in essence, of this burden of illness beyond the actual reduction in incidence of herpes zoster cases.

What is your statistical test here that you're using? Is it one that, in fact, exaggerates emphasis of the right hand tail and how do you justify that you have integrity of randomization since it appears this is an initial analysis?

DR. SILBER: Sure. Okay. I would like to call Dr. Chan, our biostatistician, to talk about the statistical methodology here.

DR. CHAN: So the question is relating to the supplementary analysis result, the severe duration among zoster cases as shown in slide 52. First of all, all the pre-specified analysis would support the indication based on the intention-to-treat analysis. So we did this pre-specified analysis just as a way to quantify the -- a second component about the duration of pain. And this, obviously, was done based on post-randomization comparative --

DR. FLEMING: What's your test statistic?

DR. CHAN: The test is based on a normal approximation stratified by age based on comparing the

mean between the two groups. And in that comparison, we also adjust for the age between the two groups.

DR. FLEMING: And how do you address the fact that this is not based on all people? This is based on a conditional sub-cohort of people that, in fact, had diagnosis of HZ. Integrity of randomization doesn't hold here. What's the validity of your P-value?

DR. CHAN: That's true. So what we have done is also done a couple of the sensitivity analyses that, one, are based on the bootstrapping techniques and that sort of doesn't take into account the distribution of some things.

DR. FLEMING: Well, that doesn't address the issue of integrity of randomization. Dan, did you want to comment?

DR. SCHARFSTEIN: Do you have data showing the --

CHAIRMAN OVERTURF: Please, identify yourself and use the mike.

DR. SCHARFSTEIN: Sorry. Do you have data presenting the demographic characteristics or health

status characteristics of these two groups?

DR. CHAN: Yes, we --

DR. SCHARFSTEIN: So you can present?

DR. CHAN: Yes. The question is whether we have demographic data about the zoster cases and we do.

CHAIRMAN OVERTURF: I'm going to ask that we suspend discussion after he answers this question. If you want to wait until this afternoon when we have time to address it, that would be fine.

DR. SCHARFSTEIN: Yes.

DR. CHAN: Can we -- can I have slide 1015? This slide shows the demographic characteristics by trimming group among the zoster cases that developed. And as you can see, there is slight imbalance in the age distribution between the two vaccine groups. Apart from there, all the other characteristics are very similar across the trimming group. And one thing to know, obviously, the age imbalance, actually what you can see is there are about 61 percent of older individuals in the vaccine group that have zoster compared to 48 percent.

So that in effect, there is actually in the comparison that was performed that is reflected in the other slide that comparison takes into account the age differential in there.

DR. SCHARFSTEIN: Are there other clinically relevant factors that you are not including on this slide that could explain differences between populations?

DR. CHAN: The questions are there in the clinical characteristics.

DR. SCHARFSTEIN: But relevant characteristics you're not including on this slide that could explain differences between these two cohorts.

DR. CHAN: We haven't identified any other characteristics that are different between the two groups.

DR. SCHARFSTEIN: Can I just ask one more important question about this? I'm sorry. You considered cases as being evaluable or non-evaluable. The rate at which you considered cases as being non-evaluable was much higher in the ZOSTAVAX group as

opposed to the placebo arm. Can you explain?

DR. CHAN: Yes. For that question, I would probably turn to Dr. Silber.

DR. SILBER: Now, this question relates to the rate of non-evaluable or cases that were not found to be evaluable cases of herpes zoster in the Shingles Prevention Study. And I think that it would be useful to turn quickly to slide 45, please. What one sees is that the fraction of cases that turned out not to be herpes zoster is the same in the two groups if one uses as the denominator the entire population who would come in with anything.

The ones who develop suspected herpes zoster, in fact, were more likely to be in the placebo group than in the vaccine group. So the fact that the rate of non-evaluability is higher in the vaccine group reflects the smaller denominator, because the vaccine was, in fact, efficacious.

CHAIRMAN OVERTURF: I'm going to ask that we go ahead and take a break, because we're a little bit limited on time, I ask everybody to be back at 15 minutes after the hour for the FDA presentation.

Thank you.

(Whereupon, at 11:09 a.m. a recess until 11:24 a.m.)

CHAIRMAN OVERTURF: I would like to ask the Committee Members to, please, take their seats, members of the audience, sponsors, please. Dr. Rohan will provide the FDA presentation.

DR. ROHAN: Good morning again. I would like to just give you a brief overview of my presentation. We will discuss the proposed indication, a little bit about the introduction and background behind this disease, the ZOSTAVAX Clinical Development Program and particularly we will discuss Protocol 004, the pivotal study and Protocol 009, finish with a summary and then presentation of the questions, which will be discussed later today.

I'm going to kind of skip over some of the slides, Dr. Gutsch, Dr. Silber did a great job in presenting a lot of the background, the indication as well, and just point out that, you know, the very serious problem with postherpetic neuralgia, the pain that can be debilitating and it can last for months or

a year or longer, particularly in the oldest age cohorts and that pain control may often be inadequate in those with the most severe cases and there may be complications or side effects from the treatments as well.

VARIVAX was licensed in 1995 and I might be able to answer some of the questions here, but I know that we have some CDC colleagues as well present in the audience. By 2003, the United States had achieved an 85 percent vaccination rate nationwide in the population for whom this vaccine is recommended. At the same time, CDC had been monitoring varicella zoster virus disease and had seen a decrease of primary varicella infections over that same period by, approximately, 85 percent.

And I would like to point out that the epidemiology of this disease may be changing and that future adult populations, these young people that are coming up that have had vaccination and we don't have circulating varicella zoster vaccine, chicken pox, out there, they may be relying on vaccination for protection from primary VZV infection.

In addition, the CDC has been interested in rates of herpes zoster. Again, we discussed earlier that there is a concern that if circulating varicella zoster virus is not out there in the community, we may see some impact on the HZ incidence as well as its manifestations. We saw that from 1999 to 2003, age standardized rates for overall herpes zoster have increased in the adult population and that upward trends in both the crude and adjusted rates were both statistically significant with P-values of less than .001 in specifically the 25 to 44 year age group and the 65 year and older age groups.

And this is from Dr. Yih and Dr. Seward, who I believe is here today, too. This is just a schematic you've seen before that older age groups have higher rates. This is a bar graph of some of the data that Merck presented earlier. I'm showing the large number of elderly subjects with pain with duration of at least one year or 6 to 12 months, 1 to 6 months and at least one month. And I would say that, you know, this data is derived from a study that was published, it was noted earlier, in 1957. And I

don't think you will see this high rate of pain with long duration from the studies that we will be discussing later.

This is an overview of the ZOSTAVAX clinical development. As I mentioned, VARIVAX was licensed in 1995. Lydick published an article in 1995 comparing subjective responses to area under the curve based on the brief pain inventory measure. The ZOSTAVAX IND was actually submitted in the fall of 1996. The last vaccination in the pivotal study Protocol 004 was administered in September of 2003.

The last case of herpes zoster was accrued in that pivotal study in the fall of 2003. We would note that the PHN definition was changed from at least 30 days to at least 90 days in December of 2003. Protocol 004 was completed in April of 2004. The incidence of herpes zoster, the duration of herpes zoster pain and the interference, significant interference with activities of daily living were all endpoints that were elevated from tertiary to secondary endpoints and success criteria were provided in June of '04.

Protocol 009 was completed in June of '04. The publication validating the use of the HZ BOI instrument was published in August of 2004. And in April of this year, the ZOSTAVAX BLA was submitted. This is a comparison of the dose ranges for VARIVAX, which is licensed for primary infection versus ZOSTAVAX. A summary of the clinical trials that are included in the BLA and again the focus will be on the pivotal study, 004. That's the study that has efficacy data.

I can probably go through this quickly, but the Committee can stop me if I'm going too quickly to try to not be too redundant with the previous speakers. The primary objectives were to reduce the incidence and severity of herpes zoster in those at least 60 years of age as measured by the BOI and to reduce the incidence of PHN.

Secondary objectives included reduction in the incidence of herpes zoster, reduction in the duration of HZ pain and reduction in interference with activities of daily living in subjects with HZ.

The ZBPI was published, as I mentioned, in

2004. It was based on 121 subjects who were enrolled within 14 days of the onset of their rash and showed that the ZBPI severity duration associated with severity duration as measured by ADLI and worsening of quality of life measurements, also that a score of at least 3 on a 10 point scale occurring at 90 days or more after the HZ rash had high agreement with pain worse than mild using a modification of the present pain intensity scale taken from the McGill Pain Questionnaire.

As you can see, there were nearly equal randomization in the older and younger age cohorts. Although, the majority in the older age cohorts were in the younger range of that, 70 and above. There were 12 clinical lots. Nine were accelerated-aged to mimic end-expiry potency.

Pertinent exclusion criteria included any subject that had more than intermittent use of topical or inhaled corticosteroids, life-expectancy less than five years, bed-ridden or homebound, cognitive impairments or severe hearing loss and those two latter criteria were not specifically defined and

weren't specifically measured or tested.

This is to point out that this study employed the 12 clinical lots. When you entered the study, you weren't necessarily randomized to one of the 12 lots. They were ruled out in sort of a dose de-escalation fashion, if you will. However, I would point out that the group 2, 3 and 4, which each include three of the clinical lots, these were the accelerated-aged.

We don't really know how the parental lot and the aged lot compare. So by saying that the nominal potency was 50,000 to 62,000 PFUs in group 1 versus 21,000 to 26,000 in group 4, we don't know whether the effect of what the parental lot was measured at may have an impact, because these are measuring live virus, but there is also a proportion of no longer living virus in the lots.

You can also see that the follow-up time is different. That the number of subjects enrolled in each of these different sort of dose ranges are different. The CMI was combined to the last group 3 and group 4. And there were different proportions of

subjects in each of these groups across the dose ranges enrolled into the Adverse Event Monitoring Substudy as well.

We talked about the vaccine report card, the automated telephone response system. We also talked a little bit about the HZ rash onset, which then triggered additional follow-up, immunogenicity and other test instruments, particularly the IZIQ and ZBPI, which measured the pain severity, which was used to calculate the BOI.

We talked about the populations used and analyses as well. I would point out that one of the very nice aspects of the study is that all potential HZ cases were evaluated by the Clinical Evaluation Committee and then the analyses were compared using these different populations and that the results were very similar. So that subjects that were evaluated and determined to have HZ by clinical laboratory methods, PCR or culture, were also evaluated in a blinded fashion by the CDC and the results were really quite similar.

We can see that the groups were balanced

in terms of gender, race and age, although it says previously mentioned, there are very few non-white subjects in this group, in this study. There was a high proportion of follow-up. Only 0.3 percent and 0.2 percent respectively of the subjects were lost to follow-up at the end of an average of three years of follow-up.

The PCR detected not only wild type VZV, but it also could detect the Oka/Merck attenuated strain in the vaccine and HSV. And as previously was mentioned, no Oka/Merck attenuated strain was isolated from any of the lesions in this study. You can see that the majority of the cases that were determined to be evaluable HZ were determined by PCR and very few by viral culture and the remainder by the Adjudication Committee.

The co-primary endpoint, co-primary is used in the study not meaning as might be thought that you would have to win on both endpoints. It's really an alternative endpoint so that you could win on this endpoint or you could win on the other co-primary endpoint and the study would be declared a success.

There was a decrease in the HZ burden of illness of 61.1 percent in the ZOSTAVAX group. There was a decrease in incidence of PHN of 66.5 percent in the ZOSTAVAX group. And as I pointed out, the definition of PHN was changed after the last HZ case. The secondary endpoints included a decrease in incidence of HZ of 51.3 percent. And this endpoint was elevated from a tertiary to a secondary endpoint after the last HZ case was approved, but prior to formal unblinding.

The duration of clinically significant pain was found to be 20 days in the vaccine group. 22 days in the placebo. It was using clinical scores of at least 3 on a 0-to-10 point pain scale. The P-value was less than 0.001 in the MITT group overall. The P-value was 0.041 in evaluable cases only. And again, this was an endpoint that was a tertiary endpoint, but was elevated to a secondary endpoint after the last case of HZ, but prior to formal unblinding.

And this is a statement from the Clinical Study Report and I think this to me sums up the issues, the impact, all the endpoints. This is

related to the secondary endpoint substantial interference with activities of daily living or SADLI. "Because Substantial ADLI can only occur among HZ cases, the benefit of vaccination in reducing the incidence of Substantial ADLI was confounded by the benefit of vaccination in reducing HZ incidence."

As you can see, the rates were 36.2 percent in the ZOSTAVAX group versus 39.4 percent in the placebo group with an 8.2 percent reduction beyond the reduction in HZ incidence with a non-significant P-value. And as I mentioned in the last slide, this is the one endpoint that does not include the impact of HZ incidence on the vaccine effect of this endpoint. It was also elevated from tertiary to secondary endpoint after the last HZ case was accrued.

The sponsor did a number of sensitivity analyses and modeling very nice to develop more information about something we don't know enough about yet. And as you can see, the thing that stands out is that age is the big factor in the severity-by-duration scores. Obviously, analgesic use, but that's sort of not considered causal and that the vaccine versus the

placebo group had a significant P-value as well.

There was a question about immunosuppression in the two groups. And as you can see, they were fairly well-balanced as far as difference, causes of potential immunosuppression. I think if you look at the rates at the top, this is sort of the flip side, the issue with looking at rates when you already have a big difference in the incidence of HZ. You have a higher rate of subjects that are immunosuppressed getting zoster, herpes zoster in the ZOSTAVAX group. It doesn't mean that the vaccine is causing that, it's just that you have fewer cases, so the rate is higher in this case, in this group.

This is a table showing some analyses by the sponsor looking at the efficacy for the major endpoint of HZ BOI by year. And, obviously, up to the first year, the subjects aren't randomized, but you can see that there is a decrease in the differential between the placebo and the ZOSTAVAX groups over time. You can also see that after year three, year four, half of the subjects are no longer in the population

and the follow-up is maybe about half a year or a little over half a year. And then in the fifth year, there are even relatively fewer subjects and even relatively less follow-up.

You can see with PHN again a decrease over time in the comparison between the two groups for this endpoint. And finally, you can see HZ efficacy, which was the secondary endpoint, you see a decrease after the first year, but then it seems to not be dropping, just from a non-statistician's perspective, as much as the others.

This is a somewhat truncated summary of the mean worst pain in both of the groups over time. And you can see that the numbers are fairly similar. On day one, the rash onset there are not too many subjects in that group relative to the other time points. Most people were seen relatively rapidly after the onset of their rash. But you can see that day 2, 3, 4, 5, 9 to 11, week 4, 6, 8, 12, 16 and 26, there are not huge differences on that 10 point pain scale.

This is looking at the effect of age on

efficacy. We can see that there is some decrease in the 70 and above age group in terms of the BOI endpoint. The incidence of PHN is similar, but the incidence of HZ appears much lower in the group that's 70 years of age and older.

FDA did a number of exploratory analyses. We wanted to try to see if we could understand further this difference in the incidence of HZ efficacy endpoint. And this is exploratory and the numbers as you get into the oldest ranges are very small, but you see a consistent decrease, a trend towards decreasing efficacy as you increase age.

We also looked at the major endpoints looking at the impact of the vaccine beyond its affect on the incidence of herpes zoster. The median HZ BOI score among the HZ cases were fairly similar and didn't appear to be statistically significant. The percent of HZ cases with PHN slightly higher in the placebo group, but did not appear significant. And the duration of clinically significant pain did not appear significant, either.

This is a graph looking at the rates of

the BOI among the HZ cases, not the rates, excuse me. And you can see that among cases those in each -- instead of looking at numbers, you are looking at proportions of subjects with HZ among each of the treatment arms and they look relatively similar.

Comparison of the BOI between a vaccine and placebo group, I would like to point out that the median HZ BOI among the HZ cases is very similar and not significant. And using a variety of approaches, the comparison of the BOI between the placebo and ZOSTAVAX group among the HZ cases, except for the Log-Rank, the age-adjusted P-value, the other P-values don't appear significant.

Comparison of the PHN incidence between the vaccine and placebo groups, the percent of PHN among HZ cases 8.57, 12.5, this was presented in an earlier slide. And this is looking at the distribution of the BOI scores between the placebo group and the ZOSTAVAX group. To get an idea, very few people had high scores. Very few people had scores, you know, as time went on. Most of the cases resolved. So, you know, when you are looking at 90 or

120 days, you are looking at a relatively small proportion of subjects.

Comparison of the BOI among the PHN cases, you can see that the median HZ BOI among the PHN cases again is not that different and it's not statistically significant. Comparison of the BOI between the placebo and ZOSTAVAX groups among the PHN cases using a variety of approaches, the P-values, even age-adjusted, don't appear significant.

Now, I would like to switch gears and look at the immunogenicity. There was a lot of very interesting data. The sponsor used three different assays, but it didn't seem the Responder Cell Frequency or the gamma interferon ELISPOT provided any additional data, at least at this point, compared to the gpELISA. So I'm going to focus and limit my comments to the gpELISA data.

Here we can see the various -- these are the clinical lots that were -- then the data were pooled between two of each of these lots to represent the parental lot from which these age lots were derived. Then the efficacy data from the paired lots

were then combined and then compared pair-wise representing the three parental lots for the lot consistency.

No differences were seen. There were based on clinical efficacy endpoints. As well, this was not part of the endpoint analysis, but you can see that the geometric mean fold rises were similar between these accelerated-aged lots.

Looking at the gpELISA by HZ status, you can see that in people that developed HZ, whether you are in the ZOSTAVAX group or the placebo, the GMTs at 6 weeks were much lower than the people who did not develop HZ. Even among the placebos there is a difference in the gpELISA levels. Looking at the geometric mean fold rise from day 0 to week 6, you can see that there is a 1.7 GMFR in the ZOSTAVAX group in those subjects who didn't develop HZ and that that's much different than the GMFR seen in people that went on to develop HZ.

We then wanted to look at the GMTs that were observed and look at the risk of HZ by 6 week gpELISA titer. And as you can see, once you reach

about 400, there are very few cases. There are three. I did go back and look at those three cases and at the end of the study they were not considered to have been immunocompromised. During the study there were no adverse events reported with these subjects. So there wasn't any particular explanation, but it looks like the majority of the cases are occurring about that level, on the chart below as far as in terms of the quantitation of the gpELISA titers.

There were no clear differences in the rates of the various reported complication among the HZ cases in the treatment groups. Again, when you account for the difference in the incidence of HZ. Also, there didn't appear to be any HZ association with immunosuppression differentially seen between the two treatment groups. The absolute numbers were similar. And as was previously mentioned, there were three subjects, two placebo and one ZOSTAVAX, who developed two cases each of herpes zoster, evaluable cases, but data from the first case, data were used in the analysis.

Comparing the immune response in terms of

gpELISA in subjects who were vaccinated to people who developed HZ on study, whether they received ZOSTAVAX or placebo, if you look, the GMT 6 weeks after vaccination in the ZOSTAVAX recipients compared to the GMTs seen 6 weeks after their onset of herpes zoster rash in the two groups are quite different, as well as the GMFR.

The safety follow-up was quite a huge undertaking in such a large group. Most of the subjects were randomized and that were randomized to the two treatments were followed in the Routine Monitoring Cohort. However, a subset were in the Adverse Event Monitoring Substudy. As well, the CMI Substudy, this is really the immunogenicity subgroup, they were a subgroup of the routine monitoring. So you couldn't be in both. They were separate.

The Adverse Event Substudy, I have to watch where I'm leaning, involved 6,600 subjects who used vaccine report cards, which specifically queried for solicited adverse events on day 0 to 4, specifically queried for temperature day 0 to 21 and allowed for subjects to report other complaints on

that vaccine report card.

The automated telephone response system, which was to be conducted on or around day 42, specifically queried for the occurrence of rash, any unusual reactions, hospitalizations, disability, life-threatening events, new diagnoses of cancer, overdose of any medication. ATRS follow-up was conducted monthly for surveillance of suspected HZ and in the AE Monitoring Substudy for hospitalization.

In addition, investigators could review available medical records on or around day 42 to look for other information related to adverse events or possible herpes zoster.

The Routine Monitoring Cohort, which is the remainder of the study, basically relied on the ATRS monitoring for 42 day safety follow-up, the same questions asked as I have mentioned before, available medical records could be reviewed for adverse events or herpes zoster, and otherwise the safety monitoring in this cohort was basically passive and, as I mentioned before, the monthly ATRS monitor for HZ in this group and monitor for HZ and for hospitalizations

in the AE Monitoring Subgroup.

Looking at the day 42 ATRS data set that was submitted to us, we note that there were 38,546 subjects enrolled. However, there are only 25,613 subjects accounted for in the day 42 ATRS subsets. 66 percent of the subjects. We saw that there were 55 percent of the total cohort who called in or either called or called the ATRS as was planned by the protocol. We also see that an additional 11 percent of the total study population had data answered by the staff for the subjects into the ATRS system.

We also noted that only 9 percent of the subjects from the AE Monitoring Cohort had data included in this database. And in addition, although subjects were to have a report on or around day 42, there are subjects, there are 1,240 additional reports for subjects that already have data in this data set and the data were entered sometimes one, two, three years after the initial report.

In looking at the source and time course of reporting, you can see that most subjects called in on or around day 42 and that their reporting rates

dropped over time. After this point, we have been told that subjects -- the system was disconnected or unplugged and so subjects couldn't call in. You can see also that staff were calling for the subjects over time and that after this point, over 4,600 subjects are having data entered by the staff. This can go out two and three years afterwards for the day 42 safety reporting. In addition, you can see that some of these, not very many, are entered well before day 42.

This is a table showing the AE rates based on the vaccine report card monitoring. You can see that temperatures didn't seem to be wildly different between the two groups as far as high temperatures or even feeling like your temperature was abnormal, even if the documented temperature was less.

The statistically significant differences were seen in erythema, pain and tenderness and swelling. And I would point out those were three things that were specifically queried for on the vaccine report card. All had P-value for the difference of less than 0.001. Regarding unsolicited adverse events, I would note that there was a higher

rate of pruritus in the ZOSTAVAX group and some increase in reporting of warmth.

This is looking at systemic adverse events reported in the AE Monitoring Substudy between 0 and 42 days. And you can see that in the different body systems, they are fairly similar. Now, looking at serious adverse events, in the Routine Monitoring Cohort, the group that was more passively monitored, the large portion of the study subjects, there is a slightly higher rate of SAEs reported in the placebo versus the ZOSTAVAX group.

If you look in the Adverse Event Monitoring Substudy, there is a higher rate of serious adverse events reported in ZOSTAVAX versus placebo. And although this difference is not as marked in the younger group, it is even more notable in the older age group. The rate of deaths reported in the first 42 days were similar between the two groups.

These are the report causes of death. Obviously, things could be coded in multiple ways, so something that was coded, reported to us as a myocardial infarction sometimes it would also say

heart arrest or cardiovascular disease. So these are sort of in a hierarchial, if you will, exploratory, obviously for safety. There were similar rates of serious adverse events resulting in death in the first 42 days. The cardiovascular causes appear fairly similar.

So we didn't really see a difference as far as cause. I know that was a question that had come up earlier. But I would note that of the deaths that are reported, 26 of these are coming from the Routine Monitoring Cohort. They were more intensively monitored in that first 42 days, but not afterwards. We also had a question about hospitalization and you can see that the overall rate of hospitalization was similar and didn't seem to be a huge difference in the rate for HZ-related causes as well.

Deaths overall for the entire study period appeared similar in both age cohorts and overall. There is no information that has been submitted to date on the proportion of subjects with ATRS contact at each month overall by group and by site. And this is important in terms of safety follow-up, because the

AE Monitoring Cohort were being queried for hospitalizations. Also, "Due to the passive and inconsistent nature of the safety data collection in the Routine Monitoring Cohort from day 43 through the study end, caution should be exercised when interpreting these particular data."

Looking at the AEs that occurred at rates of at least 1 percent in either group from day 43 to study end, again we don't see huge differences in all the various body systems that were being monitored.

And now, I'm going to have a few comments on Protocol 009. The objectives, comparison of the safety and tolerability of a higher potency ZOSTAVAX vaccine with that of a lower potency dose. And also, that among adults 50 years of age and older, the higher potency ZOSTAVAX will be generally well-tolerated as compared to the lower potency of ZOSTAVAX. And I think most of this was already reviewed.

The endpoints were, the primary endpoints included the difference between the higher and the lower potency vaccine groups in the risk of

investigator-determined serious adverse experiences occurring up through day 42, postvaccination, and the other primary endpoint is that the upper bound of the 95 percent confidence interval for the incidence rate of moderate or severe injection-site pain, tenderness, soreness or swelling, composite endpoint of those events occurring on days 1 through 5 postvaccination would be higher -- in the higher potency vaccine group would be less than 21.5 percent. And this is based on the historical rate reported for PNEUMOVAX[23].

Secondary endpoints included monitoring varicella, varicella-like rashes, HZ and HZ-like rashes and fevers as well. The primary endpoints, there were no investigator-determined vaccine-related serious adverse events. The rate of the composite local adverse events in high potency group was 17.2 percent. The upper bound being 21.0, which met the pre-specified criteria that it be less than 21.5 percent.

The secondary endpoints, there were no occurrences of varicella or varicella-like rashes. The zoster or zosteriform rashes were similar in the

two groups and temperatures were similar as well. These are a listing of the serious adverse events that were reported day 0 to 42. You can see that there was one in the low potency group. There were four in the high potency group. And these two were in the lower age cohort. These two were in the 60 and above age cohort.

There were no deaths reported in comparing the injection-site reactions based on the composite endpoint. You can see that there was a higher rate in the high potency group, not surprisingly. And also that higher rates of injection-site reactions were seen in the younger cohort compared to the older cohort, but this was particularly notable in the higher potency vaccine comparing the two age ranges.

So in summary, the ZOSTAVAX issues and summary of the data. Reduction in HZ incidence is 51 percent in relatively healthy adults age 60 years and older, postvaccination. 64 percent in those 60 to 69 and 38 percent in those 70 years and older. There is a reduction in the PHN incidence of 67 percent at 90 days following HZ rash onset. There is a reduction in

the HZ BOI score of 61 percent over the six month period following HZ rash. And the effect on PHN incidence and BOI appear relatively small after accounting for the affect of the vaccine on the incidence of HZ.

In persons with HZ, there is no clear correlations seen between the reduction of BOI scores and measures of clinical benefit. For example, things like mortality, serious morbidity, hospitalization, use of pain and medication of or interference with activities of daily living. In the completeness of the safety, the ATRS and study termination follow-up is unclear at this point.

And age appears to be the strongest factor in determining vaccine effect and in an exploratory analysis, efficacy appears minimal starting in around the 75 years of age and older, which I would suspect would be the age group with potentially the largest burden of disease as far as prolonged and severe pain.

The relative increase in the rate of serious adverse events seen between day 0 and 42 in the AE Monitoring Substudy was most notable in

subjects age 70 and above. However, there was no specific pattern of serious adverse events seen. Exclusion criteria, those not expected to live at least five more years, not ambulatory, chronic use of corticosteroid use, cognitive impairment, make it difficult to draw conclusions as to the generalizability of Protocol 004 efficacy and safety analyses to a typical population aged 60 years and older.

Protocol 009, this includes a younger cohort of subjects 50 to 59 years of age, but there is no comparison of the older age strata to previous age groups based on ZOSTAVAX studies, particularly the pivotal study. The vaccine dose is four times higher than any previously studied, but again there is no comparison or bridging to the previous ZOSTAVAX studies.

The clinical relevance of the study endpoints that were chosen, the primary endpoints are not clear. And I wanted to also acknowledge there are too many people to thank that have made this project what it is, but I would like to specifically thank Dr.

Ahnn, the statistician, Dr. Pratt, Dr. Finn, who I wouldn't be here without their help, Dr. Goldenthal and Captain Matrakas.

So I would like to go back to the questions for the Committee to reiterate from earlier today. Are the available data adequate to support the efficacy of ZOSTAVAX when administered to individuals 50 years of age and older in preventing herpes zoster; in preventing postherpetic neuralgia; preventing postherpetic neuralgia beyond the effect of the prevention of herpes zoster; decreasing the burden of illness; decreasing the burden of illness beyond the effect on the prevention of herpes zoster? And, if not, what additional information should be provided?

Are the available data adequate to support the safety of ZOSTAVAX when administered to individuals 50 years of age and older? If not, what additional information should be provided?

And finally, please, identify any issues which you feel should be addressed, including post-licensure studies and, in particular, please, address the use of the vaccine in persons with co-morbid

conditions. For example, those who might typically reside in assisted residences, excuse me, assisted living residences and nursing homes; use of the vaccine among persons taking chronic immunosuppressive therapies including corticosteroids; use of the vaccine in certain subsets of the sponsor's proposed age indication, for example, those 70 years of age and older, those 80 years of age and older; the duration of immunity and the sponsor's proposed pharmacovigilance plan, which we really didn't discuss in our presentations, but we could expand on during the discussion this afternoon.

So that concludes my presentation. Thank you.

CHAIRMAN OVERTURF: Are there questions from the Committee Members for Dr. Rohan at this time? Yes?

DR. SCHARFSTEIN: The follow-up of the pain data says that it's measured day zero through 182 after the occurrence of the rash. How was that data collected and can you comment on the completeness of those data?

DR. ROHAN: Well, the sponsors might want to answer that.

DR. SCHARFSTEIN: Yes.

DR. ROHAN: Because they probably would be able to do a better job, but subjects, once they had suspected HZ, were seen. And, as I pointed out, Dr. Oxman and his colleagues did a phenomenal job in the surveillance, evaluation, treatment, determination of the HZ cases. So within usually a couple days within the onset of the rash, subjects were seen and that's like two or three days a lot of the subjects were seen.

Then they were followed. There were a couple, maybe about every several days, there were some windows for the time points that they were asked again and again how is your pain? You know, there were a number of instruments that were involved. I think in my briefing document I have a list of those.

But then they went out after the first week or two to weekly evaluations for several months, and then they went to monthly evaluations. If that's -- you know, if people had pain, they continued to

have weekly follow-up.

After day 30 if their scores fell below 3 at two consecutive time points, then they weren't followed again, but they did then have the monthly follow-up so that should they have pain that increased or recurred or occurred, then they would be captured in the area under the curve with those monthly time points and again go back to the weekly follow-up to capture the full burden of the disease.

CHAIRMAN OVERTURF: Dr. Royal?

MEMBER ROYAL: I also have a question concerning the pain data. It was said earlier that significant postherpetic pain was that which was scored as 3 or worse on the pain scale. And going back to the BOI data, if you calculate those numbers using just those patients who had that severity pain or worse, what do your comparisons show?

Also, it was stated that the frequency of neurologic complications was decreased in the immunized group. And could you speak to whether that -- what the complications were that were seen and whether there was an even decrease across that list of

complications or whether some were lower than others within the vaccinated group?

DR. ROHAN: I don't know if the sponsor wants to answer the question about the neurologic complications?

DR. SILBER: Yes, one point of clarification. The surest way to prevent a complication of herpes zoster is not to get herpes zoster. And so I think our presentation and Dr. Rohan's presentation basically said the same thing in two different ways in that there was, indeed, across the population a reduction in the neurologic and the other complications of herpes zoster.

What Dr. Rohan was presenting was that once the herpes zoster developed, the fraction of cases that went on to develop the neurologic complications was neither higher nor lower. And so the reduction in complications is from the reduction in the case outright.

DR. ROHAN: You had a second, actually your first question. Could you repeat that?

MEMBER ROYAL: It concerns the group of

patients with significant postherpetic neuralgia with pain scores of 3 or better. When one does the severity duration calculations and compares the two groups, do you see the same, especially if you take away the most severe pain duration scores?

DR. ROHAN: When you're saying when you take away the most severe pain duration scores, can you clarify?

MEMBER ROYAL: Well, a bar chart was shown of those individuals who had the most severe with the highest pain duration scores. If you take that group away and look at those who are left who had significant postherpetic neuralgia, do you see a difference between the treated and placebo groups?

DR. ROHAN: I don't know if a subset analysis, if you will, was done looking at different ranges of pain.

DR. AHNN: I think he is mentioning page 47.

DR. ROHAN: Slide 47?

DR. AHNN: Yes, slide 47. Yes, that's just the comparison of the distribution of area under

the curve only among the PHN cases. So it's -- the comparison is in a non-random subgroup, so it's hard to make any conclusion statistically, but it's just for the exploratory purpose that we just want to show the distribution of the area under the curve.

MEMBER ROYAL: Right, but --

DR. AHNN: Between the two groups.

MEMBER ROYAL: Theoretically, those values could represent individuals with low pain scores and long severity duration, so it represents a mixture.

DR. FLEMING: Can I comment on that, because I think this is an important point that I wanted to pursue as well, and I would like to walk through a few slides in progression to amplify this point.

If we start with slide 45, what we're looking at here is an alternative attempt from what the sponsor presents to get a sense about whether, given that you have an HZ case, is there a difference in the BOI? So is there a difference in severity? And while the sponsor had a P-value slightly below 01, these P-values predominantly are showing little

association or a fairly comparable balance.

Whenever you see a Log-Rank P-value lower than the other P-value, it's suggesting if there's a difference it's in the right hand tail, these are importantly rank-based analyses where the sponsor had a parametric analysis that is going to be heavily sensitive to this difference in the right hand tail.

So if you go to slide 47, what we're seeing is the difference between the FDA analysis showing really no meaningful difference in distribution and the sponsor claiming that there is, I suspect is driven by these cases here in the right hand tail.

And I suspect that it's an artifact or it's a result somewhat of the definition, because the definition if someone is 3 versus 2, but the 3 is only counted for -- the 2 for 30 days and the 3 for 180 days, then it's really giving the 2 versus 3, not a 3 to 2 weighting, but a 10 to 1 weighting. So my read on this is that the BOI really becomes tantamount to is there a difference in the fraction of people who have sustained level 3 or higher and not something

more general than that.

So if you go ahead to slide 40, the question is is there a difference in the message in BOI from the message in HZ, and the answer is at least in part. When you're below age 70 where more than half the patients were, there is no difference, but there is a suggestion that there may be, in fact, more benefit than just prevention of HZ when you're looking at those people above age 70.

Then if you could go to slide 41, what we're seeing here is there is strong evidence that there is an age effect of HZ. It dwindles as you get older. Now, to the extent that the BOI data are interpretable, and it's complicated by this oddity and the way BOI is calculated, but if you put any interpretation on it, it seems to me it's in there. Beyond preventing HZ, is there some added evidence that the most severe prolonged cases are occurring less frequently?

If you put that interpretation on from the analysis on page 40, if the answer is no, not at all in the age 59 to 69 categories, but above age 70

maybe, so could we go back to 41, could someone produce this slide for the BOI by age? If we go back a slide, you have pooled together all the people above age 70 to suggest there is some difference.

It would be interesting to see how this breaks out by half decades, next slide, as you do for the HZ. Does that slide exist?

DR. ROHAN: It doesn't exist. I also wonder whether the right hand tail is the older age group or not.

DR. FLEMING: That's exactly a rewording of my question. That's exactly what I'm trying to get at. I suspect if we go back to slide 40, that it must be predominantly at least people above age 50 -- above age 70, excuse me, because you don't see any difference between the HZ and the BOI for ages 60 to 69.

It's showing up for people above age 70. That is suggesting to me that if you go back to slide 47 that these people might be the older people. Where are they in that distribution of older people?

MEMBER ROYAL: I would still like to see

the data for those, the BOI data for those with significant postherpetic neuralgia pain only, given someone with lesser pain with longer duration would be scored equally as someone who has more severe pain and shorter duration.

DR. ROHAN: So your comment is based on this 10 point scale, scores of 3 and above were included, but your question is what about people 8, 9 and 10. Is that what you're asking?

MEMBER ROYAL: Well, this chart shows individuals with pain scores of 0-to-10. I would like to see those with pain scores from 3-to-10.

DR. SCHARFSTEIN: Can we get a figure that demonstrates the completeness of the data for day zero, you know, the evaluation times for pain and how it differs between treatments groups because I --

DR. ROHAN: I think it's small and I don't think we have analyzed it, but I think there might be some small differences, but there are small numbers of subjects in the follow-up not -- in the proportion of subjects who had follow-up for the whole 182 days, the numbers are fairly similar, but there appears to be

slightly less follow-up in the ZOSTAVAX arm in sort of the mid range versus the placebo group.

DR. SCHARFSTEIN: I think there is a lot of imputation going on here.

DR. ROHAN: Right.

DR. SCHARFSTEIN: And there is probably a fair amount of missing data along the way and then there is some impute, you know, trapping in these lines between time points and I would be interested to look at the distribution of the number of people who showed up at each visit or, you know, provided data at each of those post-rash evaluation points.

DR. ROHAN: Right. But I guess it's also sort of confounded by the design in which if you fell below a score of 3, you weren't going to be asked again the way people that had 3 or above will be asked every week until they went below for two times points. If you were below 3, you wouldn't then be asked until the next monthly, whenever that occurred, sort of protocol-mandated follow-up for everyone with PHN.

DR. SCHARFSTEIN: Right. So there is sort of structural missingness and then there is

unstructural missingness. I'm really interested in the unstructural part of that.

CHAIRMAN OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: Yes. I would like to ask some advice so we can ruminate properly over lunch. I don't know, Gary, if you want to tell us or FDA, but it seems like we're heading towards having to decide. There may be people who are in favor of 60 plus and not 50 to 60.

So one question is are we going to be able to separate those out on the vote? And then the second thing is what is the precedence for accepting an argument based on logic rather than data?

I know we have rejected things based that way, but they were going the other way, and my previous experience on the Committee was not wanting to extend things to older people, but this question of extending it to younger people is somewhat different.

And I'm wondering does the FDA or you, Gary, have anything to tell us to guide us as we think about this?

CHAIRMAN OVERTURF: I think if the

discussion this afternoon generates concern and controversy about various age groups, then I think we may need to split it out and we'll probably split the vote on that. The other issue, I would make a strong recommendation based upon the consensus of the Committee for approval of the vaccine at a given group.

Now, the other issue is that I'm not sure that there is going to be sufficient agreement also on the way the question is currently read, is it's we're actually -- the question is whether efficacy is supported by at least three parameters and I'm not sure that there is support for all those parameters. But that may not affect the discussion as much as the issue of the age. So we could get clarification of that during the lunch period. Dr. Hetherington?

DR. HETHERINGTON: One other issue that might help when we try to deliberate on that point is the persistence of immunity by age group. I realize that it's rather short in duration, what you have now, but to look at whatever data there is available.

Between the 50 and 60 year group, 60 to

70, 70 to 80, etcetera, what is the data that we have today on persistence particularly with regard to titers above 400 or 500, which was a cutoff that I think was implied in the FDA presentation, and also by geometric mean fold rise. If we had those data after lunch, that might help us a little bit.

CHAIRMAN OVERTURF: I think I'm hearing also everybody is in favor of taking a break for lunch, so we'll break for lunch at this point and reconvene at --

DR. FLEMING: Should we ask the additional questions for the FDA after lunch then?

CHAIRMAN OVERTURF: Yes. There will be time for additional questions for both the FDA and the sponsor after lunch. So we'll reconvene at 1:30.

(Whereupon, the meeting was recessed at 12:21 p.m. to reconvene at 1:33 p.m. this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:33 p.m.

CHAIRMAN OVERTURF: I would like to ask the Committee Members, members of the audience and the sponsors to, please, take their seats. I would like to call the afternoon session to order at this time. At this time, we have time slotted for an open public hearing, so I will turn the meeting over to Christine Walsh.

MS. WALSH: Good afternoon. As part of the FDA Advisory Committee Meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee.

I have not received any requests at this time. Is there anyone in the room who would like to address the Committee? I see no response. Dr. Overturf, I turn the meeting back over to you.

CHAIRMAN OVERTURF: Thank you. We'll proceed further with the FDA presentation and the questions after we give some allotted time to the

sponsors to address some of the questions that were asked this morning. So I will ask the sponsors to come forward now and address those questions.

DR. SILBER: Thank you, Mr. Chairman. I would like to just spend a few minutes touching on several points that were recurring themes in the questions this morning in the hopes of bringing some clarity and closure to them.

I would like to preface the comments by reminding the Committee that at the primary analyses on the modified intention-to-treat population of subjects enrolled, in those primary analyses for the key endpoints for support of the labeled indications that the sponsor and CBER are in agreement on the primary endpoints and where the different analyses and cuts of the data are leading to sometimes different interpretations comes on the conditional supportive analyses specifically among subjects who developed herpes zoster.

And so it's important to remember also that the burden of illness is a composite that includes the incidence and severity-by-duration. Once

incidence is removed, it's still a very clinically important issue to deal with, severity of illness or severity-by-duration or area under the curve as we call it, but we need to make sure that we don't call that burden of illness, because the way that the study was set up from the outset was with an understanding that both incidence and severity-by-duration were important clinical components of the disease.

And so with that in mind, I would like to touch on five points quickly that have come up and I would like to first address this issue of whether there was a benefit of the vaccine over and above the incidence of herpes zoster and particularly for the severe cases.

You will recall that in the presentation this morning, I showed a histogram starting with those individuals with scores greater than 600. I would like to show slide 1026 now, which uses different cut points. And so, as you see here, 600 is what we looked at this morning.

What we have now is using different cutoff scores from 400 out through 1,000, meaning with each

cut we are dealing with successively smaller subsets, but those people with the more severe cases were out at the tail. And what we see here, if we go to the right hand column, the relative reduction in the likelihood of having this high score goes steadily up as the bar gets raised. The more severe the case, the greater the percentage reduction.

So I would like to go then to 1028 because, as Dr. Fleming pointed out this morning, in the younger age cohort a lot of what we are seeing is based on incidence. In the older cohort it's the issue of pain. And so if we look specifically in the older age group, what we are dealing with here is, again, increasing benefits with the increasingly severe cutoffs. I would like to turn next to slide 654.

DR. FLEMING: These are nested, so when you say increasing benefits, what you really have is--

DR. SILBER: It's a relative reduction.

DR. FLEMING: -- a signal at the highest level and then, of course, lesser, in fact, imbalances as you then increment next down scores.

DR. SILBER: That or, alternatively, the more severe the case, yes. Okay. And in terms of the reduction in the incidence of PHN among those subjects who developed herpes zoster, what we see here is a 38.5 percent reduction. So this is among those with zoster, 38.5 percent reduction. In those 70 and older in whom the incidence of PHN is greater, it is a 47 percent reduction in the incidence of PHN among those who have developed herpes, excuse me, herpes zoster. So that is point number one.

Point number two is an issue that Dr. Fleming had raised about the scores less than 3. And in the presentation this morning I had commented on the fact that a number of sensitivity analyses had been conducted and that those were virtually identical to the primary, and so I would like to put up slide 630 which gives the sensitivity analyses on the herpes zoster burden of illness and I would like to focus specifically on the third line here, the MITT using the full AUC scale over the six month follow-up.

And, again, you see a point estimate of 61.2 percent, the same as what we had overall. It

does not address all of Dr. Fleming's points, because the frequency of follow-up was less when pain was less. Nobody was lost to follow-up, but the frequencies were different. But in terms of taking all of the scores that were obtained, there was no impact on burden of illness.

The third point that I think got lost was a question from Dr. Fleming on the 80 plus population. And we agree with Dr. Fleming that there were 2,500 subjects enrolled, which was actually a fairly sizeable population in this age group, and I would like to focus first on the efficacy in this population because there had been questions about efficacy in the older age group. So if we could start first with herpes zoster on slide 248.

We have the age stratification at 60 and 70. We have further split this out not in five year increments, but at least 60s, 70s and then 80 plus. And what we see here for the herpes zoster analysis is the 64 percent efficacy that we saw earlier today and among the individuals 70 to 79, roughly 40 percent efficacy with a lower bound of 27.6 percent.

And for those over 80, the efficacy for herpes zoster did fall to 18.3 percent, some reduction, but a confidence interval now below zero. We're dealing with a relatively small percent, again about 7 percent of the overall population, and the study was not powered to observe efficacy at this level.

But, again, as you get older it's the pain that becomes more severe and adds even more to the burden. And so if we could pull up slide 250, please, which is on the herpes zoster burden of illness, first we see that with the 61 percent overall, we have got 65.5 percent for the 60 to 69s, 59 percent, very well-preserved in the 70 to 79 group, and a point estimate of 38 percent. So still preservation on a very clinically meaningful and clinically important endpoint. Although, again with the small numbers, the confidence interval going below zero.

Lastly, on the PHN endpoint, slide 252, we have very good preservation of efficacy in the older group, 74 percent, and with increasing numbers, tight confidence intervals in the 70 to 79 group. Again,

somewhat lesser efficacy, point estimate 39 percent, with the wide confidence intervals.

So the conclusion from all of this is that whereas the incidence of disease and the prevention of the herpes zoster is the critical parameter for the younger cohort, in the older group who suffers disproportionately with severe and long-lasting pain, the vaccine's effect is strong and persists for these endpoints.

With respect to safety, there is a question that also came up, and I would like to put -- we have a question about the serious adverse experiences. So if we could get to slide S-2, please? This is the overall cohort and the split in serious adverse experiences was 27 versus 21.

In this slide we have it broken out by body system and it's a fairly symmetrical mix here. I will get to the cardiovascular in a second. The skins were a couple of skin cancers. The metabolic/nutritional were a couple of dehydrations. But, in general, for many of these serious adverse experiences it was just one in one or the other

groups.

Slide S-1 gives the specific breakdown among the cardiovascular events, so if I could get S-1. Oh, it's S-3 now. Okay. What we have here is, again, a mix of different events. There were three atrial fibrillations, three myocardial infarctions, but then there is a coronary occlusion in the other group and one MI. So it does not look as though there is any particular specific serious adverse event.

There was among the individuals 80 years of age and older one possibly vaccine-related serious adverse event. It was an 80 year-old male who developed some symptoms shortly after vaccination, was not diagnosed ultimately until about day 80 with polymyalgia rheumatica. This is a fairly common condition in older adults, often takes a long time until diagnosis, but that was the only possibly vaccine-related event in that group.

The next question is on persistence. The question on persistence came up shortly before lunch. As I had mentioned, after zoster and after vaccination, the immune markers tend to fall back

toward baseline relatively quickly and I would like to refocus the discussion for a moment on persistence of efficacy, which in the end is what we really need to be thinking about.

So if we could start with slide 704. There is an analysis in the study report that was submitted in the dossier looking at efficacy by year. We detected a drop, as I pointed out in the presentation this morning, a drop in the first year followed by steady decline. And so I'm going to be showing you some tables now showing year-on-year, but also splitting out the first year into months 1 through 6 and months 7 through 12.

So here for incidence of herpes zoster, and we'll focus ourselves on the right hand column of these slides for the vaccine efficacy, what we find is that in the first six months postvaccination an observation that will recur in the next several slides, which is 75 percent efficacy in that early time period.

In the second half of year one we're at 51 percent, which by chance was exactly the estimate that

we saw over the entire period of follow-up and, as I think you saw earlier in the day, that we have got point estimates of 47, 43, 51 throughout. So, really, from month seven on there is no indication from the trend that there was any decrease or any waning of the efficacy of the vaccine.

Now, I would like to split this out by the two age cohorts, so if we could go to 708. This is the year-by-year efficacy for herpes zoster in those 60 to 69 and you will note that there is actually no drop-off at all in this younger cohort. So this is, again, part of the 64 percent overall and persistence that we think will be predictive of vaccination in the adult population under 70.

And then for age 70 and up, slide 709, please, here we do, in fact, see a decline from year one, 60 percent efficacy, relatively flat point estimates. We're dealing with smaller cuts of the data. These confidence intervals do get wider, but at least the trend among the point estimates is for stable efficacy over time. So that is for herpes zoster.

Now, if we could turn to 714, please, and we'll get to the PHN endpoint. Again, you'll recall 66.5 percent overall, 93 percent efficacy in the first six months following vaccination. Remember, smaller numbers here, fewer cases of PHN, but again dropping somewhat in the second half of the first year. No clear pattern or suggestion that there is a waning of efficacy. Directionally, there is still a reduction in the vaccine group.

So if we could then split this out by age. 718, please. Among those less than 70 years of age, there were relatively few cases of PHN. You see very high point estimates the first two years, small numbers, 4411 thereafter, but again getting to the important point. In the older individuals, slide 719, where there is much more PHN, again very high efficacy in the first year, 83 percent, with very stable point estimates in excess of 50 percent from year two and thereafter.

Lastly, on the burden of illness, slide 724, 92 percent reduction in burden of illness over the first six months dropping to 70 percent. And,

again, you will recall the 61 percent overall. From that point forward, one sees again no indication of clear waning over time and we can cut this by age also.

Slide 727, please. Burden of illness beginning at 83 percent in the first year for the younger cohort and then the percentages as shown, again not reflecting any clear waning. And, lastly, for 70 plus, a similar pattern after year one, stable estimates at 40.

So the last point that I would like to address refers to some of the safety follow-up. There were a lot of questions about that. I would like to call back slide 36, the pie chart, from the main presentation.

You will recall a number of 66 percent that was offered by CBER, which I think reflects the green and the magenta, but the fact is that if we combine the different means of follow-up, we come back to the fact that by one or another of the methods, 93 percent of the subjects did have follow-up.

There was a comment that these staff calls

began or were clustered after day 50, and that is because the ATRS was open to the subjects until day 50. When that day came and went, the sites received faxes to inform them that the patients, the subjects, had not called ATRS. And within virtually a week or 10 days thereafter, a large majority of the calls were made to follow-up where the subjects had not.

Importantly, the information that was captured, the script that was used by the sites in their discussions with the patients, with the subjects, was exactly the script that was used from the ATRS. And so the follow-up was comprehensive and it was consistent across the population.

In terms of timing, I would like to turn to slide 407, and this is the distribution of staff calls for the routine cohorts, so these are the calls to the ATRS. You will see that it was about 13 percent of the subjects overall, but a very large majority of these happened before day 60.

And, again, these would be clustered from day 51 to day 60 because of the way the ATRS was structured, and it was a relatively small percentage

of the overall enrollment of 31,000 subjects who had any follow-up that was after day 60.

For slide 408 we have got the follow-up to the faxes and, again, you see that a large majority of these were occurring before day 60 shortly after the ATRS was turned off for the subjects, only a little over 1 percent of the subjects beyond that.

There was a question about the demographics of these people who had the later follow-up.

DR. FLEMING: Could you go back a slide just before we lose the thought?

DR. SILBER: 407, is that --

DR. FLEMING: I think it was the previous slide to this.

DR. SILBER: I'm sorry. I can't see who is even asking. Oh, okay.

DR. FLEMING: Are these to be -- basically, are the bottom five rows mutually exclusive as they appear to be and should they add up to the staff called ATRS line?

DR. SILBER: These --

DR. FLEMING: I mean, I'm sorry, into the placebo? Should the bottom five lines add up? I think they do. The percentages don't add up.

DR. SILBER: Should be.

DR. FLEMING: Okay. All right.

DR. SILBER: Should be.

DR. FLEMING: Go ahead. The percentages don't add up, but go ahead.

DR. SILBER: Maybe some rounding. Okay. There was a question about the demographics and that is still being looked at, but in terms of gender and age, and we are looking now at functional status and other health markers, we have seen no differences at all yet among any of these parameters for those who followed-up for safety in the various different ways.

The last point briefly was about opting out of the Adverse Event Monitoring Substudy and we have Dr. Levin who could speak for the Shingles Prevention Study investigators on this point.

DR. LEVIN: Dr. Silber is correct in that there was a delay until the sites got started, but once they were set and ready to go, that the patients

who were offered sequentially the opportunity to be in the substudy, they were not selected. And all I can report is in my experience and that of Dr. Oxman, who I was in close contact with, that roughly 95 percent of people accepted it at that time, and there was no bias in individuals not being in the study. Everybody who was offered it, essentially, was willing to be in it. Questions?

DR. FLEMING: You said everybody that was offered was willing to be in it?

DR. LEVIN: Well, 95 percent, and we had no reason to believe that a select group of people were choosing not to be in, but we don't --

DR. FLEMING: And that choice was made at time zero, at the very beginning?

DR. LEVIN: At the time that they were offered it.

DR. FLEMING: And remind me, that time was?

DR. LEVIN: At time zero. When they entered the larger study, they were asked if they would be willing to be in the special substudy. I'm

sorry, I can't speak for --

DR. FLEMING: And people didn't drop out beyond that point based on willingness to participate. So at time zero, 95 percent agreed to be in?

DR. LEVIN: Now, that is my experience and Dr. Oxman's. I can't speak for the other sites and we do not have records on that, but that's our perception.

DR. FLEMING: And once somebody was in, you had or you retained them for long-term safety assessments in what fraction of cases?

DR. LEVIN: They were retained the way all the other subjects were retained for the long-term assessment. Actually, they had more. They had additional follow-up and then all hospitalizations as well were reported in that specific group. They were actually looked at more carefully.

But I think your question was were they demographically different. We don't have specific records to that, but there is no reason to think that they were selectively chosen or they selectively chose to be in the substudy.

CHAIRMAN OVERTURF: We can address further questions to industry as we begin to discuss the questions, so I think I will ask the FDA to come back and re-present the questions to us again.

DR. SCHARFSTEIN: Could we ask a couple questions of -- wait?

CHAIRMAN OVERTURF: Let's wait a minute.

DR. ROHAN: Once again, questions for the Committee's consideration. No. 1. Are the available data adequate to support the efficacy of ZOSTAVAX when administered to individuals 50 years of age and older in: (a), preventing herpes zoster, (b), preventing postherpetic neuralgia, preventing postherpetic neuralgia beyond the effect on the prevention of herpes zoster, (c), decreasing the burden of illness, decreasing the burden of illness beyond the effect on the prevention of herpes zoster? If not, what additional information should be provided?

Question No. 2. Are the available data adequate to support the safety of ZOSTAVAX when administered to individuals 50 years of age and older? If not, what additional information should be

provided?

And Question 3. Please, identify any other issues that should be addressed, including post-licensure studies. In particular, please, address: (a), the use of the vaccine in persons with co-morbid conditions, for example, those who might typically reside in assisted living residences and nursing homes, (b), use of the vaccine among persons taking chronic immunosuppressive therapies, including corticosteroids, (c), use of the vaccine in certain subsets of the sponsor's proposed age indications, for example, those 70 years of age and older, those 80 years of age and older, (d), duration of immunity and, (e), the sponsor's proposed pharmacovigilance plan.

CHAIRMAN OVERTURF: So we will actually begin the discussion and, at this time, if there are additional questions that the Committee Members want to address to either the FDA or the sponsors, we have a few more minutes to do that. Dr. Markovitz?

MEMBER MARKOVITZ: Yes. I would still like to get the take of the FDA on, if there is someone who can speak to the idea when we addressed

the 50 to 60 group in lieu of data, what considerations are there from an Agency point of view, if someone can answer that.

CHAIRMAN OVERTURF: Dr. Baylor?

DR. BAYLOR: Norman Baylor, FDA. We would like you to try to address the questions based on the data presented. We really need the advice based on your interpretation of the data. I don't think you should use logic or gut feelings so, please, use the data.

CHAIRMAN OVERTURF: Yes, Dr. Word?

MEMBER WORD: I just want to go back to the issue with duration again. I know the sponsor showed a slide, but I guess one of the questions I had, you know, if you looked efficacy and they said in the 60 to 69 age range I think it was like 73 percent and maybe it dropped down to 38 percent in those older, so then I'm looking at, well, that's when it was administered at 60.

If they are proposing to administer at 50, do they anticipate that there is going to be a change, that suddenly those numbers are going to drop or is

there going to be a point where you think that do I need a booster?

And I guess the other part of the question I have is right now for individuals who are born, I think it's after 1965, the adult immunizations recommend that they all get varicella vaccine if they haven't had it. And so then do you have any information about if they receive varicella and then you want to offer them this, because they are close to that age group, what would you give them?

CHAIRMAN OVERTURF: I'll let the sponsors answer that. My own personal feeling on that issue would be that, obviously, we need data in that regard. I mean, if we -- and, actually, I don't think it's restricted to the population less than 50, because we only have data that we're being presented today that is really, essentially, a four year period.

So the issue, well, this obviously has to be part of the pharmacovigilance issue, is to continue to look at that in order to justify the vaccine. Does the --

DR. SILBER: Okay. I think I heard three

questions, so I will take them in turn.

In terms of the expectations of what might happen at the age of 50, again, for the herpes zoster incidence endpoint as we went out over time, we were at roughly 65 percent efficacy and stayed pretty much right there throughout the period of observation. With the younger individuals, younger immune system, we would expect that the durability of the response should be at least as good, let us say as good, in the 50 to 59. So 60 to 69 experience we think will be predictive in that regard.

With respect to the possible need for a booster vaccination, which I think was your second question, which is really a question whether one vaccinates at 50, at 60, at 70 or at any other age, that is not known at this time.

One of the really critical questions that we're answering or hope to answer in the persistence substudy of the Shingles Prevention Study is to take these people out to 10 years, is the target right now, and to determine whether there is any waning of efficacy at any point. Again, after the initial drop,

we have not seen that yet.

But should that happen, what could be explored certainly is to define when or if a booster is needed and then, if we use this population basically as a bellwether, then we would be able to assess the potential benefits of booster vaccination ahead of those populations who would be receiving vaccine in the general marketplace later. So we don't know but the persistence substudy, we hope, will give us that answer.

Lastly, with respect to varicella vaccination and what advice -- I think the question was what would the advice be if someone had varicella vaccine?

MEMBER WORD: Right now in the adult recommendations, now they point blank just put it in as a recommendation if you didn't have varicella or if you were born after 1965, that you have to -- to immunize them. So they are in your 50 year-old age range now.

DR. SILBER: Right, yes. And what we know from the VARIVAX experience is that the very large

majority of the cases, of the doses of VARIVAX, have been administered in childhood. We do not have -- other than as part of our booster studies, we don't have data that speak to the benefits of someone with prior varicella vaccination, but even in that these were seropositives. And so it will be some time until there will be a body of data really to be able to answer that question.

CHAIRMAN OVERTURF: Do you have a predefined signal for lack of efficacy of the vaccine in those that you continue to follow beyond? At this time, is there any predefined signal or are you simply going to --

DR. SILBER: This is something that will be looked at by annual summaries and other than a signal of a lower bound of efficacy falling below zero, there are no specific criteria at this time.

CHAIRMAN OVERTURF: Dr. Fleming?

DR. FLEMING: Could I have the FDA slide 47 which I will get to in a moment, but at least we can pull it up. My sense is you have shown us after the break now quite an array of additional slides and

I am not sure that too much of it is what we hadn't already seen.

You showed us a lot of slides on persistence of effect, which I don't think was something we were challenging as controversial. As your slides point out, in fact, your curves that you presented earlier, S-48 and S-50, were very descriptive of how effect occurred over time and did, in fact, show that it was a larger relative efficacy in the first six months. In fact, what you didn't show is it's probably even larger in the first three months and then after six months, it seems to be fairly constant.

The controversial issues are age, how is that an effect modifier for effect, and is the BOI, which is intended to look at severity-by-duration beyond incidence, telling us something beyond what just the incidence is telling us?

And what your data seem to be showing us as it relates to age is that while we had pooled ages 70 and above before, now when we're looking separately at 70 to 79 and greater than 80, there does seem to be

a gradient for PHN by age as well as for BOI. And we also see, as we had already seen before, that at age 60 to 69, the BOI relative efficacy is the same as the HZ relative efficacy.

In terms of the explanation of the BOI, I don't contest what you were showing, but it seems to be entirely consistent with what the FDA already showed in slide 47, which is that there is, in fact, the appearance of this number of people that had very high scores that are more prevalent or predominant in the placebo group.

Although, if we go to the next group that you didn't go to, then there is a bit more of those in the intervention arm, which is part of why a Log-Rank analysis is going to be a little more sensitive than a Wilcoxon analysis. I actually -- oh, go ahead.

DR. ROHAN: I wanted to make a comment at this point. We had talked about the PHN. The duration of follow-up was 182 days and there were equal proportions of the subjects followed in either the vaccine or the treatment arm out to 182 days.

But if you look at other increments in

more the mid range, and I don't have those data with me, there is some difference in the proportion of subjects being followed and I think it would be important to look at the pain scores that had been accrued at that point.

Obviously, it's in an exploratory manner, but to look at the pain scores in the subjects that were then lost to follow-up, didn't have complete follow-up, because if we see, for example, half a dozen subjects in the zoster group that don't have that sort of mid range follow-up that had scores in the hundreds and only one in the placebo group or if we see a number of subjects in the placebo group that had zero or very low scores and very few in the zoster group, that would also skew this because the vast majority of the postherpetic neuralgia cases even in the older subjects, they resolve after several weeks and a smaller proportion are carried out --

DR. FLEMING: Right, yes.

DR. ROHAN: -- to 60 or 90 days.

DR. FLEMING: Yes. Could you go to slide, your slide, 68, FDA slide 68? You did answer one of

the questions I had asked the sponsor this morning and that is to give us information on hospitalization and HZ-related hospitalization.

DR. ROHAN: This is the sponsor's data though, I will point out.

DR. FLEMING: Okay. But you showed it so I'm asking you about it. It's interesting to me how few of all hospitalizations are HZ-related, so that at least as we look at what might be an anticipated effect on something as significant as hospitalization mediated through a vaccine effect on reducing HZ-related hospitalization, we would expect almost no effect. And, of course, we see almost no effect. Hospitalizations in total are 22 in excess, which is entirely consistent with random variability.

But, basically, what this is telling me is we didn't reduce any HZ-related hospitalizations but, then again, they are so incredibly infrequent I don't suppose it really matters so much.

DR. ROHAN: Well, I think that sort of speaks to two different, I guess, factors. I think, first of all, the question of the subjects that were

enrolled and the exclusion criteria, etcetera, I don't know if the burden in very ill subjects that might not be candidate for this vaccine that might not be -- had been enrolled might be a factor, but I also think it also speaks to Dr. Oxman and his colleagues and the care that they have provided, keeping people out of the hospital.

So I think it's the investigators, as well, that deserve -- you know, maybe they are sort of a victim of their own success in that respect, as well, and you might not have seen this low hospitalization rate out in the general community. You might have seen more people hospitalized.

DR. FLEMING: Well, they weren't keeping them out of the hospital, 1,115, 1,137, but at least those people that would have been HZ-related hospitalizations on placebo didn't --

DR. ROHAN: That's what I was talking about. I'm sorry.

DR. FLEMING: So I take more your first point to heart and that is we didn't look at a cohort here where in the placebo arm, there was very much

prevalence or incidence of HZ-related hospitalization and, in turn, we didn't decrease it at all either.

DR. ROHAN: I probably wasn't clear, but what I meant was that I think that the health care that was provided in HZ-related disease may have kept subjects out of the hospital, been more effective than you might have seen in a community setting.

MEMBER FARLEY: I would make a comment on that, too. As a clinician, I think that the idea that they were highly educated on the signs and symptoms of zoster and that they were instructed to immediately consult their study physicians and then they were given antivirals within this window, and I think these people were cared for at a higher level at an earlier point on average for sure than the general population.

DR. FLEMING: But what all that would mean is we can, in fact, do something about HZ-related hospitalizations. We don't need this vaccine to do it. We just need the kind of surveillance and quality care that you have referred to.

Either that is the conclusion or the conclusion is we didn't look at a sufficiently high

risk group. We excluded a lot of the people that really would have been at risk and we never found out what the efficacy was in that group.

CHAIRMAN OVERTURF: Actually, that addresses one of the subsets of the questions under Question 3, which is obviously the patients. The vaccine use in patients with co-morbid conditions and those taking corticosteroids has really not been answered by this study and clearly is an issue that has to be addressed in any post-licensure procedure, because it's clearly not asked. And it's actually the dilemma that we actually still face somewhat with the varicella vaccine. Yes, Dr. Hetherington?

DR. HETHERINGTON: I just want to come, I think, to closure on some questions we had earlier about dosing and I'm sure you have the information, but I'm not sure that we have finally come to resolution.

And that is, and I will try to ask it very specifically, what are your release specifications going to be for the upper limit, if any, for the potency of this? And I ask the question to try to get

some idea of what is the potential range of doses that one might get once this is approved, assuming it's approved? And in that range of potential doses that one would receive, would you expect to see a difference in immune response?

Another way to ask the same question is do you have any dose ranging data on immune response over different plaque-forming unit doses and, in particular, how did you come up with 19,000 as a minimum for your dose?

So there's a number of questions in there, but I think it tries to get to the same sort of understanding about the dose and the immune response.

DR. SILBER: Well, I think there were two main questions, so I will go to the second question first, which was with respect to dose ranging and immune responses.

What we saw in the early studies is that at the low end, basically the varicella, the VARIVAX-type potencies, less than 10,000, that there was not a response. We ended up getting a dose response going up to about that 17,000/19,000 level that I had spoken

to with very little dose response beyond that. In our studies conducted since then, there was likewise little dose response over the range once you get into a range above what has been defined as the expiry.

With respect to specifications, the lower specification just is defined by the efficacy study. The upper specification would certainly be no higher than 207,000 plaque-forming units but will be an ongoing discussion between us and the FDA.

DR. HETHERINGTON: All right. So just a two pointed edge on it. The pharmacodynamic response, if I can borrow that term, for immunogenicity, once you hit about 20,000 it's flat going above that. And what you showed in your high/low dose study shows that the relative safety and adverse event rates were similar across the range that you just described.

DR. SILBER: Yes. And perhaps even more importantly than immune response over the range that was studied is the fact that the vaccine efficacy appeared to be relatively flat over the ranges that were studied in the efficacy study.

CHAIRMAN OVERTURF: A somewhat related

question. What about the relationship between pre-immunization antibody and adverse events? Was there a relationship between that, particularly local reactions? Actually, you implied that when you commented on the studies when there was a comment made in patients who were 50, the 50 to 59 year-old age group, that there might be a relationship.

DR. SILBER: I'm not sure that we have specific safety tables related to baseline titer, but in three of our studies we had second doses, one at an interval of six weeks, one at an interval of about two years, one at an interval of about eight years.

In all of those the baseline titers were higher than we see in a typical population receiving a first dose, and the second doses had safety profiles in each case that were really the same as was seen with dose one.

CHAIRMAN OVERTURF: Dr. Rowbotham?

DR. ROWBOTHAM: I have a question that I think would be good for Dr. Levin to comment on, and that is that it relates to the hypothesis behind this as a treatment, and it doesn't seem to me that it

would be mutually exclusive for younger subjects who have younger immune systems to have primarily a zoster prevention effect, but then in older subjects who have greater immunosenescence to have less of a change in the incidence of zoster, but a change in the natural history of zoster once they get it, such that they might have a change in the burden of postherpetic neuralgia.

DR. LEVIN: So the question is why do we see this difference between the young-old people and the old-old people? Well, I don't know the answer, but the way I look at it is that in the younger people, they have a more vigorous immune response and actually you can show that and, therefore, they have a memory component, a T-cell memory cell response to VZV, that when they reactivate it quickly comes to the fore and the reactivation is often subclinical. You don't see anything. If they do have disease, it will tend to be mild because they have responded so quickly.

In the older individual, there is a delay or they don't mobilize their memory response to

reactivation so quickly. The virus takes hold. It does reactivate. You do have some zoster, but then it comes to the fore more quickly than in someone not vaccinated and it limits the disease or attenuates it. And I think that concept fits perfectly with both the efficacy and the immunologic data that we have.

CHAIRMAN OVERTURF: Would any other Member of the Committee like to address any of the specific questions? Dr. Wharton, you had a question.

DR. WHARTON: This is not related to FDA-specific questions, but I have two questions I would like to ask the sponsor.

Was the information collected on the vaccine safety card and in the 48 day telephone call follow-up comparable since they are apparently being used interchangeably as far as safety follow-up is concerned and, specifically, do they both collect information on hospitalization and medical encounters during that 42 day period?

The second question I have has to do with postmarketing surveillance. Once this vaccine is in use in an older population with a high level of co-

morbidity, I can anticipate that there will be deaths that occur among recently vaccinated persons and would like to know what plans the sponsor has that will help evaluate such episodes when they occur.

DR. SILBER: Okay. I will address the first question and someone else will get up to address the second question with regard to postmarketing safety.

With respect to the follow-up information, again, the follow-up information for those events that were defined by the typical -- by the ICH and in GCP as serious adverse experiences were collected uniformly, consistently the same way from everybody.

So those questions were asked in the vaccination report card. They were part of the script. They were part of the follow-up, in fact did not have to happen and it was encouraged not to happen at the end of 42 days, but all serious adverse experiences were to be -- were asked to be reported as soon as possible after onset.

So in terms of that sort of safety follow-up, the mechanisms were the same in all types of

follow-up, whether diary or otherwise. And I think Dr. Gutsch will get up to talk about the post-licensure.

DR. GUTSCH: Yes. Our post-licensure plans build upon the experience that you have all heard about today with the Zoster Program and upon the experience with the VARIVAX Program using the same active component in over 56 million subjects.

In the placebo-controlled trial for ZOSTAVAX in which no specific adverse experience was identified as being clinically significant for follow-up, we have a great safety profile and we have reasonable power, 97.5 percent power, to detect an adverse experience with a frequency of about 5,500. So this trial gives us a good backdrop going into the postmarketing period.

In addition, we're going to have an additional opportunity to look at the safety in another 17,000 or 18,000 when you combine the Shingles Prevention Study and Protocol 007 in which the placebo recipients are going to be vaccinated.

In addition, we plan to conduct

surveillance in the marketplace looking for signals as they are developed and in those instances where some signal might arise from our surveillance systems that are in place, we plan to evaluate those, discuss those with the Agency and, where necessary, adjust the label accordingly.

I think that other than the other things that I mentioned about the identification program to try and get a handle on any AEs and whether they might be related to vaccine and placebo constitutes the package of what is coming up.

And then there's a few other studies that are in place, which we mentioned earlier the Concomitant Use Study and the Bridging Study for a new formulation, which are ongoing. In those studies we are now enrolling subjects 50 to 59 in addition to the older age cohorts so that we'll get additional data in those groups.

And I might add we have also made an effort and are having some success in increasing the minority representation in those studies. So that constitutes the plans that we have.

CHAIRMAN OVERTURF: What is the cohort size over 80 in that placebo group? Do we know, have an estimate, since that was a specific previous question?

DR. SILBER: I think that the number enrolled in the study over 80 was about 2,500 and so it's about 1,250 additional vaccine recipients now through this follow-up.

CHAIRMAN OVERTURF: Dr. Fleming, you had a question.

DR. FLEMING: A question for the FDA. Could I get FDA slide 60, please? And while that is coming up, a quick question for the sponsor. I am pleased that you had a Data Monitoring Committee in place. I am concerned, if not disturbed, that they didn't routinely automatically have unblinded data from the beginning of the trial.

My question is was this a fully independent committee? Were the members of the DMC fully independent of the sponsor?

DR. SILBER: The DSMB met periodically throughout the course of the study.

DR. FLEMING: That's not my question. Just simply, were they independent?

DR. SILBER: I'm sorry? They were completely independent.

DR. FLEMING: Completely independent.

DR. SILBER: In fact, you are here today because of one of the independent people, I think, who served on the committee.

DR. FLEMING: Okay. So all members of the committee were independent?

DR. SILBER: Everybody. Yes, they were all external, independent members.

DR. FLEMING: Then a question for the sponsor relating to slide 60 or, excuse me, a question for the FDA for slide 60. In the FDA presentation, you don't have to show it, in slide 83 you say the completeness of safety ATRS and study termination follow-up is unclear.

And I find myself still struggling to understand the level of completeness that we can be assured has been achieved by the nature of the surveillance, so I think it's slide 60 that you have

that I wanted to go to. And I always think of a threshold or a tolerance level for safety in a benefit to risk fashion.

And so what is the benefit here? The benefit appears to be per 1,000 person-years a reduction of 5.7 HZ cases and a little less than one per 1,000 person-years PHN cases, none translating at least in this study into something as significant as reducing hospitalization. So clinically meaningful events, quite infrequent in their occurrence, are being reduced something on the order of 50 percent.

It makes me, from my perspective, believe that understanding safety with great thoroughness is important to make sure that benefit to risk is favorable and, as you have noted here on this slide as well as on the slide that I was quoting from, 83, that were reliant on a fair level of what we might call passive surveillance.

The sponsor again just echoed the rule of 3, i.e., assuming that you look at 19,000 people, we can rule out events that would occur in one in 5,500. Assuming we didn't see any such events, then we can

rule out rates at that level under the assumption that were such an event to occur, we would capture it and that subtle, if not not-subtle, assumption is there.

How confident are you? You know the data better than I. You know the system better than I do. How confident are you that this system that has a non-trivial amount of passive surveillance with a fairly low threshold level for safety, given the nature of efficacy, can be reliably capturing events that, if they were occurring, would in fact meaningfully impact benefit to risk assessment?

DR. ROHAN: I guess one of the issues is looking at the vaccine report cards versus the ATRS safety data. The ATRS specifically queried for these things.

The vaccine report card, and this is part of sort of human nature, if you will, as well, specifically asked for local reactions through day 4, specifically queried for temperature through day 21, and then if subjects felt that they were feverish or felt their temperature was abnormal, they could record their temperature and it also allowed them to record

unusual or other events, but it didn't specifically ask were you hospitalized, I don't believe.

I don't believe that it asked these specific questions. So I would think that -- I would be concerned that subjects will be focusing on the first four days of local reactions and temperatures for 21 days every day and that what they reported in the vaccine report card, the rates, etcetera, might differ from the data in similar subjects reporting to the ATRS follow-up, and I am not sure.

I, you know, saw the slides that the sponsor put up. This is from the data set that they provided with us and, as I said, the 4,639 are not all clustered between day 51 and 60, but they go out for several years and there are hundreds and hundreds of people in the second and the third year being added into the database and I don't know what to make of that.

The sponsor has told me that there is no window for the day 42 safety follow-up and, as you can see, people are being enrolled before they were vaccinated, which I take day minus 5 in the first

couple weeks, and I don't know if that data is the same as data at two years or three years involving the 42 day follow-up period. So that is an issue.

I don't know how many people are actually calling in on the monthly phone calls, how many of the subjects are having data entered by the investigator, the investigator's site, by month. And, obviously, subjects were followed for an average of three years but many were followed for about two. Some were followed out to five, so there is a variety of issues.

DR. FLEMING: And this is just about three quarters of the study, i.e., when you add up all these numbers this is about three quarters. This is about 28,033.

DR. ROHAN: 66 percent of the total population.

DR. FLEMING: Okay.

DR. ROHAN: 55 from the subjects calling.

DR. FLEMING: Plus 11 percent.

DR. ROHAN: 11 from data being entered.

DR. SILBER: Can I clarify?

CHAIRMAN OVERTURF: Yes, please.

DR. SILBER: First to Dr. Fleming's comment. This was active safety follow-up of all subjects through day 42, all subjects in the AE Monitoring Substudy, all subjects in the routine monitoring cohort.

The passive surveillance for vaccine-related serious adverse experiences and deaths is as is done in all studies. It does become passive beyond that point. The 66 percent figure, again, does not include the 16 or 17 percent with vaccination report cards and again --

DR. FLEMING: Plus the gray region, right, your 11 percent?

DR. SILBER: Well, the magenta and the gray were some of these that -- again, as I showed right after the lunch break, about 80 to 90 percent of the magenta and the gray were between day 51 or at least prior to day 60. And the total before 60 was, again, 93 percent across the entire study of both cohorts.

With respect to these calls that may have gone out beyond day 60 or day 90 or the ones that came

before day 42, this table is not one per subject. These are all contacts. So if somebody called the ATRS or there was some other contact for an AE on day 6 and then there was another one on day 44, this would show up twice.

DR. FLEMING: That's why this is only 66 and not 75 percent.

DR. ROHAN: Right. And, in fact, many subjects had two or more, up to six additional entries, so some people had seven entries in the day 42 safety data set and this could occur at day 42, a year later, two years later. There are additional entries being put into this data set for a particular subject.

DR. FLEMING: With, approximately, 1,600 people who died. Certainly, that also impacts the nature of safety information we would get from those. Can you comment on that?

DR. ROHAN: Because there was an anticipated relatively high rate of deaths in this particular population, deaths were monitored but narratives and further details weren't necessarily

collected. They were collected in the first 42 days with the follow-up of serious adverse events, so we have more confidence, more knowledge about that time period.

But overall deaths and I guess you could also say that deaths that occurred within the day 42 day period might take longer to be reported since the subject themselves had died, you know, that kind of thing.

CHAIRMAN OVERTURF: Dr. Farley?

MEMBER FARLEY: Can I ask a quick follow-up to this? Can you tell us what the study termination follow-up was to be? And I think if I remember your report, it was missing in a high proportion. How important is that? What was that going to provide us and should we be concerned at all about that?

DR. ROHAN: Well, we recently actually have gotten a little bit of clarification on the termination procedures. Subjects were contacted. There was a determination of whether the subject had been immunocompromised during the study or at study

termination, whether they had developed herpes zoster or PHN, whether they had died and, if so, there were additional data elements that were included at that point.

MEMBER FARLEY: But was it, in fact, missing in the very high proportion of cases?

DR. ROHAN: We recently became -- I guess were in discussions. I guess it was clarified why those elements were not filled in and that the data resides in a different -- in a column rather than in the row that is left blank, that the actual date is actually in a column that is not called date of last contact.

It's called exam date. So even though the question with when was the subject last contacted is left blank in the majority of the cases, the information is in a column that is termed exam date, but we just were informed of this a couple of days ago.

CHAIRMAN OVERTURF: Yes, Dr. Rowbotham?

DR. ROWBOTHAM: I have a couple of questions. One is related to the issue of vaccinating

patients in the 50 to 59 age group. So from the earlier discussion and Dr. Levin's comment, one would expect that in that group you would primarily see an effect on preventing zoster and perhaps even less of an effect on zoster pain or development of postherpetic neuralgia.

And the other thing that came out of the data presented earlier is that if you get zoster, the amount of immune response, the ELISA titers, is much, much greater than what is achieved with the vaccination.

So if you are vaccinating people in the age 50 to 59 category and at this point don't know how long that protection is going to last, especially compared to getting zoster in your 50s when the risk of postherpetic neuralgia is lower, we may not be doing the patients that much of a favor by shifting their zoster episode from the mid 50s to their mid 60s or into their 70s without knowing when would be an appropriate date to give follow-up vaccinations.

The other aspect is that in the younger population, since there is a lower risk of zoster in