct, and then move on out from there.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Edwards, please.

DR. EDWARDS: In regards to (a) and (b), I actually would hope that some of our CMV experts might help us get a little bit more information across the room in terms of those issues because I feel a bit

inadequate in addressing (a) and (b).

I do think there are some things about (c), however, that I would like to suggest. I think one is that if we are concerned about the sexual transmission, that we should monitor both cervical secretions and semen in the studies.

Now, Dr. Britt may say that the yield in general from wild type is much greater with nasopharyngeal than semen and cervical, but I think that if we're going to be doing these studies, we need to get all the information that we possibly can. So I would add those secretions to the list of things we're going to collect on the vaccinees.

In addition, I feel uncomfortable about the children greater than five years of age. I think that adults can consent for themselves, and certainly the complexities of giving an attenuated strain of CMV, I think, is hard enough for us to understand, let alone children that perhaps are in the five to ten year age group. So I really think those children that live in houses that are getting these vaccines, I think that should be a greater exclusion, and you may want to start out with no children or conceivably seropositive children.

But I'm uncomfortable in the primary

studies not excluding children greater than five.

I also wanted to just note that I applaud actually ten conduct or the design of the study. I think it is carefully done.

I also applaud the educational piece, and I think Dr. Adler has shown at least in an abstract that I think I remember rightly that education in terms of mothers that are seronegative and obviously highly motivated mothers can really serve very well to prevent transmission from their babies, and so maybe we should ask Dr. Adler how that can be done.

But I really think that the educational piece is very, very important, and if he has some pearls that from his earlier study that seem to be effective, then I think those should be added, as well.

And then finally, I think the issue that Dixie raised about seropositive sexual cohorts, at least for the first two of each group or the first ten individuals that are being recruited, I don't think that would be an unreasonable thing to look at, and again, it may be not absolutely required, but I think it's another precaution that would make me more comfortable, and that's only ten people, and the seroprevalence is 50 percent. So it's not going to be

like looking for a needle in a haystack.

So I think those issues that I would have for (c), and again, more information for (a) and (b) from the experts.

ACTING CHAIRMAN DAUM: To clarify and to push you just a little bit before we let you off the hook, we're not voting today like we usually do, but I would like to hear specifically, Kathy, if you believe the available data relative to safety are sufficient to proceed with this clinical trial.

DR. EDWARDS: I think the available data that we have seen are sufficient to proceed with the trial, with the caveats I've added for (c).

However, I really think that Ms. Fisher's comments about animal models I really think are very important ones, and that's why I would like to make sure that Question (c) is addressed, and if there are other issues that could be addressed in Question C that people that know more about the models than I do, then I think that might need to be reassessed.

So I really don't feel I can -- I think what I've seen, yes, but I would like some more information about three.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Huang.

DR. HUANG: I'm perhaps more supportive of this than what we've heard so far, and the reason for this is I'm very haunted by a young woman who came to visit me some years ago, and she was asking whether she should go ahead and have another baby because her first one was born after she was infected during pregnancy with HCMV.

That was a terrible experience that she had, and even though she was assured that the second baby, now that she's seropositive, would have a much greater chance of coming out fine, she was still very worried about what would happen.

And I guess when you see cases like that -- many of us have done that -- you begin to wonder about what can be done about that, and let's put all of this in context. It isn't as if we are talking about a whole new infection. We have actually seen lots of people infected with HCMV. Many of us are positive, and there are no untoward effects that we know of.

And we are taking two strains, the Towne and the Toledo, which there's some information about it already, and if we are going to move towards a vaccine that has any usefulness, we're sort of at a position now in which that movement cannot go ahead

because of the inability of testing in animals and having in vitro data that will help us gain new information about pathogenicity and virulence and all of those things that we all worry about.

Therefore, I believe that given the situation that we're at, the tests in seropositive subjects is one that can certainly seem to go ahead.

I will defer to my colleagues on my right in suggesting that initially some seropositive contacts, sexual contacts be included. I think that that's just a nice extra little precaution to take, and I think that some of the children that are seronegative under age ten may be at some risk.

If we've gone this far in designing a very safe trial, I think those two could be taken under advisement.

so I support going ahead in the seropositive subjects.

ACTING CHAIRMAN DAUM: Dr. Stephens, please.

DR. STEPHENS: I think there's no question that there's a need for better prevention strategies for CMV, and that's been very clearly outlined and obviously was supported by the IOM study. I must tell you thought that I have serious concerns about this

particular approach in terms of the use of a live attenuated CMV vaccine for ultimately the prevention of CMV.

My perspective is a little bit different in that I take care of adult patients with reactivated CMV disease in the AIDS setting and in the transplant setting, and that's a very devastating and complicating infection, and thus, the long term potential of an attenuated vaccine is of great concern to me.

I must say that this debate about the animal models isn't completely settled in my mind, and I'll yield to the experts, but it sounds like that there is some potential macaque model or other animal model that might shed some light on the potential for attenuation of these vaccine candidates.

And I must emphasize that at least from my perspective, we don't have any real evidence that these potential four chimers are attenuated. They may, in fact, be wild type in terms of the their activity.

I have concerns, as was expressed by Dr. Edwards and others, about the contacts and the exposure of these vaccines in terms of the contact issue, and I think those are my concerns.

My concerns still regard all three of these issues as not being settled.

ACTING CHAIRMAN DAUM: Ms. Fisher.

MS. FISHER: Well, because the molecular basis of CMV pathogenesis and virulence is unknown, it seems very speculative to go forward with a clinical trial using a chimera. It seems that you need to go back and do more basic research into CMV, and that if you're going to go forward with experiments with a chimera, that you do it in an animal model, starting out with non-human primates.

And so I would say no to (a), and I just answered (b), and I think that's all I have to say.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Estes, please.

DR. ESTES: Well, I think there's a clear need to have a vaccine to try to prevent congenital infections, and I think for transplant patients, and think if one believes that a live attenuated vaccine is the way to go, then I think we have to address the first question here.

Initially, it seemed to me that it was fairly straightforward to go ahead and to do experiments in seropositive people, that the risk would probably be quite small, and I think that that's

still true except with the caveats that have been described here.

I think you're not really doing a study in seropositive subjects if either children in the household or contacts, in fact, are seronegative. And so that's really my major concern about moving forward with this, and I think the other concerns have been addressed.

ACTING CHAIRMAN DAUM: Do you think the available data regarding safety are sufficient to proceed with this clinical trial, in a word?

(Laughter.)

DR. ESTES: I can't say just yes or no.

ACTING CHAIRMAN DAUM: Okay.

DR. ESTES: In seropositives with the issues that I just raised I think everyone has to be seropositive because you need to know about transmission first.

ACTING CHAIRMAN DAUM: Dr. Hartigan.

DR. HARTIGAN: I'm afraid I don't really feel competent to answer most of these questions. There doesn't seem to be any relevant long term safety data available, and the short term safety is, as far as I can tell, probably available, and the caveats about doing it in everybody being seropositive sounds

like a good idea to me.

ACTING CHAIRMAN DAUM: Dr. Peter.

DR. PETER: Well, I think most of my comments have already been made by others, but I do think the available data is sufficient to proceed with a study, with the one caveat that I don't feel competent to comment on the question about the relevancy of animal models and chimpanzee infections. So that's an issue in which I wish I knew more.

I think with respect to the adequacy of precautions, since the goal is to prevent inadvertent transmission and children under the age of 18 can't truly give informed consent, I would urge that the study be limited to adults who do have not household contact with young children or children at all simply because they can't give informed consent.

I'm less concerned about some of the other issues, such as sexual transmission, but I am concerned about children who can't really consent and who may face transplants in the future or HIV infection.

Certainly for the adults that can be explained in an informed consent that they can then know the risks.

ACTING CHAIRMAN DAUM: Dr. Ferrieri.

DR. FERRIERI: Well, first, I'd like to say that I'm absolutely dedicated to having a CMV vaccine. It's a very high priority in my opinion, and I can match Dr. Huang's stories with many babies I've diagnosed with CMV over the years, but I'm very concerned about this vaccine unfortunately.

And very briefly, I feel we don't understand the biology of the attenuation. We don't know what we have attenuated. We don't understand the basic genetic characteristics of what gives this virus its punch. We don't understand the genes that really regulate virulence,' and I am adamantly opposed to proceeding with the vaccine in seropositive patients.

I think we have no guarantees of what will happen, and unrelated to what I've just said, I see a complete disconnect between the information gathered and how we could ever proceed to seronegative subjects, patients.

Now, if we had basic -- we need more basic research, as Ms. Fisher indicated, and if we put our money into that, that would be the pivotal basis for proceeding with live attenuated virus for a vaccine.

So I think the beauty of our committee in that we have a lot of diverse opinions.

ACTING CHAIRMANDAUM: Dr. Nelson, please.

DR. NELSON: I think a lot of my feelings have been expressed by most of the committee. You know, I think that we really need a vaccine. Is this the vaccine that we need? I don't know. I mean maybe it will work.

Is there a safety issue? In my opinion, yes. I think that because it's unknown that safety issue still remains, and until we can identify the genes that might be involved in pathogenic processes, you know, we just don't know.

ACTING CHAIRMAN DAUM: Can I ask you a question? Because I think we all need your comment on this. Do you think the available data relevant to safety are sufficient to proceed with this, the proposed clinical trial?

DR. NELSON: In the seropositives. So it's a risk versus benefit, and I guess in my mind I'm not clear what the benefits are. I mean I don't understand what the endpoint is going to be for them to say that this is effective or not effective.

So that's the main issue I have.

ACTING CHAIRMAN DAUM: Dr. Riddell, please.

DR. RIDDELL: I would like to say a couple of things. One is that from an immunologic

perspective I think there are a lot of real advantages of a live attenuated virus in the CMV setting, and I think that a lot of those have been outlined, but the ability to get a broad, diverse immune response is likely to be essential for this virus.

Now, having said that, I will also say that that doesn't mean that subunit viruses couldn't work if we figure out the right combinations to use and if we figure out how to immunize people properly.

And I think that there is a real defect in our research activities just in how to vaccinate people effectively.

So having said that, to get to the questions at hand, I think that the first issue really is the safety issue. In the context of this trial, I think the safety data is sufficient because in a sense, what we're really doing is providing a virus that in all probability recombination is occurring all the time in CMV seropositive individuals. We're infecting individuals who get reinfected with a recombinant virus.

And I don't really think that there are substantial safety issues beyond that, and certainly ones that can be addressed, I think, which is the real issue here.

If we had an animal model I would certainly encourage that to be done, but I don't think that we do.

But I do share Jay's concern about where you go from here, what you learn from this trial and how you proceed because I think the issues there are going to be much more complex in terms of safety and also interpreting the immunology of the situation, what kinds of responses you're eliciting.

I don't think we're going to learn very much from here because we're going to be boosting prime responses as opposed to initiating new responses, and I really actually would like to hear from Aviron how they might view how they would proceed and how they would design a subsequent trial because even if this trial goes forward, really what we all want is a CMV vaccine, and for that ultimately to proceed, we need to have some sense of direction beyond this particular trial.

In terms of the last question, I do agree with the previous speakers about transmission. I would encourage the participants to either not have children or the children be seropositive.

ACTING CHAIRMAN DAUM: Okay. Dr. Britt, please.

DR. BRITT: I really have very little to add, except that probably more than anyone in this room, I would like to see a CMV vaccine because each of us recounts an anecdote, but I do them daily and have walked 15 or 20 women through pregnancy who acquired CMV infections in the first trimester. so I understand the comments and the needs for a vaccine.

In terms of addressing each one of these points, I'm not going to rehash that, but I would say that my problem with this -- not with this approach -- with this discussion is, again, a risk/benefit. I'm not sure this is necessarily the approach to eliminate this congenital infection. As such, it's hard for me to weigh the safety issues.

If this was the only approach, then I would say, okay, then we weigh the safety issues, but I think there are other considerations here besides just the Questions (a), (b), and (c).

ACTING CHAIRMAN DAUM: Thank you.

Dr. Myers.

DR. MYERS: If a live virus vaccine is to be developed, every time we get to clinical trials, this will be the same issue. So developing enough information prior to going to clinical trials in seropositives, I find it difficult to see how we would

have more information.

So with all due respect, I think animal model data, having spent a lot of my career dealing with animal models, the problem is that there's a lot of experience in Rhesus versus human herpes virus models where strains are intensely virulent Rhesus monkeys that are not in humans, and vice versa. so I don't know how that data would help us, either if it showed us it was virulent or it showed us it were not virulent.

so I think this is the type of -- whether we decide to go forward with this or not, that with live virus CMV vaccine, this is going to be a recurrent issue, and this may be as much data as we have.

That said, these strains may be attenuated. They may be fully virulent, and we won't know until they're administered, and I really agree with Dr. Edwards that whether they're seropositive or seronegative, I don't think six year old children have the capacity to give informed consent on this. It's difficult enough for us to address,

I remember in the initial Towne strain studies that, in fact, that candidate vaccine was given to celibate seropositive individuals, and so I

guess I would echo what everybody else said. I think it would be appropriate to test these candidates in seropositive individuals in the setting that minimizes the potential for transmission.

ACTING CHAIRMAN DAUM: Okay. I think perhaps, Dr. Sheets, you could help us by putting on the second list of questions, and I guess I would just ask our FDA colleagues if they felt like the first set of questions got an adequate airing in terms of committee opinion.

Do you know how the committee feels about these questions?

PARTICIPANT: Yes.

ACTING CHAIRMAN DAUM: Okay. Then I think we're doing well.

My own views, I guess, just very briefly are that my comments were already made by various people around the room. I think that there probably are sufficient data to go forward with the first proposed study, but I'm not at all clear as to how or whether it's going to be possible to learn the things we would like to learn from that study that's going to allow proceeding into an additional trial.

And so the question as it's put, I would say, yes, there's enough safety data, but I'm not sure

that unless that road map is clear, which to me it right now is not, whether it be helpful to allow it to go forward.

And I'm concerned about the definition of attenuation. As has been said before, I mean, this is neither the Towne virus nor the Toledo virus. This is a new virus, and I don't know whether it's attenuated or not, and I don't think there's any easy way to find out.

So we coming back to the committee now, we sort of help with this second group of questions, which I think I would ask as I go around the room, in the interest of time, that a lot of comments have already been made regarding this question. Is it appropriate to study other populations, such as seronegative subjects, larger numbers of subjects like Phase 2 or 3 trials, or potential target populations, given what we know at present?

So I think given the consensus that I think I've heard, we can deal with this much more quickly. Maybe I'm wrong.

Let's start with Dr. Kim.

DR. KIM: Well, I think my response to these issues at this time cannot be given conclusively, and we don't have any information. So

these questions are in some ways speculative, contingent upon the data, and contingent upon knowledge gained from the prior studies, as well as from other investigations going on on issues that have been addressed by others in the previous discussions on the molecular pathogenesis, and the Avirons and, you know, the other issues and/or matters. All those things need to be incorporated before we begin to, at least to me, begin to address these issues.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Snider, please.

DR. SNIDER: Well, I share the concerns that have been expressed earlier, as I said the first time around. I mean this is the question to me. What do you do next?

And it seems that a lot of us share concerns that we don't really understand how we would proceed from the proposed Phase 1 study to study in other populations, which is not to say there are not potential ways.

For example, the data that were shown to us on seropositivity show an extraordinarily high seropositivity rate in homosexual men. So, you know, one might conceive of certain high risk populations where if there was a body of data from seropositives

that indicated the absence of acute adverse events of concern, et cetera, again, I don't know what can be said. I'd be interested if there were data that indicated immune responses.

I'm more concerned about cell mediated responses, but would like to see both, as has been implied.

It might be possible to proceed, but I think it needs to be more clearly laid out. I don't understand. I can only speculate about some possible avenues that can be explored, and therefore, I'm very reticent at this point in time to make any definitive comments that we should proceed to study these types of recombinant viruses in these other populations or in larger numbers of subjects.

And I'd like to see that laid out much better.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Edwards.

DR. EDWARDS: Obviously this is an exceedingly complicated question to address. One of the -- and I apologize that I didn't hear the earlier presentations, but I think one issue is: what are the correlates of immunity? Are there other studies that could be done to really dissect these issues?

I think that would be very reassuring if we knew that a durable CTL response was what we needed. I think that would be very helpful in proceeding and also taking the data from the seropositives to address some of these issues.

So I really think that I'm not prepared to answer this question because of the paucity of data, and hopefully that if and when the first study in seropositives is done, that we might have the opportunity to see what is learned before we can answer this second question.

ACTING CHAIRMAN DAUM: Dr. Huang, please.

DR. HUANG: I would like to take this chance just to make some general comments about vaccines, which is relevant to Question 2, if I may, Bob.

Rather than focusing on live recombinant viruses, I'd like to just talk about live viruses as vaccines and their attenuation.

I think ideally if we had all the information that we had, knowing about the antigenicity that will elicit both B and T cell responses and memory responses, and also knowing those virulence genes in each of the viruses, we would construct a virus, a new virus that would contain

those antigens that we need and delete those virulence factors that we don't need, and put them in a system that would replicate.

So basically the best virus vaccines that we have are those that are live. Because they're long lasting, you have to give them once and it will do the job.

So that would be the ideal virus vaccine we would like to see. We have over the years seen things like subunit vaccines. We are seeing DNA vaccines that are very exciting, but none of them have really panned out in the sense of what we are looking for in the experiences that we have with live virus vaccines.

So in this case, I think that you virtually in the long run have to say where in the history of viral vaccines, where have we come from and where are we likely to go, and I speak of this because we're all facing another vaccine that's going to come down the road sometime and we have to make some hard decisions about that, and that's the HIV vaccine.

Now, as far as animal studies go, for herpes viruses and for many of them, we know that we can do all of the animal studies that we can possibly do, and even when we come down in the end to something

that tends to work in animals, such as a drug against herpes virus, and we try it in humans and we find that it doesn't work because of problems in causing other diseases in the drug trials.

So although it's nice to have other markers besides having to work in humans directly, to have other systems in vitro or in vivo ones, sometimes we just have to face that decision that the only place that we're going to get the final answers are going to be in humans if we're going to protect humans.

So that's the lecture for today.

(Laughter.)

ACTING CHAIRMAN DAUM: Thank you, Dr. Huang.

Dr. Stephens, please.

DR. STEPHENS: Returning, I guess, to the specific issue of these chimeric vaccines in regards to Question 2, I remain concerned about issues of attenuation, issues of biology, issues of sequelae and safety that make it very difficult to answer these what I would presume to be subsequent questions.

I don't think we've heard very much data today or very much information to help us really address any of these areas.

ACTING CHAIRMAN DAUM: Ms. Fisher, please.

MS. FISHER: I think you have to know more about CMV before you create a new virus and inject it into seronegative subjects, and I think you have to try to do everything you can to learn as much as you can from animals before you go into humans.

ACTING CHAIRMAN DAUM: Dr. Estes. Thank you .

DR. ESTES: I think it's premature to really be able to make decisions about going forward. I think we do need to know if these chimeric viruses are attenuated or not, and that information might come from a Phase 1 study in the seropositives, but I don't think that we can -- we'd have to look at that data very carefully before we could make comments on future studies.

ACTING CHAIRMAN DAUM: Dr. Hartigan, please.

DR. HARTIGAN: When you start over again, it seems to me that that's what you'd be doing in other populations, particularly the seronegative subjects, which is where you want to go eventually. You'd still have to do Phase 1 studies to see what happens in those populations. I don't think you can move directly from a study in seropositive persons to large numbers of seronegatives.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Peter.

DR. PETER: I think that assuming that safety and immunogenicity is demonstrated, that Phase 1 studies in seronegative individuals are absolutely essential before you do any large population studies.

My concern is that in this proposed study I don't really know what the endpoints are. The numbers are small and may not be conclusive when you have only five patients in each group.

And I guess I would only ask that the sponsor develop some specific criteria together with the FDA that might lead to testing of one of the chimeric vaccines in seronegative individuals.

ACTING CHAIRMAN DAUM: Dr. Ferrieri.

DR. FERRIERI: Given our limitations of knowledge right now of the attenuation, I think it's difficult to speak precisely to this point, but if the limited Phase 1 studies should proceed, and depending on the analysis of the data, what is learned about various immunologic responses, I would think that an expanded Phase 1 trial would have to take place in seropositives, gleaning all that you could about the immunology and the responses before moving into a limited Phase 2 study, going into expanded studies.

I think we cannot intelligently address this question, FDA.

DR. NELSON: Yeah, I guess I would just like to know what Aviron's criteria for moving into the next phase, which would be into seronegatives, and what they expect to -- what would be a positive result that would say that this is safe and that this is effective, and I think they need to address that.

ACTING CHAIRMAN DAUM: Okay. Thank you.

Dr. Riddell.

DR. RIDDELL: Yeah, this is where I have a problem, too. I have the same concern.

I guess what I would like Aviron to tell us is what criteria will we learn from the study that's proposed in seropositives that will tell us whether these viruses are attenuated or not because unless we know they're attenuated, I think we'll have a hard time saying that we could go into seronegatives.

ACTING CHAIRMAN DAUM: Dr. Britt.

DR. BRITT: I heard a comment that there was very little data presented today, but I will give you one piece of data that will address 2(c). In a well screened population of seropositive women, that are women that had seropositive virus before delivery,

and developed babies with symptomatic disease, a third of those, a third of those came from women with seropositivity before pregnancy. Okay?

So a third of that group. It was a small group, 23, 24 women. It's published in Pediatrics.

Therefore, I would be very concerned about the safety issues not only for attenuation, but for reactivation before I would launch into adolescents, at least adolescent females.

ACTING CHAIRMAN DAUM: Dr. Myers, please.

DR. MYERS: I think all the points have already been said. The core issue in my mind is if one or more of these strains are fully virulent, and so that I think initially testing in populations that minimize transmission and testing in individuals who are well informed and are fully immunocompetent are critical.

And then like Dr. Riddell, I really need to know what the endpoints would be for assessing virulence.

ACTING CHAIRMAN DAUM: Yeah. I throw in my comment at this point as being most closely allied with that of Dr. Ferrieri, which is basically that I think that the first study would have to be done. We'd have to do the more familiar committee gathering

point, which is to look at the data from it, and really have another complete session about what those data mean and how to interpret them before we can answer Question 2.

And with that, the committee's comments are complete, and I'd like to see if there's one Aviron representative who would like to comment for literally one minute about how they would interpret the data from this Question 1 trial, from the current proposed trial to launch an approach to the issues in Question 2.

This is Dr. Fast.

DR. FAST: Okay. First of all, I'd like to agree with Drs. Riddell and Nelson and Britt that the immunologic data from the first trial will be only kind of preliminary. We might see a boost, but it's not really where we're going to get our immunologic data. We need the seronegative trial.

Secondly, this is the statistical analysis of what we based on our small sample size. We think we can eliminate nonattenuated strains if they resemble the Toledo strain.

The Toledo strain, in the left, the probability of an event in a population obviously, the point estimate is .8 because eight -- I'm sorry --

four of the five, 80 percent of the people had some abnormality, eitherlaboratoryor clinical abnormality or both.

So that's obviously a rough estimate, but if that's the true incidence in the population in a Toledo, if Toledo being given to seropositives, then we would have 99 percent chance that we would see an abnormality like that in the five people that we would be inoculating.

If we see abnormalities that appear to be CMV induced abnormalities, we would not go forward into seronegative people with that candidate. We would select a candidate that caused no problems.

So the first screen is a screen for safety. We think this is actually reasonably robust. We're going to be looking at levels in blood. We're going to be looking at shedding. We're going to be looking for atypical lymphocytosis. We're going to be looking for any kind of clinical symptoms and a variety of screening labs that Dr. Heineman showed you, cvcs, liver function tests, renal function, and so on.

So that's how we think that we would find out about attenuation. Clearly, selecting the final candidate would require evidence from a seronegative

trial in which we would look very carefully at the immunologic parameters, the length of time that they were -- the strength and the length of time that they were determined, and they would need to look somewhat like wild type infection and not as weak as the Towne vaccine.

There's about a tenfold difference in the antibody responses, for example, to Towne and wild type. So we think that we have some room to look there.

ACTING CHAIRMAN DAUM: Thank you.

That was a very helpful -- a little more than one minute, but helpful just the same -- comment.

I think I'd like to move on to Question 3 now, and my sense in hearing comment about Questions 1 and 2, that I would encourage committee members to be very brief because I suspect that most of what you have to say has been said.

On the other hand, if there are new points to make, please feel free to make them.

Dr. Kim, please.

DR. KIM: I don't have any new additional comments regarding Number 3. The points that I want to address have been addressed previously.

ACTING CHAIRMANDAUM: Dr. Snider, please.

DR. SNIDER: I would respond to Number 3 by saying that I would agree with those who have said that it would be desirable to continue basic research on CMV, as well as the research that's been suggested on this particular vaccine.

I would also add that I think that trying to -- going back to two and combining it with three, I think it's very important for the company and FDA to try to chart their course with the kinds of studies that would need to be done to move this vaccine along. Otherwise we get into the problem of discarding a potentially very important vaccine based on concerns that may in the end not turn out to be valid.

So I think it's important to put the effort in to see how to get there from here as best we can and not discard this because I think, although I appreciated Alice's lecture earlier about how we would construct the ideal recombinant vaccine, I don't see how to get there very quickly either.

And so it's either one or the other candidates, and we have no assurance that one of these other candidates is going to prove to be efficacious. So I think it's premature to throw this out, as well.

DR. EDWARDS: I think that research is a little bit like apple pie and motherhood. We all like

it, but perhaps some money or some NIH or NIAID funding to really focus on the issues that are regarding vaccine issues might be a further impetus to more ongoing research.

DR. HUANG: I certainly support getting more information. I think that is always useful.

I should just say that if we held a polio virus to these criteria, we would not have a polio virus vaccine right now, and so the question is really a tradeoff of how much information we want versus how fast we want to have something that might work and be helpful to people.

DR. STEPHENS: Nothing really to add. I think we all agree that additional studies would be helpful.

MS. FISHER: I'll let my previous comment stand, except that I do want to talk a little bit about the fact that this vaccine would not be given alone. It would be given in the context of many other vaccines that adolescents are given and that children are given, and that any studies look at the fact that it will be given in combination.

DR. ESTES: I don't have anything to add.

DR. HARTIGAN: I don't have anything to add either.

DR. PETER: I have nothing to add.

DR. FERRIERI: I have nothing to add.

(Laughter.)

ACTING CHAIRMANDAUM: Wow, someone senses the question.

Let's just make sure from our FDA colleagues that they have heard opinion about each of the issues they need to hear about. I believe you have vis-a-vis these questions, but do you agree?

DR. GOLDENTHAL: Yes, I agree.

I also sense that the committee would like to see the data from the seropositive study prior to any studies in seronegative individuals.

ACTING CHAIRMAN DAUM: Yes, I certainly feel that way, and I sense a lot of others do as well.

Well, that having been said, it's lunchtime. Now, before we all stand up and make noise, how long do we have?

MS. CHERRY: I think it's probably up to Dr. Greenberg.

CHAIRMAN GREENBERG: Five minutes.

(Laughter.)

MS. CHERRY: On second thought, let me answer that question.

(Laughter.)

CHAIRMAN GREENBERG: One, forty, be back at 1:40.

(Whereupon, at 12:55 p.m., the meeting was recessed for lunch, to reconvene in closed Session 4 at 1:40 p.m., the same day.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee
Session No. 3

Before: DHHS/FDA/PHS/CBER

Date: November 4, 1999

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.