the first place, the issue of risks and the vaccination becomes more important and that you make it closer to the risk of the vaccination being close to the risk of just having zoster during that decade, and we don't have a lot of information about that.

CHAIRMAN OVERTURF: That actually begins to address the first question, but I would echo that I think there is considerable issues concerning immunization of individuals 50 to 59 without -- and I think it's clear that there are not data that clearly support that. And, although I appreciate what the sponsor has initiated, I think there are problems in trying to make a recommendation for that group.

DR. SCHARFSTEIN: I would like to come back to an issue I raised before and maybe I can just get a yes or no answer to this regarding PHN and both BOI depend upon the quality of the pain data.

Can you assure me that the pain data is of high quality and there is not a lot of missing data, so that we're actually getting proper measures of PHN and BOI?

DR. ROHAN: I believe that there was about

91 percent 182 day follow-up in the PHN cases, so follow-up over that period, but in the intermediate periods, which I don't have that data, there are some differences. Whether they are clinically significant, etcetera, this is obviously going to be exploratory but, you know, it would be, I think, important to look to see if there were more cases in the ZOSTAVAX group with higher AUCs, up to the point where they were missing and at what point they became missing versus the placebo.

DR. SCHARFSTEIN: All right. So to define AUC, you have to have --

DR. ROHAN: A time.

DR. SCHARFSTEIN: -- to be following. Keep a complete follow-up.

DR. ROHAN: Right.

DR. SCHARFSTEIN: So there's probably very few people who have complete follow-up over that time period. I don't know. We haven't seen any of the data. So two of our endpoints critically depend upon the quality. Yes, you have the data? Do you have it?

DR. SILBER: Yes. Actually, I would like

to just clarify one other point. Again, in terms of the termination interview, 95 percent of the subjects enrolled in the study completed a termination interview. 4 percent died. Less than 1 percent were lost and so did not have follow-up. Month by month, a very large majority had ongoing follow-up throughout.

So now, if I could turn to slide 1501. I think this speaks to the issue of follow-up. And I think it's important to realize people were not lost to follow-up. What happened was the pain fell below a certain level, so the frequency of visits decreased. At any given time point for a particular visit, about 90 percent were at a visit and the BOI does cover the entire period.

What we see here, again, is that 91 percent completed. Another 5 percent were within a stone's throw of 182 days by having at least 175 days. We're talking about roughly 5 percent who had incomplete follow-up and, among the 33 out of the 950 or so, there were 11 deaths. And, as you can see here, among the individuals, several of them had a

healed rash and a score of 1 or lower at the last visit and then there were just a little handful who had no follow-up.

DR. SCHARFSTEIN: So when I see more than 100 -- put that back up. When I see more than 182 days, does that mean the person was around the whole time and reporting at all your visits or does that mean oh, that person only came in twice before 182 days, but I saw him at 190 days?

DR. SILBER: No. What happens is the primary analysis truncated at 182 days. Those who had ongoing pain due to PHN continued to be followed beyond the six months.

DR. SCHARFSTEIN: When I look at the people, the 287 people who had more than 182 days --

DR. SILBER: It may have been 183, 184.

DR. SCHARFSTEIN: I understand, but does that mean that they reported at -- you have to measure the pain, right, a bunch of times. I mean, is it reported every time during that period? Probably not.

DR. SILBER: It was about 80 or 90 percent of the time points, I think, were covered.

DR. SCHARFSTEIN: At each individual time point, right?

DR. FLEMING: That is a key point that Dan is asking. It's not enough just to know that 90 percent had at least an assessment. It's important to know how many people, what fraction of all assessments were, in fact, captured.

DR. CHAN: During the course of the six month follow-up, on the average around 80 to 85 percent of the subjects that have the mandatory visits that they are supposed to come in for the pain measures. And at the last visit, as Jeff just showed you, pretty much over 90 percent have the complete follow-up at the last visit besides those who don't have pain follow-up, about two and four in each group.

DR. FLEMING: 20 percent missing. This is pretty high.

DR. SCHARFSTEIN: I don't think that answers the question. I mean, he said that 80 percent of the people had complete data in every one of the monitored visits up until 182 days?

DR. FLEMING: Can he repeat? I thought

you were saying 82 percent of all visits that were to be performed were performed. What? Could you repeat what you are saying?

DR. CHAN: On average for a given visit, around 80 to 85 percent of the zoster cases came back for their visits. Sometimes, some of these visits are on a weekly schedule. So if they are off by one day, they got slotted into the next schedule which is the next week.

DR. FLEMING: So much less than 80 percent had all visits.

PARTICIPANT: Much less.

DR. FLEMING: Yes.

DR. SCHARFSTEIN: At each visit, you said 85 percent of the people showed up, right? Is that what you said?

DR. CHAN: Right, of all --

DR. SCHARFSTEIN: In order to calculate AUC, you have to have information at all the visits, that for which they are --

DR. CHAN: Say if somebody skip a visit and have to visit on prior on the next --

DR. SCHARFSTEIN: Then you just extrapolate between the two.

DR. CHAN: Exactly.

DR. SCHARFSTEIN: Right.

DR. CHAN: And that is sort of a --

DR. SCHARFSTEIN: So some people you're just extrapolating from one missed visit, some you're extrapolating for two missed visits. Some you are extrapolating for five missed visits. Right?

DR. CHAN: That is the method of calculating the AUC, is really just not all the subject have the pain scores from every day of the visit. So by design, that is the way that AUC was constructed, yes.

CHAIRMAN OVERTURF: Dr. Royal?

MEMBER ROYAL: I have a question about just pain itself. And granted, to just look at pain scores you're leaving out some parameters that are going to be important to a quality of a person's life. But when you compare just the pain scores themselves initially and at the end of follow-up, what do you see when you look at the two groups?

How do they compare? How does the distribution compare? And, specifically, those who are considered to have significant pain, what sort of comparative distribution do you see?

DR. ROHAN: I don't think that the study specifically -- and, again, I think you had asked this before and probably I didn't actually answer the question. Hopefully, I can now. I don't think that the study was designed to look at different gradations of pain. Anyone that had a score -- all scores up to the first 30 days after rash onset were counted.

Scores of 3 and above on the 10 point scale were counted at time points after 30 days, but I don't think that there was any kind of analysis done on people with the highest pain scores. There were many instruments that were administered with quality of life, health care utilization, etcetera, that were monitored during the study though.

So it was fairly extensive as far as the impact of the disease not just in pain. And although a lot of our conversations have focused on the pain and the area under the curve, really the sponsor

looked at every imaginable impact in people's life, quality of life, pain medication usage, etcetera.

MEMBER ROYAL: My understanding is that pain scores were collected for every patient at every reporting point during the study. So one should be able to know what the individual scores were, what the median, the range for the group --

DR. ROHAN: We do have that.

MEMBER ROYAL: And you should be able to make those comparisons.

DR. CHAN: Slide No. 39. Dr. Ahnn, could you?

DR. AHNN: Yes, that --

DR. ROHAN: And I presented this earlier, so this gives you an idea of the mean.

DR. AHNN: Yes.

DR. ROHAN: Worst pain at these various time points.

DR. AHNN: We kind of omit the number of subjects who actually take the questionnaire. So, for example, the day 1 in placebo group, there are like 58 patients who answered the IZIQ, the initial

questionnaire out of 642. And the day 1, I mean, the day 2, the next day of the rash onset, 158 patient out of 642 HZ cases actually answer either IZIQ or ZDPI, mostly I think IZIQ. And day 3, 242 placebo HZ cases had answered the questionnaire out of 642 HZ cases.

So, you know, I don't think, you know, everybody who developed HZ has same number of questionnaires answered. You know, it's very variable.

DR. SCHARFSTEIN: Some of that is structural, right, because --

DR. AHNN: Yes.

DR. SCHARFSTEIN: Some of that is structural. The question is what is the unstructured level of missingness in the study?

DR. AHNN: You know, the data like 642 HZ cases in the placebo group and all other like, you know, all others are structural zero. But even with those, among those 642 cases, there are still, you know, the area under the curve zero because they didn't develop any pain at all.

So, also, that's the same for the ZOSTAVAX

group, too. That's the real zero and mostly others are structural zero like automatic zero in terms of the area under the curve.

CHAIRMAN OVERTURF: Dr. Farley?

MEMBER FARLEY: I wonder if you could clarify again for us the definition that changed in the course of the study that I -- as I recall, it was for postherpetic neuralgia and the time frame, it was earlier. It had been planned to be 30 days, I think, and it was changed to 90 days.

Can you just help us understand why that change was made halfway through and if that is something that we should be thinking harder about?

DR. ROHAN: I guess I would let the sponsor answer the question, but the change was made after the last HZ case was accrued. The study was completed and terminated about six months after the last case was accrued, but the change was made after the last case.

DR. SILBER: The question relates to it was a protocol amendment to. This was actually generated, I think, at the request of the DSMB quite

a time before that and Merck and the VA -- and this was based on emerging literature among pain experts and in the medical field that the definition of PHN was, in fact, evolving and that the concept of acute and chronic pain was changing.

And, in fact, there was much debate as to whether the change should be to 90 or 120 days. In fact, two members of the DSMB are part of the literature that has emerged on this. And if we could go to slide 623, please.

So this was something that was discussed amongst us and then in the end submitted to the FDA about the time the last case was accruing, but prior to unblinding of the data. And I had mentioned earlier when I went through the primary PHN analysis that a sensitivity analysis using different time points had, essentially, the same information.

What we have here is that with each successively later time point, the point estimate for efficacy goes incrementally up a little bit. At the same time, there are fewer subjects at the time points and so the lower bound of the confidence interval

remains the same. But this is a change that, again was driven by the DSMB and was driven by an evolution in the medical literature and the understanding of pain in the community.

And then if I could just turn to 625 for a moment, I would like to try to get back to Dr. Royal's question. I'm not sure if this quite gets there, but if we take sort of in the theme of levels of pain, this slide shows the different time points.

And, also, if we were to use a cutoff of 2 or a cutoff of 4, and again what we see, as we have seen as a recurring theme, set the bar higher. Use a level of 4 and relative to what we saw with the cutoff of 3 or now the cutoff of 2, the vaccine effect is just a smidgen higher.

CHAIRMAN OVERTURF: Dr. Scharfstein?

DR. ROHAN: I just had one comment. In changing the definition of PHN, the sponsor specified that the point estimate had to be at least 62 percent for this endpoint. And you can see that from the slides that were previously presented, at day 30 and day 60, that endpoint would have failed based on the

specified endpoint of at least 62 percent. So it was changed to 90 that if you look at the time course, that's the first point at which it was above 62 percent.

CHAIRMAN OVERTURF: Dr. Scharfstein?

DR. SILBER: If I may clarify. The time point and the point estimate were actually changed in concert and so if the 30 day time point had remained the point estimate observed at 30 and 60, it would have met the original criterion and so --

DR. ROHAN: But the original criteria did not include a point estimate, I believe. It did? It was -- excuse me? 59 percent. So I guess, obviously, what -- the minimum efficacy that is expected depends on when you see it. But, again, it was changed after the last case was accrued.

CHAIRMAN OVERTURF: Dr. Scharfstein, you had a comment.

DR. SCHARFSTEIN: This is a naive question. Is it possible that the effect of this vaccine is not to prevent herpes zoster, but to just prolong its occurrence?

PARTICIPANT: No, sir.

DR. SCHARFSTEIN: Because it shifts the time at which you would get herpes zoster, so we have only got three years of follow-up on each patient.

CHAIRMAN OVERTURF: Actually, that issue has been raised already, I think, and I raised it.

DR. SCHARFSTEIN: Yes.

CHAIRMAN OVERTURF: All right. Thanks.

DR. SCHARFSTEIN: Do you want another answer?

CHAIRMAN OVERTURF: Yes, but I think the sponsor might want to answer that.

DR. SCHARFSTEIN: Well, are you satisfied with the response?

DR. SILBER: Well, although it's certainly reasonable that the vaccine efficacy might wane over time, we have not seen this and this again being a memory response, people are boosting due to endogenous and exogenous exposure to the virus all the time. One would expect that this T-dependent response would come back with a subsequent vaccination.

In fact, booster vaccinations or a two-

dose regimen in a short period have shown that the response does, in fact, come back to the level seen after a first dose. So we would anticipate that should the data evolve to demonstrate that there is waning efficacy, that there would be benefits from a subsequent dose.

CHAIRMAN OVERTURF: Yes. I think actually that addresses actually a couple of questions we have not addressed in the 3(c) and (d), which is that I think post-licensure studies have got to include some component of active surveillance or relatively active surveillance to look at this issue, because we really have a four year period of duration right now in any age group.

And it will require, I think, some continued look at this because I think the question you asked is pertinent and relevant to what we are all considering. So I think that we will probably agree, unless somebody disagrees, that some active component or some active subset needs to be continued to be looked at very actively. This may be done in a number of settings.

We talked yesterday about using VSD data to look at this, which would be one active component, and obviously there will be -- it might be actually included in the vero subset, which is the occurrence of herpes zoster following -- it should be reporting of herpes zoster following the receipt of the vaccine ought to be part of the vero subset as well. Yes, Dr. Gellin?

DR. GELLIN: I want to go back in follow-up to a question that Monica started about the medical care of the patients or the subjects in this, and that we heard early on the medical need for this vaccine was because there was -- available therapies had limitations, but built into this was both pain management and antivirals.

Now, I wonder what we have learned about modern day intervention of ready access to these through this trial.

CHAIRMAN OVERTURF: Clearly, it was a benefit of the trial, I think. I think they have made that point, was that enrollment in this trial actually enrolled you in some very good pain management.

DR. SILBER: Obviously, the trial is not designed to look at the treatment of herpes zoster. But when we look at the fraction of individuals who received antivirals, who received anticonvulsant medication such as gabapentin, who received opiates, and when we compare that with large databases that look across a general population, the frequency of use of all of these medications was actually substantially higher than is seen in general medical practice, so again speaks to the level of care across all of the subjects, vaccine and placebo recipients who might have developed zoster.

CHAIRMAN OVERTURF: Dr. Fleming?

DR. FLEMING: I was actually going to wait to make this comment until we were answering the question, but I think our colleagues have raised this issue and it maybe is better to have it open in the discussion.

And I would like to just pursue a little bit further the idea of might we be delaying? And to the credit of this trial, it provides very good data in terms of durability of effects out to three to four

years, but this issue of whether we are allowing people to remain at risk to a later point in time is certainly a very relevant one.

The data that we see indicates that there is a substantial immune response that is provided by the vaccine, but roughly in terms of geometric mean titer ratios, twice that that comes from an actual case of herpes zoster. And so the question that I might wonder, is herpes zoster the best approach to protect against a PHN case?

Well, the issue is not if there is, in fact, a risk of a PHN case when you have herpes zoster, but the data that are fascinating that the sponsor has put forward is where you have high levels of risk of herpes zoster relative to risk of PHN is in your 50s.

And if you have 1,000 people and, based on the data, maybe if the sponsor said 300 of them over a 25 to 30 year period would, in fact, be at risk for a case of herpes zoster, during that first decade of the 50s, if you start at age 50 for example, you're accumulating five to six cases per year that you're

preventing. That adds up to 50 to 60 cases out of those 300.

Would it have been better for those people to have, in fact, had cases of herpes zoster where they are at, essentially, no risk for PHN, and this is a question specific to starting in your 50s, rather than to allow those or are you better to prevent those cases or allow them to occur when the PHN risk is going to be low in your 50s?

DR. WHARTON: I would point out that in otherwise immunocompetent subjects, once you have a case of herpes zoster, your risk for having a subsequent episode is 5 percent or less based on literature.

DR. FLEMING: Precisely. Therein lies the issue we're discussing.

CHAIRMAN OVERTURF: Any further questions, comments? Dr. Hetherington?

DR. HETHERINGTON: I apologize if this was covered previously, but did you look at the use of pain medications across treatment arms as a potential confounding factor in the pain assessment?

DR. CHAN: So your question is whether we have looked at the pain medication uses as part of the assessment of vaccine efficacy. We did. Obviously, when we look at the zoster endpoint, the pain medication don't come into the picture because all those come after the zoster surveys.

When we look at the supportive analysis in terms of the severity-by-duration of zoster pain among the cases, we did take that into account, and all we found is in general the pain medication uses are very balanced between the two groups and there is no effect on the vaccine effects because of use of the antiviral or pain medications.

DR. SILBER: I would like to get back to Dr. Fleming's point again about the potential for delaying. The evidence that we have is that the vaccine effect is durable and, although people in the 50 to 59 age group do not have PHN at the rate that older individuals do, they have often very severe, acute pain.

200,000 people a year have acute herpes zoster in this age group with severe pain. The rate

of complications, other than PHN, is about as high in people 50 to 59, including the ocular and other potentially severe complications and so --

DR. FLEMING: Then why weren't they included in the trial? If it's so obvious that these people are at such considerable risk and potential for benefit, why weren't they in your trial?

DR. SILBER: Well, again, to go back to the original point, that the primary benefit that we would anticipate to see in the younger individuals is from prevention of the episode outright. The scientific information available to Merck and the VA in 1997 when this trial was initiated, in 1992 and 1994 when the protocol was drafted was that the vaccination could not accomplish that.

Further to the point, even if the vaccine at some point wanes and is not durable, that doesn't mean there is no benefit to the individuals. And, again, what we have seen in three different studies with second vaccinations and as we would anticipate since this virus is kept quiescent for many years is that immunologic boosting that could eventually be

given with a second dose, if necessary, would biologically plausibly prevent that episode from happening at a later time.

CHAIRMAN OVERTURF: I would agree that it's biologically plausible, but the issue really is why wasn't it studied? If it was part of the original hypothesis, then it should have been studied. And, obviously, you have explained a little bit why it was not and I'm sympathetic with that, and I think the issue is almost more of a public health issue at this point.

This is going to be an issue about how best to control herpes zoster in this population, and I think the question before the Committee to me is do we have data to support this method of control for this public health problem? Dr. Royal?

MEMBER ROYAL: Just going back a minute to potential effects of treatment of individual patients on some of the parameters that you measured.

Is there any reason to think that patients who are treated with an antiviral might have had some differential difference in the frequency with which

you isolated your vaccine strain virus versus non-vaccine strain from the lesions themselves? So I believe you found your vaccine strain in two patients, in lesions from two patients, but not in the rest.

Do you think that their being on an antiretroviral would affect that at all?

DR. SILBER: The question refers to the isolation of the VZV in the PCR. I think we may be dealing with two separate issues. In the Shingles Prevention Study, the Oka strain was not seen in any individuals during the efficacy follow-up. All of the cases of zoster that occurred were with wild type. All of the rashes that occurred that had specimens within 42 days were wild type.

In two other trials, one subject each developed -- among those with VZV-like rashes, there was these two individuals who had rashes from whom the PCRs disclosed Oka strain. In one case it was a 92 year-old man who had just a few, some papular lesions 17 days postvaccination, in the other study a 23 year-old female from the VARIVAX study who was seropositive and had some lesions about a week after vaccination.

So this was in the immediate postvaccination period.

DR. GUTSCH: One other point to this question is that the samples for PCR were collected before acyclovir was being administered.

CHAIRMAN OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: I'm curious how the decision was originally made to only give one dose of the vaccine. It seems like, you know, you obviously have efficacy in certain populations. I'm wondering why a booster given a month later or something wasn't pursued. I know you did that in some of your earlier studies, but I'm curious why that strategy fell by the wayside.

DR. SILBER: A question about the single dose regimen. Again, the studies that had been conducted previously and, in fact, the studies that have been done subsequently have indicated that there was not further immunologic benefit from a second dose, that it got back to where you were with dose one. Now, whether that could translate into some qualitative difference was not studied.

CHAIRMAN OVERTURF: Hearing no further

questions or comments from the Committee, I think we'll progress to the main questions and we're instructed to answer these questions as they are asked.

If there are portions of the question that any given Committee Member, when polled, disagreed with, please, state your reasons and provide input to the FDA on what you think needs to be done in order to fully support that particular indication.

So I'm going to start with Dr. Karron. And the first question is "Are the available data adequate to support the efficacy of ZOSTAVAX when administered to persons greater than 50 years of age in preventing herpes zoster, preventing postherpetic neuralgia, preventing postherpetic neuralgia beyond the effect on the prevention of herpes zoster, decreasing the sponsor-defined burden of illness and decreasing the sponsor-defined burden of illness beyond the effect on the prevention of herpes zoster? If not, what additional information should be provided?"

MEMBER KARRON: Herpes zoster is an

important cause of morbidity in the elderly and a vaccine that effectively prevented zoster and its complications would make an important contribution to public health.

The sponsor has shown that ZOSTAVAX is effective in decreasing the incidence of zoster, preventing postherpetic neuralgia and decreasing the sponsor-defined burden of illness in individuals who are 60 to 69 and over 70 years of age.

However, as shown in the additional analysis, efficacy against the incidence of zoster is substantially decreased in individuals over 80 on the order of about 18 to 20 percent, though there may be better efficacy against postherpetic neuralgia, burden of illness or prevention of perhaps the most severe pain complications. Though, obviously, the numbers are small and here the confidence intervals overlap zero.

Although the sponsor has asked for an indication for use in individuals over 50 years of age, only 185 individuals in the 50 to 60 year-old age group have been studied and those individuals have

been studied for safety.

While it's likely that a vaccine that is efficacious in individuals over 60 would also be efficacious in individuals in that 50 to 60 year-old age group, the question needs to be addressed more completely. Perhaps additional assessments of immunogenicity with a bridging study could be contemplated since the rate of zoster is quite low in the 50 to 60 year-old age group.

An additional important issue that has been touched on by many of the people here today is the issue of duration of protection against zoster. And this is not only a question regarding the need for booster doses to prevent the breakthrough disease, but also importantly the question of whether immunizing the young elderly, those say 50 to 70 years-old, will only delay the time to occurrence of zoster potentially with worse complications in older individuals.

So my conclusions are that the data are not adequate to support efficacy in persons over 50 years of age, though there may be data to support

efficacy in a subset of that group.

CHAIRMAN OVERTURF: Dr. Fleming?

DR. FLEMING: Well, I too think this answer requires some specific consideration of groups or subgroups of patients. As the question relates to people in their ages of 50 to 60, there are no data that have been presented to us. And I do believe in principle that labels should reflect what the eligibility criteria and exclusion criteria are in clinical trials. And if people have been systematically excluded in their 50s, it seems logically inconsistent to then judge we can use evidence from that trial to address whether or not efficacy has been established and safety has been established in that group.

It is the case that PHN risk is low below the age of 60. And I think that does, in fact, provide some logic to why those participants weren't included in the trial. And as we were discussing in our open discussion period, there is at least uncertainty about the issue of the prudence of delaying herpes zoster cases in people in their 50s

when they are at very low PHN risk to then be at continued risk in ages later in time when PHN risk is much greater.

As it regards to efficacy for preventing herpes zoster in patients over the age of 60, I believe that there are positive efficacy data to establish effects on herpes zoster. As an aside, I would argue as always we should be doing an ITT analysis. The sponsor here did an MITT analysis excluding those cases in the first 30 days, where, in fact, there was evidence of benefit. So as an aside, again we see an instance where start at time zero and count everything that happens, both analyses would have shown essentially the same thing in this case.

The issue though is one of generalizability, as has been pointed out, and we're going to come back to those issues of generalizability. One of the aspects though of generalizability is specifically age. And experience has shown that it's treacherous to look at results by subgroups with the risk of being misled that differences that are uniform may be interpreted or

facts that are uniform may be interpreted to be different by subgroups.

However, I do think in this case the evidence for a waning effect or for a lessor effect in older participants is very strong with estimates for herpes zoster on the order of about 64 percent relative efficacy, if you are from 59 to 69, dropping down to 44 in your early 70s, 36 in your late 70s, 20 in your early 80s and about 12 above 85. A monotonic trend in a study of this size that provides very strong indication of an effect that is, in fact, age-specific.

And we see a similar type of evidence for PHN and for BOI. So as we move forward to Part B for preventing PHN, I do believe that there is evidence here in this study for reducing PHN at targeted levels, protocol-specified targeted levels for people who are in their 60s to 80s. But for people who are above 80, the overall PHN efficacy is well below the targeted level. And a similar situation arises with BOI where there is evidence of benefit in those who are in their 60s to 80, but above 80 one again is

below targeted levels for efficacy.

Now, key questions are also asked in BNC about how much of the effect goes beyond the prevention of herpes zoster. So specifically, in B, how much of the PHN effect goes beyond prevention of herpes zoster? My own sense about this is again this is an age-specific answer. If you are in your 60s, there is no difference at all.

So the evidence, in fact, would considerably suggest that if you are in your 60s, the effect on PHN is essentially reflecting the effect on herpes zoster. For participants who are in their 70s though and even into their 80s, there is an indication that the effect is exceeding that effect that is simply represented by herpes zoster.

For the similar question as it relates to BOI, I struggle a bit more. Again, it's very clear. If you're in your 60s, there is no evidence that the BOI measure of efficacy exceeds at all what was simply attributable to herpes zoster. There is a suggestion though as with PHN that when you are in your 70s and 80s, there may be some added value, i.e., it's not

just incidence, it's severity-by-duration.

But I'm still struggling to understand the BOI. I think the definition is somewhat problematic. The ascertainment of the outcome is not as consistent as one would hope. I do think there is a suggestion in the right hand tail, which would explain why the FDA and sponsor's analyses are so different. So at least, at this point, I'm willing to say like with PHN, there is a suggestion that there might be more than just the herpes zoster effect when you are in your 70s and when you are in your 80s.

I'm going to stop at that point, because you are talking about what additional information. I don't know if you want that answer later, but one thing I have skipped over, because it comes in Question 3, that I think is critical, at least in my answers to A, B and C, is not only does this approval or does this conclusion have to depend on the age, but it certainly is problematic that we have an absence of or very limited information in critical cohorts.

Obviously, nothing in the 50s to 60. In patients with co-morbidities or chronic

immunosuppression, we have also no evidence. We have minimal evidence in blacks and Hispanics. And the evidence that we do have in those above age 80 and certainly above age 85 is very concerning in terms of lack of persuasiveness.

So the answers here, I believe, as has already been stated are very dependent on the nature of the baseline characteristics and risk groups of the participants.

CHAIRMAN OVERTURF: Dr. Word?

MEMBER WORD: I don't think I'll be as long as Dr. Fleming. I think he summed it up very nicely. But anyway, I think what the sponsor actually -- the indication that the sponsor is seeking is really in individuals greater than 50. However, they really only provide us with data that examines those and provides evidence for those that are greater than 60 years of age. And that's where I struggle with this.

I mean, we're really based or asked to make a judgment call based on some immunologic data or, you know, as you would say a leap of faith, well,

if it works better. We know they are younger, so that they should have a better immunologic response. However, what we are missing are the hard and fast data. So if I stick to what you say, then, you know, some of the questions that I had, it still goes back to the duration of the effect of the vaccine, giving it in this 50 year-old age group.

I don't know about the need for the booster or the effect administering the vaccine that has been brought up by others if you give it earlier to people, what long-term effect will that have. So I guess if I took away the year 50 years and I took it to 60, then the answer would have been yes. But because it stayed at greater than 50, I would have to say my answer would have to be no to all three.

CHAIRMAN OVERTURF: Dr. Scharfstein?

DR. SCHARFSTEIN: I think the sponsor showed that there is a short-term effect of the vaccine on preventing herpes zoster in the 60s and 70s. I'm concerned about the 50 to 59 year-old category as well as the over 80 category. I have serious concerns about the quality of the pain data.

It may be fine. I just haven't seen it. And so the endpoints, postherpetic neuralgia and BOI depend critically upon that.

So I would say that I am uncomfortable concluding that the sponsors have shown an effect on preventing postherpetic neuralgia or on BOI. I also have concerns about the analyses that are conditional on the presence of herpes zoster as those populations may or may not be comparable. We saw some data suggest that there were a couple on basepoint characteristics. However, there could be unmeasured confounders that can explain some of these differences.

So again, I'm not comfortable concluding that the sponsor has shown an effect of preventing PHN above and beyond its effect on herpes zoster or its effect on BOI above and beyond its effects on herpes zoster.

CHAIRMAN OVERTURF: Dr. Rowbotham?

DR. ROWBOTHAM: For the great majority of persons who develop and episode of herpes zoster, it's a very severe, but fortunately, relatively short

illness. But for those whose pain lingers beyond a month, and even more so for those who still have pain at six months or a year, there is no way to really underestimate the burden of suffering.

This brings up the importance of the right hand tail in the data, in that those patients who have the very high burden of illness scores over the six months after an episode of zoster, those people are very likely to continue to have pain a year or even longer and be really quite severely disabled as a result.

However, it's difficult to answer the three questions here, because of the lack of direct data in the group between the age of 50 and 59. So I can's answer any of the three questions on that. It would be speculative for me to provide a direct answer. For the first question of preventing herpes zoster, the answer is quite clear. That if you are year 60 or greater, there is a very definite effect and that seems to carry on with some reasonable confidence on up into the 70s or perhaps even into the 80s.

With regard to the question of preventing postherpetic neuralgia, there is a semantic difficulty which is that if you don't have herpes zoster, you can't possibly get postherpetic neuralgia, as we usually define it. So to put out an indication for preventing postherpetic neuralgia would encourage patients to try and get vaccinated as soon as they get an episode of zoster in the hopes of preventing postherpetic neuralgia.

And I'm already getting calls from patients asking to be vaccinated even though they have had postherpetic neuralgia for the past 5 or 10 years. So there needs to be clarity as to what exactly the vaccine can do. And what is most clear is that in this age group between 60 and 70, that the vaccine is very effective in preventing herpes zoster.

Now, in the older age group, there is evidence that there is a preventive effect on postherpetic neuralgia beyond the effect of preventing zoster. And there, the labeling language would need to be very careful to try and avoid confusing both patients and clinicians. With regard to the third

question of decreasing the sponsor defined burden of illness, the problem there is that the way it was defined also included the preventive effect on herpes zoster.

And so it's difficult to answer that question, because it's really something that should be split out into looking at the burden of illness in those who have developed zoster. And again, the data suggests that especially in the older patients that in the pivotal study that the patients over the age of 70 did have less severe pain, even when their pain persisted. And so there, I think the burden of illness question is very important and it does support that there is an effect on burden of illness in those who are unfortunate enough to develop zoster despite being vaccinated.

The most difficult problem that will come up in the other questions is what to do in the group between 50 and 59. And there we are really hampered by the lack of information on the durability of the vaccination and whether or not patients who are vaccinated at 50 should be revaccinated at some

additional time point before they turn 60, when the likelihood of developing postherpetic neuralgia after zoster starts to greatly rise.

CHAIRMAN OVERTURF: Dr. Gellin?

DR. GELLIN: I'll avoid summarizing a lot of the data we heard, but given the question as framed, are there data available to support efficacy of ZOSTAVAX when administered to persons greater than 50? We simply don't have sufficient data in the 50 and above. So for me that makes the answer to all the subparts easy, that there is not the data to support that.

CHAIRMAN OVERTURF: Okay. Dr. Wharton?

DR. WHARTON: I would echo Dr. Gellin's comments regarding the adequacy of available data to support the efficacy in persons 50 years of age and older for herpes zoster, postherpetic neuralgia and burden of illness.

That said, there is good data in the pivotal efficacy trial to support efficacy for prevention of herpes zoster in persons in their 60s and 70s, yet into their 80s, as others have commented,

postherpetic neuralgia and burden of illness evaluations in those age groups are very strongly driven in the younger part of that population by reduction of herpes zoster. It does appear on the higher end that there may be independent effect, but it was less definite than one might like.

CHAIRMAN OVERTURF: Dr. Royal?

MEMBER ROYAL: Thank you. I would also like to stick to the question as posed to us. Looking at the data for patients 50 years and over, there is non-uniformity in response and inadequate data for the 50 and 60 year age groups. So for that reason, I feel that the studies do not support efficacy for patients greater than 50 years.

CHAIRMAN OVERTURF: Your industry opinion, Dr. Hetherington?

DR. HETHERINGTON: Well, my comments will parallel pretty much what you've already heard. Just to put it in different words, durability is a relative term and for the older age group, three to four years may put you in the ballpark of something reasonable. But as you get to somebody in the 50 and 60 year-old

group, who has 30 to 40 years of life left, then durability of three to four years really doesn't mean much.

And until the question of durability or strategy to deal with any waning immunity in those who might be immunized at a younger older age group is answered, I don't think you could make a recommendation in that 50 to 59 year-old group. The standard of approving therapeutics is still based on data and data for the population that has been studied. And that again is still lacking.

That said, for the subparts, there certainly is data showing this vaccine could be effective in certain age groups for preventing morbidities associated with zoster. Most of the improvements or benefits seem to be in reducing the frequency of actual cases. I confess some indecision about whether the things such as burden of illness or preventing PHN is beyond the effect of prevention of herpes zoster. Nevertheless, I think the bottom line is that there is an overall effect and a potential for this therapeutic.

CHAIRMAN OVERTURF: Dr. Farley?

MEMBER FARLEY: I agree that as posed my answer to Question 1 would be no, that we haven't been presented with adequate data in the 50 and older category. I do think that it's important to acknowledge that they have shown what I think is quite impressive reduction in the incidence of herpes zoster in those 60 and over. And I do believe that that's something that needs to be visited with the idea of whether it has a role currently in terms of the approval process for those for which it was tested.

I believe that the additional data that we all want and would emphasize is in the 50 to 59 age group. Perhaps also in the immunocompromised older elderly, but in the 50 to 59, the emphasis not only on some sort of consistent bridging information, but with a mandate to really look at the issue of the waning immunity and the idea of boosters and data on the boosting effect over time.

So I would vote or answer no to the question as posed, but would prefer to also keep the idea of some consideration for the 60 and older

category for consideration of approval.

CHAIRMAN OVERTURF: Yes, Dr. Markovitz?

MEMBER MARKOVITZ: Yes, I would like to echo a few things that were stated, but a few additional things. First of all, I think that, obviously, we cannot say there are any data to support licensing this between age 50 and 60 or 50 and 59. It is unfortunate in the sense that my guess is it will work once the company actually does the studies, but until we have the studies, we can't really comment.

And I'm a little reluctant to endorse, at least without a lot of thought, a bridging study. I suspect an efficacy study would really be substantially better. That being said, I like the data for people over 60. I think they are pretty strong data. And I believe that it shows efficacy certainly in preventing herpes zoster.

Now, the issue that people have raised about postherpetic neuralgia and burden of illness, I think that's important in terms of the labeling. But it's my impression that at least clinically if you can actually improve on those parameters by simply

preventing zoster, that's still a very important improvement.

So while I think there may be some discussion about how to label this if it does get approved, I think in terms of real life clinical efficacy, I think that preventing zoster and then impacting on those other measures would be fine with me. So I vote, I guess I'm voting no for 50 to 59 and yes for 60 and above, if that's allowed.

CHAIRMAN OVERTURF: Yes, I'm actually splitting the vote on this. I would like to really congratulate the sponsors on what I think was an excellent and a difficult trial. It's a trial because it's one of those -- it's similar to many vaccines that we now are beginning to develop, which really have to deal with long-term consequences that occur long after the vaccine is given.

I suppose that was always true, but with childhood vaccines, we are often dealing with issues like rubella that would occur very shortly after immunization or would have occurred very shortly after immunization and we're somewhat universal and didn't

also carry some of the chronic and difficult consequences like zoster does.

That said, actually I think I could move into the hypothetical realm and use what I know about the immunological data in the 50 year-old age group and would have been willing to. I think the biggest concern here is that you're really talking about giving this to a universal large population with what I don't think are adequate safety data yet.

That's perhaps the biggest limiting factor and perhaps probably needs to be the most important prerequisite for post-licensure, if that's going to come. It does also -- and I think another issue is the long-term public health consequences of that vaccine given in that age group and whether that's the best strategy. And I don't think we have enough information.

Plus, we don't have enough -- this sounds to me like it echos an awful lot on what we used to say about when the varicella vaccine was first licensed. We were all -- there was so much concern and still is some concern that we were going to be

delaying the problem until a later point in which the severity might be greater. And I think that still is an issue here. Although, obviously, with the varicella vaccine, which the sponsors have also provided, we have eliminated perhaps an awful lot of the wild disease that would have contributed to part of this problem.

So I think to me the data do support the use of the vaccine very clearly in individuals over 60. I think there were strong suggestions that it probably does lower not only the incidence, but probably also somewhat the severity of the disease in individuals over 70. And I think even though at times the data suggests a minimal effect, I think that could have major public health consequences, even with the minimal effect. So I would support the use of the vaccine in individuals over 60, at this point.

We need to proceed to the second question and I think, at this time, what I would suggest we do is at the time I polled the Committee at this point, I would -- if you have additional questions that you want to address under Question 3, I would make that

point at this time. If there is any further or last minute clarifications that you think should be brought out by either the FDA or the sponsors, we'll take that at this time as well.

And we ended with Dr. Markovitz and we'll start with him on this one. The second question being "Are the available data adequate to support the safety of ZOSTAVAX when administered to persons greater than 50 years of age? If not, what additional information should be provided?"

MEMBER MARKOVITZ: Well, the simple answer for me would be yes, again, talking about really over 60. Although, there are some pretty decent safety data for over 50. So I guess here we could even say over 50. I am a little concerned about various follow-up issues that have been raised and the statistical issues that have been raised. Although, I think I would probably defer to my more statistically sophisticated colleagues to talk about that more.

So my overall answer is yes, I think the safety data are okay. The second question you raised,

Gary, in terms of Question No. 3, "What else do we need?" I think it's obvious we need 50 to 59. We need more data on the more elderly. As I mentioned before, I wonder if really one dose is really the optimal way to proceed with this vaccine or one might be better off with two in the long run.

And then the obvious thing is the people who suffer the most clinically with zoster are obviously people who are immunosuppressed, people on steroids, people with HIV. For these people, this problem is a disaster. Not to downplay the problems with an otherwise healthy person, zoster is an awful disease in those people, too. But I think we clearly need data on the immunocompromised and I don't mean just minor impairments, but truly immunocompromised people.

CHAIRMAN OVERTURF: Dr. Farley?

MEMBER FARLEY: In terms of No. 2, I'm satisfied with the safety data as presented for those 60 and older, of course, not for -- and I'm not for those under 60. Just a couple of comments on No. 3. I'm actually -- I have much less concern about the

Subgroup A in that I think these people may get a benefit. It's possible it may be a little less beneficial. These patients may be -- because of their co-morbidities might respond a little less, but they also because of who they are and where they are living, their life span may be shorter than those who were in this study.

So I'm not all that concerned about expanding or generalizing or at least making it available to those in the Subgroup A. I think Subgroup B will need some very careful attention in terms of post-licensure studies that would assure the safety of the use in that group. I think that it would be to our collective benefit for us to really be establishing good monitoring systems for and in an active way and this isn't necessarily all driven by the sponsor, but also by CDC and elsewhere, active surveillance for herpes zoster.

I think it is important from the standpoint that we have now, you know, generation coming along without wild type disease, without native disease, that are vaccine protected, never had chicken

pox, where will they go with zoster, and those who would have been boosted by that, the elderly and then introducing this vaccine, all of these things are going to be a complex mixture to be studied and that we need to have a system that accurately assesses it in the best way possible with the best tools.

And let's see, I think I'll close at that.

CHAIRMAN OVERTURF: Dr. Hetherington?

DR. HETHERINGTON: I think I would put a qualified yes on the adequacy of the safety data. There are a couple of issues that I'm still wrestling with and I hope that the FDA will drill down on these as they complete their review. What is the dependence upon recall, patient diaries for the collective safety data? And the second is the use of the subset. While we were told it was comparable to the general population in the study, we weren't shown the data. It wasn't shared. And there may be some subtle differences that may need to be explored a little bit more. And again, I hope that the FDA will take that into account during their review.

The presentation of the safety data, I

think, was somewhat limited, but on the top line looked fairly reasonable. For Question No. 3, I'm just going to pick on two issues. One is interaction studies with other vaccines and I believe the sponsor showed that they were planning on doing a study to look at the interaction between flu vaccine and this vaccine. And I think that will be critically important.

The second, I think, would be Part A under 3 and that is the use of vaccines in persons, particularly those who are residing in assisted living situations or nursing homes. While in this population you didn't see any of the vaccine strain appearing, any herpes zoster, perhaps that would not be the case in somebody in more of a debilitated state, somebody who was on some sort of chronic immunosuppressive therapy and in a nursing home setting. There may be the potential that the vaccine strain could be spread cutaneously. So these are the things that I think that the postmarketing pharmacovigilance study would need to address.

CHAIRMAN OVERTURF: Okay. Dr. Royal?

MEMBER ROYAL: I would also say that the data as presented does to a limited extent support the safety of the vaccine and individuals greater than age 50 years. Although the data in the younger age group could be a bit stronger, I do feel that it's good enough, at this point. I would also like to recommend that the sponsor consider looking at a group of patients that can provide information that's more generalizable to the general population by looking at individuals with chronic conditions, not necessarily chronic, immunosuppressive conditions.

I also feel that it would take a more special look at that group. And also to keep in mind the fact that even within the VA population that there is a fair amount of variability in the care that's given, given the fact that many veterans don't use the VA as their only point of care.

CHAIRMAN OVERTURF: Dr. Wharton?

DR. WHARTON: As written, as the question is written, I don't believe you have all the data adequate to support the safety in persons 50 years of age and older. Although, I would give a qualified yes

for persons 60 years of age and older. I'm still troubled by the fact that there were information on 7 percent of vaccine recipients were obtained more than 60 days out and I'm concerned about the ability to adequately ascertain safety information with information apparently obtained late.

That said, the information such as it was didn't suggest any safety-related problems. However, as the vaccine is -- assuming the vaccine is licensed and is introduced into general use in the elderly, there will be, I suspect, large numbers of frail elderly people with many co-morbid conditions who will be vaccinated. And it's clear that information is needed on the vaccine used in the more general population of the elderly.

And I remain concerned that safety issues will arise which may have nothing at all to do with the vaccine and maybe have to do with the underlying health status of those persons, that there will need to be a population laboratory so that those questions can be answered in a way that is efficient and can rapidly resolve the issues. And clearly, duration of

immunity will need to be addressed as well.

CHAIRMAN OVERTURF: Dr. Gellin?

DR. GELLIN: Again, as written, I don't think there is sufficient data in that 50 to 59 year-old group to answer the question overall and I won't get into the subgroup analysis. Although, I want to comment that I felt that the safety data was otherwise sufficient. On a tangential note, I had by serendipity over the past several years have met many people who have been involved in this study and I would encourage the sponsors to in some way capture the information that happened here today and report back to the volunteers who may read about what happened here today in a different light.

And I think that also speaks to these incredibly large studies and more and more people are involved in these studies. We want to make sure that people continue to want to participate in such studies.

CHAIRMAN OVERTURF: Dr. Rowbotham?

DR. ROWBOTHAM: With regard to this question, I think I would like to just point out that

the 009 study had only 185 subjects between the age of 50 and 59. And I don't think that's enough to say that's adequate safety data when the target population in the overall U.S. population is many, many millions.

For patients over the age of 60 though, I think the Shingles Prevention Study, which is really a landmark for those of us who work primarily in the pain area, is adequate to suggest that the safety is quite good, especially given the potential benefits in that age group. Through post-licensure studies, I do have a couple of comments.

I think a very good postmarketing study would be to examine patients who are living in assisted living or nursing homes. And that's a particularly difficult group to manage. If they do develop shingles, their communication abilities may be quite impaired. They may be cognitively impaired. They can't tolerate any of the more aggressive invasive injection procedures, like epidural injections that can be used in younger patients or healthier patients.

They tend to do spectacularly bad on

sedating drugs like some of the anticonvulsants and the opiates, so this is a group that's really tailor made for a preventive type treatment like the vaccine. It's important to get this information on patients with chronic immunosuppressive therapies, probably in a progressive approach with those -- starting with those who are the least immunologically impaired and then going on steadily into more and more impaired groups.

The persons with HIV infection actually offer a ready model there, because you can look at the T-cell counts and state the severity of immune system damage in that disorder. So there was an interest in looking in that particular population. You could start with HIV-positive patients who have the least damage to their immune system with a treatment like this before going on to the more severely impaired ones and that certain group that's very high risk for zoster and also has quite a high incidence of postherpetic neuralgia.

The duration of immunity as has been mentioned quite a bit, I think, is the major factor

limiting discussion of the utility of this in patients between 50 and 59.

CHAIRMAN OVERTURF: Dr. Scharfstein?

DR. SCHARFSTEIN: For Question 2, I feel that there is data for subjects over 60 years of age to support the safety of the vaccine, although I have some concerns about seeing the data with regard to the comparability of the set of people who were followed in the AE Monitoring Study and the rest of the study population, as well as the uniformity of follow-up for safety information in the study.

In terms of Question No. 3, it seems to me that A, B and D, we didn't have a lot of data on those, so it's hard to comment. In terms of C, in terms of the vaccine greater or equal to 80 years, there wasn't a tremendous amount of data to support. There was some data, but not a tremendous amount of data for over 80. And we haven't seen the pharmacovigilance plan, but I would support active surveillance if the vaccine was approved. And I also have some concerns about generalizability as this was a predominantly white population that was studied.

CHAIRMAN OVERTURF: Dr. Word?

MEMBER WORD: In terms of the available safety data, I think if you were looking at over 60, I think I would be in agreement with everyone else. I think when it comes to the 50 to 60 year-old age group, as has been pointed out, while the study seemed like it was reasonable, you have a very small number in that population.

In terms of additional studies, I think Dr. Hetherington mentioned one already when he talked about co-administration. He mentioned the -- the sponsor mentioned influenza. One of the other things that has been suggested during the age range, that they should have gotten pneumococcal and you may also look at DTaP, even though it's not been formally recommended, I think ultimately it will be for that age group for adults as opposed to just plain TD.

I guess the other question I wasn't sure of was in the pharmacovigilance plan, it talked about identification, some identification program, I'm not quite sure what that is, in terms of being able to identify, I guess, the vaccine versus wild type virus,

but I don't know how you are going to disseminate that. And the other thing that just struck me as odd is that you're looking at targeting a group that is over 50 and you have a Pregnancy Registry. So I don't know if that was just a carryover from the other vaccine, but it just seemed a little odd that that was in there.

CHAIRMAN OVERTURF: Dr. Fleming?

DR. FLEMING: Whenever I answer the safety issue, I always view this as an answer in the context of benefit to risk. So I always think of what is acceptable safety based on what is the level of efficacy. With that in mind, just very quickly again, my view is efficacy essentially is established in the 60 to 80 range. We don't have data in the 50 year-olds and in those above 80, HZ incidence was only minimally effected and BOI and PHN levels didn't meet target.

So the efficacy, as I see it, is in 60 to 80 year-olds where in that range throughout there is HZ incidence data that is persuasive. Although, only in the 70s is there evidence of added severity-by-

duration beyond the incidence. So with that as background, I'll just very briefly say that the safety data in the 50s, like the efficacy data, is lacking. Although it was interesting to me to look at the sponsor's slide 74 where there was more safety events that were occurring in the 50s than above 50. That was an interesting observation.

So drilling down on the safety in 60 to 80 year-olds, one thing that I noted was the SAE rate is relatively 60 percent higher in this cohort. And, in fact, in the 70s it's relatively 80 percent higher. That translates by my calculation into something on the order of about six SAE events per thousand people. And I put that in contrast with six HZ events prevented and one PHN event prevented, although that is an extension. That will extend over each year in the future.

So my sense about this is that based on what is known in the safety domain, the overall benefit to risk does appear to be favorable in the 60 to 80 year-olds. I remain somewhat uncertain and specifically again refer to the FDA's summary slide 83

saying "Completeness of safety ATRS and study termination follow-up is unclear." I, obviously, believe that it's going to be important for the FDA to be as confident about the completeness of this evidence as possible.

I am suspecting that when that assessment is final, that the overall sense in the 60 to 80 year-olds would be that benefit to risk is favorable. As it relates to Question -- as far as Question No. 3 is concerned and Parts A, B and C, I'll reiterate what I had mentioned before. I don't look at this just as postmarketing. I look at this as premarketing. There are categories of patients here that I would be concerned if they were included in the label.

Those that are 50 to 60, those with co-morbidities on chronic immunosuppressives and, in fact, because of the lack of benefit, those that are above age 80. Therefore, I would hope to see studies done even before marketing that would enlighten us much more clearly about benefit to risk in those categories.

In blacks and Hispanics it is

disappointing how limited the evidence is. I would urge the FDA to carefully consider that evidence. I'm stopping short of saying those categories shouldn't be included in the label, but I'm disappointed at the limited amount of information we have there and would want the FDA to look carefully at what information exists.

Regarding duration of immunity, let me just step back and first as an aside make the point that the nature of evidence that has been presented to us, for example, that was on the sponsor slide 62, indicates that ELISA titers and ELISPOT counts are correlated with the level of risk. That is what we, in fact, know.

The sponsor used orally the terminology "they are correlates of protection," and on their slides said it's correlated with efficacy. Those latter two terms convey knowledge of causality. The kind of data that is available doesn't establish causality. It simply establishes a statistical association or a correlation and I have been arguing since 1990 on this Committee.

I would prefer that we state what we know with data such as this, and that is that this evidence is correlated with level of risk rather than calling it correlates of protection or correlations with efficacy, the latter of which suggests causality has been established.

Let me though finish on a positive note. I would like to congratulate the sponsor for conducting a clinical endpoint trial not just an immunogenicity study. Therefore, as it relates to question 3(d), duration of immunity, I think we can trump the answer to the question "Is there evidence of duration of immunity?" by saying the sponsor has established over three to four years of follow-up that there is durable efficacy, and that to me is more impressive than the answer "Is there durability of immunity?"

CHAIRMAN OVERTURF: Dr. Karron?

MEMBER KARRON: So I would say that in terms of data to support the safety of ZOSTAVAX in 50 to 60 year-olds, I don't think there is adequate data. I do think there is adequate data for those over 60.

I do share some of Dr. Wharton's concerns about that missing 7 percent and that number is a bit flexible, but whatever that is, and I would at least encourage the sponsor to get to the FDA some of those demographic data to assure us that those missing individuals are not different from those for whom they were able to get data.

In regard to question 3, I don't think I will make any additional comments, except that I did want to focus on that group over 80 and a comment that Dr. Overturf made at the end of the last question, which is that I think we should not under-estimate the morbidity in that age group, in the very elderly, and that we might want to use a vaccine in that age group that has less efficacy.

I mean, ideally, there would be a vaccine that had sustained efficacy over all age ranges, but that a vaccine even with lower efficacy in that age group might still provide a substantial public health benefit.

CHAIRMAN OVERTURF: I don't think I have anything to add. I think all the questions have been

added. I also, based on what I have said previously, don't feel there is enough data to support. Although it suggests and I actually would like to believe that there is safety for the 59 year-old age group, I don't think there is sufficient data to support that.

I have been asked by the FDA to poll the Committee one more time and I don't want a lot of discussion, and I'm going to ask the same question and all I want you to answer is yes or no as to the answer about 60 versus 50 to 59. So I would first ask you again.

I think I have this recorded, but I think they want it on tape. So I would like to ask you first. You can actually ask both questions. I will ask you both questions. The first one is about safety and the second one is about efficacy for the -- specifically, if we rephrased all these questions for the 60, greater than 60 year-old age group. I think I heard one person in support of adequate data for safety for 60, maybe two.

So if I could have you -- I will poll this one more time. Let's go with Dr. Markovitz first.

Safety and efficacy for those over 60 years-old?

MEMBER MARKOVITZ: Right. I vote yes, there is efficacy and yes, there are safety data to support licensing this in those 60 and above.

CHAIRMAN OVERTURF: Okay. Dr. Farley?

MEMBER FARLEY: Let me just clarify. Is it efficacy against herpes zoster? Are we keeping it simple?

CHAIRMAN OVERTURF: We're keeping it simple.

DR. FLEMING: But how can we keep it simple? I mean, we have just gone through two hours of clarifying that these aren't yes/no answers.

CHAIRMAN OVERTURF: No, I agree.

MEMBER FARLEY: But it would be if it's herpes zoster for me at least, and my answer for 60 and older for efficacy against herpes zoster, yes, and for safety, yes, given the caveat of making sure the data is fully shared and nothing new comes up.

CHAIRMAN OVERTURF: Dr. Hetherington?

DR. HETHERINGTON: Yes. I would vote yes on both safety and efficacy in the greater than 60

year-old group.

CHAIRMAN OVERTURF: Dr. Royal?

MEMBER ROYAL: I would vote yes to efficacy and safety in the 60 year and above age group.

CHAIRMAN OVERTURF: Dr. Wharton?

DR. WHARTON: Yes on efficacy for prevention of herpes zoster, a qualified yes on safety with the reservations I expressed earlier.

CHAIRMAN OVERTURF: Dr. Gellin?

DR. GELLIN: For zoster, yes, for both efficacy and safety.

CHAIRMAN OVERTURF: Yes?

DR. ROWBOTHAM: Yes on both safety and efficacy.

DR. SCHARFSTEIN: Yes on efficacy for preventing herpes zoster and yes on safety provided -- with the additional caveat.

CHAIRMAN OVERTURF: Okay. Dr. Word?

MEMBER WORD: Yes on both safety and efficacy.

CHAIRMAN OVERTURF: Let's try you, Dr.

Fleming.

DR. FLEMING: I think I have nothing to add, i.e., a qualified yes on efficacy and safety with in-depth discussion of the qualifications already being on record.

MEMBER KARRON: Yes on safety, yes on efficacy with the qualifications on safety expressed previously.

CHAIRMAN OVERTURF: Now, I think that was -- and I also would vote yes on safety and efficacy for those over 60. I don't know if I dare ask this, but are there any further comments or discussion that the Committee would like to put forth at this point, any Members? Yes, Dr. Wharton?

DR. WHARTON: Thank you to the FDA staff for all their work, as well as that of the sponsor for putting this on today.

CHAIRMAN OVERTURF: I think with that, we will adjourn the meeting. Thank you very much.

(Whereupon, the meeting was concluded at 4:01 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/CBER

Date: December 15, 2005

Place: Bethesda, Maryland

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