Prematurity is by far the leading cause of perinatal mortality in my area, as well. As a practicing physician, this is quite frustrating to know that there's no effective treatment that I can offer to my patient.

As I look through literature, literature is flooded with negative studies of things that we do and offer to our patients, including tocolytics, antibiotics, home uterine activity monitoring, and cerclage. None of that seems to have any efficacy when it comes to prematurity. All I could offer is, as a clinician, maybe watchful eyes and give steroids.

The aforementioned NIH study by Meis gave a practicing physician like myself a glimpse of hope. I was excited to see such well-designed studies sponsored by NIH, conducted by our own network, with a positive result for once. The protocol that they used was simple and easy to follow, and it would be very easy to apply in a busy clinical setting.

As a clinician, Gestiva will ensure at-risk patients will receive a uniform and consistent drug

delivery, and protocol is easy to follow for our patients.

Unfortunately, 17P is not widely available, especially in rural settings. When the NIH trial was first published in 2003, I was trying to find 17P in the local pharmacy and I was not able to do so for many months. And compounding pharmacy is a luxury in a lot of rural area.

So having Gestiva on the market approved by FDA will ensure at-risk patients in all areas will have access to this drug with proven safe records, and the clinician can follow the high fidelity protocols and feel confident that they're doing the right thing for our patient. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Terry Grossklaus.

MS. GROSSKLAUS: Good afternoon. Thank you. I paid for this trip myself. I live in Idaho and we do have family in Sunnyvale, but I don't think we know anyone here today from Adeza, and we don't own stock in Adeza.

I'm a graduate student at Gonzaga University in Washington. I'd like to specifically recommend that patients be warned to avoid all alcohol consumption while they're pregnant and under treatment with this drug. Next.

Let's learn some lessons from my previous use of Delalutin. Next. I used Delalutin during three of my pregnancies in the 1980s for treatment of a different condition and during different gestation weeks. Next. There's the product insert. Next.

The condition I was treated for suspected corpus luteum insufficiency and the progesterone was thought to supplement the endogenous production of that hormone.

Next. The protocol that was used required a combination of progesterone vaginal suppositories and weekly injections. The protocol was for gestation weeks five through nine or five through 12, and my obstetrician modified it to extend to 17 weeks or 18 weeks. It's a little bit different for each pregnancy. Next slide. It was very successful. We have three wonderful children who

are all in their 20s now, all full-term. Next.

The concerns I have -- actually, I was very well-informed when I used this medication and I appreciate that from my obstetrician.

Next. The -- what I would like to comment on is a possible adverse interaction between alcohol and 17P when it's used for this particular treatment during those gestation weeks five through 18. Next. My son had a congenital cardiac condition, primary microcephaly, intrauterine growth retardation, that I experienced.

I actually developed what I thought was alcoholism during my pregnancy, but I do not have a history of that, and nor do I drink now. So I just had a drinking problem during my pregnancy. And those of you that have a handout can see the -- I have a graph of estimated ounces -- absolute ounces of alcohol per week on the Y axis and then on the X axis is gestation weeks.

Next. There's our son, and that was the pregnancy that was effected. On the left, he's about a year old and he's just a little bit

hypotonic and he was very delayed in his development. On the right, he's six years old. Next slide.

In 1991, when he was six years old, I decided to conduct my own literature review on all these topics: alcohol use during pregnancy, congenital heart conditions, microcephaly, teratology, intrauterine growth retardation, all of these things, and I figured something out that made sense to me for about eight months, and then I filed all my literature away.

Next slide. The subjective experience I had is that I was addicted by 15 to 17 weeks. I was never intoxicated. In fact, when I went back and calculated my approximate blood alcohol content, it would've been about .02. I felt fetal growth restriction.

The symptoms actually diminished when I stopped my progesterone injections at 17 or 18 weeks, and then they accelerated, and then at 26 weeks, a compulsive drinking problem just completely erupted. The sensation I had is that it was all my

fault for drinking in the third trimester. Next slide.

A very over simplified explanation. Alcohol, you know, is a two-tiered psychotropic drug. It's actually ethanol and acetaldehyde. I think the first portion of the chemical is metabolized, but then the metabolism is stuck at the acetaldehyde level. Next slide.

The acetaldehyde then accumulates in the mother's brain, liver, and serum, and it can serve as a teratogen, fetal growth inhibitor, disruptor of steroid hormone biosynthesis, it's addicting, and inhibits the fetal brain growth. So I think 17P is actually what restricts the metabolism of the acetaldehyde. Next.

I finally wrote my literature review up. It's over 600 pages. I need a medical researcher to take a look at it. I filed the MedWatch report with the FDA and the drug company. It's incomplete. I made some additions, and this, too, is incomplete. It's -- becoming addicted during pregnancy is just a phenomenal experience, and I'm not sure even this

captures everything. Next slide.

I think that a decision on this drug maybe needs to be delayed until I can have someone review this manuscript or at least have a very specific warning to avoid alcohol while a woman is using 17P during her pregnancy. This information needs to be communicated ahead of time. If you refer to your graph again --

MS. WATKINS: Ma'am, your allotted time has expired.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Jackie Duda.

MS. DUDA: Good afternoon. My name is Jackie Duda. I'm a Sidelines volunteer, health writer, and a mom who's experienced two high-risk pregnancies. Sidelines National Support Network is a 501(c)(3) nonprofit organization supporting women with high-risk pregnancy and their families. In the interest of disclosure, Sidelines does receive private funding from various volunteers, patients, private individuals, and industry.

I'm here to speak today on behalf of Candace

Hurley, Sidelines founder and director, in her words. In 1991, Candace founded Sidelines National Support Network after her own battle with infertility, miscarriage, and high-risk pregnancy. Eighteen years ago, she benefitted from the use of progesterone during two successful pregnancies.

Fifteen years later, Sidelines is still thriving, supporting thousands of moms around the world, having served approximately 100,000 women with education, support, and encouragement through a vast network of 7,500 volunteers who were all at one time high-risk moms themselves.

Sidelines takes an interest in treatments and technologies that will help with the devastation of pregnancy loss and preterm birth, because these are the things we deal with first-hand. If you visit our web site or read our magazine, you will see that one of our goals is to educate moms about treatments and medications used during pregnancy. We also have the responsibility of training our volunteers who support moms and speak nationally on behalf of this organization.

We have been following the use and anticipated approval of progesterone, as detailed in our 2005 publication of Left Sidelines, where we featured an article about 17P, the history of progesterone, and its use in the treatment of preterm labor.

As a representative of Sidelines and on behalf of Candace and other high-risk moms, I would encourage this panel for approval of this drug, but as a generic, not as an exclusive drug as is currently proposed. As you know, there are no FDA-approved drugs for the treatment of preterm labor, so all drugs are used off-label.

I do want to take this opportunity to express our concerns about the approval of this drug to this panel. Our understanding is that this drug is being positioned as qualifying for orphan drug status, or another form of approval that would grant one company the exclusive rights to advertise, manufacture, and distribute 17P for several years.

The concern here is that this will limit the availability of this drug, as well as drive up the price. Over the past 20 years, this drug has been

widely available and used in the treatment of recurrent preterm labor as a reasonably-priced compound within a market of free competition.

From a consumer point of view, it concerns us that pregnant moms will be the ones to pay a substantially higher price for something many pharmacies have been providing to their physicians for between $7 and $10 per dose. Allowing one company using NIH research data from the public domain to have full control over this product will create a monopoly and most certainly drive up the price for a group of people who need solutions to this problem of preterm labor.

We urge this panel to approve this drug, but as a generic drug without any exclusivity, so that the under-served and often under-insured population of pregnant moms will not be the ones to pay for the high price of approval.

One loop hole in the Orphan Drug Act states that this program is developed to encourage companies to study off-label or new drugs for small populations of under 200,000 people.

As the director and founder of Sidelines, Candace would like to state for the record that the problem of preterm labor and premature delivery is a national crisis that according to national vital statistics, affects half a million women each year, more than double the number required to give a drug the qualification of Orphan Drug status.

One in three pregnant women develop a pregnancy complication, and of over four million births in 2003, the rate of preterm births increased to an astounding 12.3% of all births.

Another important concern is the impact an exclusive approval may have on jeopardizing further research into the safety aspects of this promising drug. The American College of Obstetricans and Gynecologists recommends further studies to determine the long-term effects of multiple doses and the potential for embryo toxicity on the developing fetus. We strongly support the completion of these studies.

Our main concern is for expectant families. Sidelines, in coalition with the national March of

Dimes campaign, looks to help solve this puzzle and reduce the rate of preterm babies. This first step in the approval of this drug is one in the right direction if it is as a generic, not in the proposed form of an orphan drug or one that will grant exclusivity to one entity and thereby restrict availability, drive up price, and stifle further research.

We thank you for your time and the opportunity to speak on behalf of the families who will benefit from this approval.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presentation is a group presentation from Howard University: Davene White, Carrie Lewis, and Mikel Young.

MS. WHITE: Good afternoon. My name is Davene White. Dr. Young and Dr. Lewis had an emergency at Howard and weren't able to attend. I represent Howard University. I am not aware of any problems with my presentation. I have not had any contact with this drug agent before.

I am a clinical instructor in the Department of

Pediatrics and Child Health at Howard University's College of Medicine, and I direct our family-centered public health services at Howard University Hospital.

I am speaking to you as a result of my 30 years of experience in reproductive services at Howard University Hospital and as a neonatal nurse practitioner, where I specialized in the care of preterm infants and the support services for mothers and families.

I have particular concerns about this particular substance. Number one, pregnancy is a life-altering event for women and families, particularly when a previous outcome was less than desirable. Pregnancy is also a period during which women need and seek attention. I am interested in the continued monitoring of the effects of 17-hydroxyprogesterone and when it is no longer an intervention and what will become of this routine treatment -- what will become of it when it becomes a routine treatment.

During this study, the women were given very

special attention and I know that that does have an effect and can reduce preterm pregnancy, because women need attention during pregnancy.

So I'm very concerned about the education and training that was implemented for the study staff and whether or not this will be replicated in the OB/GYN community and other participants that would be using this drug.

I'm also concerned about studies that may be available to determine the effect of progesterone on women who experience severe emotional or economic stress, since that is a very significant factor that we have identified at Howard.

We're also concerned about the extensive issue of and painful injection sites and whether or not additional investigation is needed to determine methods that should become available to reduce this discomfort and negative effects. We do know that one issue that will deter women from treatment is pain.

My greatest concern, because I am a pediatric nurse, is the potential impact of 17-hydroxy on

developmental outcomes of children. As Dr. Wesley elegantly presented, there is some concern about communication, fine motor and problem-solving scores of these infants.

Because these infants will no longer be preterm, they will not be eligible for early intervention services in states around the country, so these families may not have these children evaluated as early as would be available for a child that was born premature.

We recognize that the benefit of reducing prematurity is wonderful. We support any and all efforts that will go to this cause. We do, however, recommend that further study is required of this medication and that the participants, persons who use this medication should receive adequate training. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our last open public hearing speaker is Cynthia Pearson.

MS. PEARSON: Thank you. I'm Cynthia Pearson, Executive Director of the National Women's Health

Network. We're an independent women's health consumer group. We've been around for 30 years. We take no money from industry. We weren't contacted by the sponsor about this. We prepared our position based on the open literature, the documents on the FDA's web site yesterday, and the presentations this morning.

And from all that, what we take is that we understand the panel -- the committee has been brought together today and asked to advise the FDA on formal approval for a product, the use for which has been accepted by the profession, at least in main part, a few years ago.

So this meeting may be something of a formality from the committee's position, or maybe you've even gotten the message that this is your opportunity to clean up kind of a mess outside, that women are getting this product, but they're getting it from who knows where, in what sort of dose, and is the education really good.

And if you take this step forward, give the -- advise the FDA to give the seal of approval, then

women will get neat and tidy 17 progesterone from a source that's inspected, that has good manufacturing practices, and all will be well with the world.

However, out in the public, we don't take your meeting today as a formality or a rubber stamp, nor, I know, do you. Because I know many of you have been on this committee for many years and struggled through some pretty tough meetings and finally, your advice is starting to be taken, albeit a little belatedly.

But we appreciate the role you play, because with you, the public gets its one and only chance to have an open discussion and viewing of the real data that underly the papers that are published which lead to the committee recommendations and other guidelines.

And what you've been asked to do by the FDA today, or to advise them about what they should do, is whether or not you should go against the typical approach of the FDA and recommend approval of a new product on one pivotal trial.

And the trial that was designed uses what, in

some sense, is a surrogate endpoint. It does not have as its primary endpoint more babies alive. It has as its primary endpoint more babies who make it inside their mom's uterus for a longer time.

Now, that surrogate endpoint has meaning and value in and of itself. The nurse who spoke earlier described some really vivid and important ways, and the moms who would speak about how important it is for them to have their baby home with them as soon as possible.

All of that leads to say that that surrogate endpoint isn't like a cholesterol reading that has no meaning in the life of people who experience it. But when you look then at the data that shows some interesting back and forth underneath that no net benefit in live babies, you start to wonder, is the surrogate endpoint important as it is in itself and robust as it seems to be in this study, where it's statistically significant on its own and it's statistically significant and all in the same direction when looked at in subgroups?

But when you look then at who's living and

who's dying, where were the deaths in this one trial, it starts to seem a little worrisome that there's an increased rate of miscarriage in women who were randomized to the active intervention. It also seems worrisome that that seems to appear in other studies.

So although the data are encouraging and the sponsor is to be tremendously complimented for doing a follow-up study in babies, having data on kids that are over two years old is wonderful. You're meeting the demands and the requests and the prayers of mothers, of consumer activists, and of the people who remember DES.

And no sponsor should have to do a prospective trial of children born -- do prospective follow-up of children born in the pivotal trial all the way out to puberty, but boy, it sure would be nice to have those data.

One piece of advice we'd like to make to the committee is to consider asking that the sponsor go back to some of the existing observational data sets where kids were followed or checked into at around

age 11 and update them. Now, we know that's an effort and it's an expensive effort, but it can be done. So that's one thing we'd like to know, what happens to kids after puberty.

The other thing we'd like to know is really more about this apparent increase in miscarriage. So overall, I think our comments to the committee are for you to act very cautiously, to consider a recommendation of delay, even though that seems to fly in the face of common practice and the results of the trial, and give us all the time that it seems like we're going to need, the extra time to get the answers to these important questions. Thank you.

DR. DAVIDSON: Thank you. Is that the end of the list?

MS. WATKINS: Yes.

DR. DAVIDSON: Okay. The committee can go back to work. One of the committee members, Dr. Gillen. Do you want to do it from there? It's your choice.

DR. GILLEN: Before the committee started open discussion, I thought as the only statistician named on the committee, I wanted to present a couple of

views of how some in the statistical community view using a single confirmatory trial and the role of probability in that versus two independent trials, and state some corrections -- or adjustments, anyway, as I should say -- to the statistics that has been presented to this time just quickly.

It's probably more formal than it needs to be, but I'm going to quote some numbers, so I just thought it would be a little easier if they were up on the screen here.

So again, we've heard already that typical criteria for approval requires the submission of two independent well-controlled clinical trials as substantial evidence for effectiveness. Of course, from a statistician's point of view, our goal is to quantify uncertainty in samples in order to make inference and to generalize to a larger population. That's what we're trying to do with these trials, in particular.

So obviously, our primary reason for requiring this consistent results on two independent trial is really to broaden the generalize-ability of our

observed results, be it through clinical centers, different clinical centers, an array of them, different training that may take place over time or learning experiences of those involved in the trial, and also, different patient pools and possibly cohort effects.

One of the things that we focus on often for at least one evidence or one criteria of evidence in a trial obviously is the P value, and so we've seen a lot of them presented today. Sorry about presenting some more to you, but I'm going to need to.

Just to define it again, it's the probability of observing our results as are more extreme than those actually observed if the no hypothesis were true; in this case, our no hypothesis being equal rates in the two treatment arms. We've all heard the magic .05 for a two-sided test or a standard for a single trial that has a one-sided P value, it would be .025; cut that in half.

So the way some in the statistical community view a single trial as posing for two independent trials is to say, well, if we were to do two

independent trials and we were to achieve our level .025 on both of those trials, then the probabilities would just multiply together. So one single criteria of evidence might be .000625, would be your new type one error level. Okay?

So this has been proposed, and there is some precedence to this being used at times. I'm not speaking for the FDA here, but this is a criteria that has been proposed in a single trial. So again, this corresponds to a threshold for two independent level .025 trials.

So the reason I kind of wanted to present this is because this is the way I'm thinking about things from a statistical perspective at times as I'm reading through the report, and if I'm going to talk about P values, I wanted to note, and I brought up earlier, that there were some interim analyses that were going on in the study.

Now, the committee should be aware that there are some adjustments that can be made -- taken into account, at least -- with having those interim analyses there. So I reformed them so that we can

view those P values, as well, and you can take them into consideration as you will.

So the sponsor reported in this study, for their 37-week endpoint, their primary endpoint, observed proportions of .371 in the active arm and .549 in the placebo arm, so we had a difference of minus 17.8%, and the reported 95% confidence interval being minus 28% to 7%, with a corresponding P value of .0003.

In reading the FDA's report, they did note that there was an interim analysis that was done. In fact, there were two interim analysis and the final analysis. They used an O'Brien-Fleming rule, two-sided again, with level .05, so splitting that between the two sides, .025 on each arm.

And we have our adjusted results presented by the FDA's report of, again, 17.8% difference in favor of active control, and our adjusted confidence interval, which again didn't change. But I went ahead and adjusted the P values because we actually never got to observe adjusted P values that take into account the interim analyses, and so I thought

it would be at least useful to see what those looked like and take that into consideration.

So my assumption is not having the full protocol at hand, but just the description given in the text, was that if we used our two-sided level .025 -- our level .05 O'Brien-Fleming boundary, the one that was used in the trial, I assumed three equally spaced analyses. I was informed today, actually, that it was 15.2% and 70% (phonetic) of the final samples size which was used.

That would make a very slight difference in the calculations that I'm using, very slight. But for -- just so you know, I'm assuming three equally-spaced analyses. And then again, our final sample size is 310 and 153, which is what we observed in the trial, and then a baseline event rate of .549.

So our adjusted P value -- and this was quoted earlier, actually, -- is .0035. This is using the sample mean ordering, so there are many ways that you can adjust P values given interim analyses, but this is what we have. So .0035 is actually with the

adjustment for the interim analyses.

It turns out that when you're performing group sequential tests, where you can stop early, in fact, your observed estimates can be slightly biased. It's usually biased away from the null, so there's some attenuation that takes place. So if we adjust for that bias in the difference proportions, it's truly 16.5%, using a bias-adjusted estimate.

Again, just for completeness so that you have this, if we talked about adjusting for the interim analyses on the 35-week, 32-week, and 28-week endpoints, we can again see some adjustments in terms of the bias towards the null, attenuation towards the null, in some of these estimates, getting lower and lower as we go down. The adjusted P values, again, are slightly higher than those that were reported in the initial analysis, so just take that into consideration, as well.

Just a final note. Again, I wanted to present these because they're things that I'm looking at and I thought it should -- it would be nice for the rest of the committee to see. My own personal

belief is that P values really only represent one criteria for evidence.

We need to consider also obviously clinical significance of observed point estimates. That, of course, goes into our questions of the observed rate and the preterm risk (phonetic) in the placebo arms, and we might think about other things, as well. Since we've got these divisions up by different gestational time periods, we could think about mean time to birth, as well. So these have been presented in some of the other analyses, but haven't been talked about so far today.

And then obviously, we need to consider generalize-ability of our findings, safety profile, and the urgency of clinical need. But I just wanted to present those P values for you so that you had them at your disposal. Thanks.

DR. DAVIDSON: Okay, thank you. Dr. Hickok, you may feel compelled to respond to that presentation.

DR. HICKOK: Thank you very much, Dr. Davidson. Could I move this computer off the top of the desktop here, if you don't mind? First, I think I'd

like to invite Dr. Anita Das to address a couple of these statistical questions that were raised in the last presentation. Dr. Das?

DR. DAS: Yes. Regarding the adjustment for the interim analysis, the primary endpoint of preterm delivery at less than 37 weeks was the outcome that was monitored by the data and safety monitoring committee. The outcomes of less than 35, less than 32, and less than 30 were not monitored by the data and safety monitoring committee. In fact, the less than 32 outcome and the less than 30 outcomes were not even in the study protocol.

So our position is that these outcomes do not need to be adjusted for the interim analysis look. The only ones that would need to be adjusted would be the one for the primary endpoint. As we have stated, is that the alpha level for that comparison would be .035 using a .05 original alpha level.

But regardless of that, if you look at the outcomes of less than 35 and less than 32, that you could do an adjustment for these based on multiple testing procedures, and considering that these are

very highly correlated endpoints, an appropriate adjustment might be something as a Hochberg method, a step-down type of method.

If you do that type of adjustment, even given a .035 as your alpha level, the outcomes of less than 32 and less than 35 would remain statistically significant with adjusted P values of .027 for both.

With that said, I would also like to agree with the panel statistician that you just can't just look at the P values when you're determining significance of these endpoints. It's the generalize-ability, it's the consistency that you're seeing across of all of our subgroups. It's the consistency that you're seeing with the neonatal outcomes, also showing benefit. So these all have to be taken in together when determining if there is a benefit.

DR. DAVIDSON: Okay, thank you. We can go -- unless you have some special introductory remarks, we can go back to questions.

DR. HICKOK: Thank you, Dr. Davidson. I don't, but I'm pleased to entertain more questions.

DR. DAVIDSON: Okay. If the interest persists,

on our list here, we have Dr. Viscardi.

DR. VISCARDI: My only question was related to, again, this difference between the rates of -- higher than expected rate of preterm delivery in the control group. One of the analyses that wasn't discussed earlier, I believe, was looking at the actual indication for preterm delivery.

As Dr. Romero eloquently presented at the beginning of the day, there actually are some subgroups, and particularly indicated delivery, preterm labor versus preterm rupture of the membranes, and I think there were some differences between the groups, as far as the type of preterm delivery.

DR. HICKOK: If we go back to the efficacy analysis from our core presentation, we provided you with preterm birth rates less than 37 weeks, and I believe on that same slide was less than 35. But in addition, we have indicated preterm delivery rates in the two groups, which we'll share with you in just a second here.

Forgive me. I'm not getting exactly the data I

want up yet, but let me tell you when we do find that exact number that's going to come up, we did find a very similar and not statistically different rate between the 17P and placebo groups in terms of indicated preterm deliveries. And it's very important, as you pointed out, to take a look at that because if you have an imbalance of that, you could result in bias towards one group or another by your indicated preterm deliveries.

I apologize that we don't have this up on the screen yet, but I'll give you those numbers very shortly.

DR. VISCARDI: The other reason I bring that up is that one of the things that really hasn't been addressed, and again, Dr. Romero brought this up, is a very important cause of preterm delivery, which is intrauterine infection.

And again, trying to get some idea of what might be mechanism, as I remember looking at that data, there -- it was about the same rate of indicated delivery between the two groups, but there was a higher rate of preterm labor in the control

group, but no difference for the preterm premature rupture of membranes. So it looked like the effect was primarily in the preterm rupture group. Am I remembering that correctly?

DR. HICKOK: Yes. Let's first look and address your first question, if we can, about the indicated preterm delivery rate in the two groups. As you can see here, if you can see around the bottom of the podium, the indicated preterm delivery at less than 37 weeks for the 17P group was 8.1%, as opposed to 9.8% for the placebo group. So this rate was very similar and obviously not statistically significant, and we didn't do any adjustments beyond that.

We do have rates, for example, that we can share with you about rates of BV in each one of the groups, which some people could say would be a potential prognostic factor, and we would be glad to share those data with you also, if you would like.

Right? Okay. I think if we can turn to Slide 614, I believe. We have information about bacterial vaginosis and trichomonas that was collected at two different time periods on the case

report forms, first at baseline, by patient report and by record review, and then during the study on the case report form, that was for record of antibiotic use that was taken at each visit, if it was appropriate. This included not only the antibiotic use, but also, the reason for the administration of the antibiotic.

Secondly, there is information on clinical chorioamnionitis, which was an outcome that was collected at the time of labor and delivery, and it can be found on the delivery summary case report form.

I might add that in this study, as again, it was a preterm birth prevention study examining the influence of 17P, that infections were diagnosed by the treating physicians based on their methods and their customs at their own individual site. So, for example, again, there wasn't routine collecting -- or routine testing of patients for bacterial vaginitis in a standardized form throughout.

If we first look at the outcome of confirmed clinical chorioamnionitis in the 17P versus the

placebo mothers, we see at the time of delivery, this occurred in 3.3% of 17P mothers, 2.4% of mothers in the placebo group. Again, a value that was not significantly significant.

Turning to the incidence of BV, I said before that we had information prior to randomization, and prior to randomization, 13.2% of 17P mothers had bacterial vaginosis reported, as opposed to 13.1 in the placebo group. In the time period from randomization through delivery, the total was 8.7 in the 17P group and 5.2 in the placebo group. If you express that as any time during pregnancy, it was 20.7% in the 17P group and 15.7 in the placebo group.

One might wonder what antibiotics did women receive during pregnancy and for what reasons, in terms of vaginal infections. If we look here at the patients with bacterial vaginosis, we see that 10% were treated with metronidazole in the 17P group, as opposed to 5.2% in the placebo group. There were low rates of vaginal administration of metronidazole and again, any rate was 10.7% versus

5.9%. Again, this reflects I think clearly the slightly higher rate of bacterial vaginosis in the 17P treated group.

The next logical question is how does this reflect in terms of outcomes? We examined preterm birth less than 37 weeks in mothers that did not have bacterial vaginosis and those that did. Again, in the mothers with no bacterial vaginosis, the preterm delivery rate 35.8% in the 17P group and 51.9% in the placebo group. Again, in the 17P group, this was 42.2% in the 17P group and 70.8% in the placebo group.

This, in general, kind of reinforces what we've seen of the epidemiology of bacterial vaginosis and that it indeed is a risk factor for preterm delivery. I think one of the panelists pointed out earlier, however, that there really is no current evidence at this time that treatment of bacterial vaginosis, if it's identified during pregnancy, has an impact on pregnancy outcome.

Nonetheless, we did another analysis and we looked at bacterial vaginosis during pregnancy and

the outcome of that pregnancy, and these numbers are fairly small because again, we just had 64 women with BV in the 17P group and 24 in the placebo group. But as you see here, there is low rates of miscarriage, stillbirth. The rate was elevated in the preterm -- for preterm PROM in the placebo group, but low rates of neonatal sepsis, and then no cases of cerebral palsy, as we determined from the actual follow-up study.

DR. DAVIDSON: Dr. Burnett?

DR. BURNETT: You just answered some of my questions with that last one, so I'll pass at this moment.

DR. DAVIDSON: Okay. Dr. Merritt?

DR. MERRITT: Could you please go to your Slide 42, Dr. Hickok?

DR. HICKOK: I'm sorry, Slide 42, did you say?

DR. MERRITT: Please.

DR. HICKOK: Yes. Slide 42.

DR. MERRITT: I think we've dwelt on this before, but could you attempt to justify again for me the imbalance in your treatment versus

placebo population when it comes to risk factors?

DR. HICKOK: I'm sorry, I was having trouble understanding you. To talk about the adjustment that was performed in this? Is that what you --

DR. MERRITT: There's apparent risk factor difference, and you were going to discuss something about an adjustment, but I didn't catch that in the subsequent discussion.

DR. HICKOK: I'm sorry. We did not do a formal adjustment for these risk factors, but have chosen to, instead, give you that qualitative assessment. Again, there's a limit to the kind of adjustments that can be done for this. But Dr. Das, would you like to address this just briefly? It's more of a statistical question.

DR. DAS: Yes, we did do an adjustment for the number of previous preterm births, so we adjusted the primary outcome of using the logistic regression. The results remained highly statistically significant. They had a P value, I believe, of .001.

DR. MERRITT: So is that Slide 45, please?

DR. DAS: Yes. Slide 44, I believe. Here, I've got it up on the screen for you. So it's the second P value on the row, so for the intent to treat analysis, the logistic regression adjustment resulted in a P value of .001, and in the all available data, it was adjusted to .0006.

DR. MERRITT: That's not what I am addressing. My concern is that the placebo group had a larger number of patients at risk in Slide 42, at greater risk.

DR. DAS: Yes, that adjustment takes care of or adjusts for the fact that there's an imbalance between the placebo group and the active group with the number of previous preterm deliveries. So that's the standard adjustment for when there are treatment imbalances on a prognostic factor.

DR. DAVIDSON: Okay, Dr. Wenstrom? Dr. Carson? Oh. Dr. Lewis?

DR. LEWIS: All right. I would just like to pick up briefly on a point raised by Dr. Carson earlier on about the pharmacokinetic data in -- for sort of rates -- absorption rates of this compound.

I wonder if you've looked at -- stratified your results in any way according to the mother's BMI? Because you have very few data on the pharmacokinetics of this compound, period, let alone adjusted for such a wide range of BMI as was apparently reported in the 2003 study.

DR. DAVIDSON: Let me introduce another variable. You know, the maternal blood volume increases about 50% during pregnancy, and the larger the woman is, the larger that volume increase. So if you looking at the pharmacokinetics, it may be very different than what it is in a non-pregnant woman.

DR. HICKOK: Yes. Give me one second. We did look at -- over the noon hour, we pulled out information on body mass index, and I may have left it on my chair right here. We did stratify by BMI in terms of safety, but not efficacy, so we don't have an answer for you in terms of efficacy. But when we looked at safety outcomes, we did not see a difference based on body mass index.

DR. DAVIDSON: Dr. Nelson?

DR. NELSON: Dr. Wesley raised the point about gestational diabetes and preeclampsia being more frequent in both studies in the treatment arm, and I wondered if there's been any -- since -- or one of the open hearing comments was -- written comments, anyway -- was about caution with carbohydrate metabolism. What I wonder is since both of those conditions might have implications for the mother's future health, whether there's anything further known about those complications in pregnancy in the two arms?

DR. HICKOK: Yes. Let me take both of those issues separately, if I might, and first turn to the rate of diabetes. What we observed in terms of the rate of diabetes -- and I might add that this is slightly different than the data that you have seen, but it does not make the 17P group look better, let's say, so I'm not trying to bias you towards a better result.

Again, in women with no history of diabetes in the Study 002, we found a rate of gestational diabetes -- and again, this was described on the

labor and delivery form. There was a check box that said does the mother have gestational diabetes? That rate was 5.8% in the 17P group and 4.7% in the placebo group.

If we look at this and then go to the 001 study, the prematurely terminated study, we see some curious, curious numbers in this, in that we see 9% in the 17P group, but none of the 52 women in the placebo group were recorded who delivered as having a history of gestational diabetes, which is clearly lower than what we would believe should be there.

So if we look at the integrated data, then, between the two studies, we see that the rate of gestational diabetes -- this is in women without previous insulin-dependent diabetes, for example -- is 6.5% in the 17P group and 3.5% in the placebo group.

So naturally, we asked ourselves the question also, what could account for these kinds of differences? So first, with the observed differences, although they are different, again,

they weren't statistically significant in their differences, but we went to the American Diabetes Association, which compiles rates on this, and found again that the standard rate that's quoted by the American Diabetes Association is a 7% rate of gestational diabetes during pregnancy.

We also looked into the literature, which you know is quite voluminous in terms of non-pregnant women with various progestins having various different influences on the rate of type one -- or the rate of type two diabetes, depending on the type of progestin.

But I'd like to say just two points to this first. There really isn't any information to date on gestational diabetes during pregnancy -- well, really, three points. The second point being that the rates in this study were very similar to that of the American Diabetes Association, so we don't think that we're way offline. There is a differential that's been seen, but again, not a large differential.

The reproductive endocrinology people can

probably tell you also that although there can be differences by progestins, and especially, the progestin-only pills, on the rate of glucose intolerance, in many cases, those observations that come from the laboratory don't make a big difference on clinical rates of type two diabetes.

DR. DAVIDSON: Dr. Steers?

DR. STEERS: I know I'm treading on thin ice as a urologist, trying to comment on preterm delivery, but I'll take a shot at this. On one hand, if I was a patient with high risk, I'd be reassured by the generalize-ability that's being argued in addition to statistics for approval of this drug.

On the other hand, with regard to efficacy, generalize- ability, in my view, is for a very defined population, and we seem to have a heterogeneous population, based on one clinical trial that's being examined based on race, vaginosis, birth weights, which leads me to think that this drug is being proposed to work fairly equally on all mechanisms which, in my view, would be highly unlikely, that if you propose a shotgun

effect, I've not seen data with any of these analyses that there's a subset, nor intent to define a subset, where this drug would be indicated and it leads, again, with the high-risk placebo group, how you can say, this is working equally.

If it was just -- do we have data, for example, on the miscarried fetuses, on the vascular abnormalities of the placenta? Do you have any other data that suggest either a mechanism of some specificity with this agent, rather than it's working equally in all groups and it's generalizable with everybody? That isn't reassuring to me as a mechanism of action, and --

DR. HICKOK: Thank you, Dr. Steers. Let me say that, in terms of all different mechanisms, we are first proposing that that mechanism being fairly narrowly defined as those women who have had one or more prior preterm births.

If we go back to Dr. Romero's talk this morning, I think he described how there were a lot of different mechanisms that go into -- whether it's thrombosis, infection, hemorrhage, things like that.

We are proposing that this is a very narrow indication for women with one or more prior pre-term births.

I will, for example, also, if you'd like, talk about -- a little bit about proposed mechanisms of action, if that would more directly address your question.

DR. STEERS: I guess I'm confused. Mechanism, you're looking at a risk group where it's not an independent mechanism, and I guess if there's -- these women continue to have preterm -- you're always saying this is due to one mechanism, but isn't it possible that the immunologic abnormality, their socioeconomic, racial (inaudible), environment, infection, put all these women in different mechanisms; they just happened to have expressed it as multiple preterm deliveries.

I mean, it just -- I just don't understand that -- preterm delivery in that -- yes, that is just one mechanism for that.

DR. HICKOK: Yes, there's a joke that when somebody discovers the true mechanism of preterm

labor, they're going to win a Nobel Prize for it. But your question is a good one, because a lot of preterm deliveries are unknown as to what their etiology are.

If you take other mechanisms, like women with multiple pregnancies, it's presumed due to uterine over-distension and stress. And for example, the one study that we know on 17P that looked at women with multiple pregnancies, the Harketene (phonetic) and Sorrey (phonetic) study, 17P was not successful in those women.

So we know that at least for that other indication, with the data that we know right now, that 17P may not be successful in that group, and hence, Adeza will very narrow in our labeling to limit this to a subset of women that, again, have one or more prior preterm births.

DR. STEERS: Did I hear there's a study ongoing with greater than two -- twin and triplet births, as well, that's not being reported yet?

DR. HICKOK: There is an NICHD maternal-fetal medicine network study ongoing with multiple

pregnancies, and we don't have any data on that study to date from my knowledge today on that.

DR. DAVIDSON: Okay. Dr. Wesley?

DR. WESLEY: Yes. I just would -- something we had begun addressing in our impromptu question and answer session, the question about whether there is any availability of meaningful long-term data? It would seem as though with the 44-year experience with Delalutin, that there would be some information, although it may be difficult to interpret.

However, Dr. Hickok had previously, in response to Dr. Steers, said that there was some information, long-term information from the manufacturer. I don't know whether that consists of some sort of voluntary registry or what form that takes.

Could you please comment on the quantity and the quality of that information? And then, secondarily, has the FDA had an opportunity to review that and are there any observations or conclusions that can be drawn from that information?

DR. HICKOK: Yes. As I mentioned previously, there is a long-term safety database that's managed called the AERS and ADRs databases, and I'd like to call on Dr. Dove to briefly discuss that. We have obtained that database, and we'll -- I'm sorry. I'm going to call on Dr. Meis, actually, to give a kind of broader view of the safety issues. Not only has he been the P.I. of the NICHD study, but Dr. Meis, as you know, has also published information on safety data, and he's going to share with us some long-term safety data.

DR. MEIS: First, before we -- I address that, we have examined the results of our study according to BMI, and these -- treatment was effective against broad ranges of BMI in the participants. A high BMI was somewhat protective in the placebo group, but the treatment did have efficacy across the broad ranges of BMI.

I'd like to just talk about what information is available about longer-term effects of treatment in teenaged and older individuals. There are a few studies that have been published, as it was

remarked, that Delalutin is a drug that has been around for a long time.

I would just like to mention some of the studies that have been published. A study by Kester (phonetic) in 1984 examined a group of adolescent males exposed in utero to Delalutin and performed a battery of psychological tests on the patients and on matched control subjects. The mean age of the subjects was 15 years, and the two groups were comparable in demographic and baseline characteristics.

Prenatal exposure of a male to 17P had no significant effect on type and direction of aggression expressed, the need to conform to group norms of social behavior, the gender identity, interest in sports, games, and rough and tumble play, visual spatial ability, interest in reading and type of books selected, and selection of television programs.

The only significant difference that Kester found was that the males who had been treated with 17P watched more television.

Dalton has published several studies. Dalton, in the '50s, performed some trials of prophylactic use of progesterone in prevention of pre-eclampsia, which seems to us a strange concept, but at any rate, she then had the opportunity to do follow-up on the children who were in her trials.

They reported no case of masculinization of the girls observed, and compared with controls, the children exposed to progesterone in utero had earlier attainment of standing and walking, greater attainment of above average school grades at nine to 10, and later, she found that the children who were exposed attained higher levels on national examinations and were more likely to enter a university.

Renish (phonetic) studied children aged five to 18 years exposed to progestins and estrogen in utero and compared the subjects to their unexposed siblings. There were a number of agents that they were exposed to, but basically, the progestin-exposed children had significant higher scores for independence, individualism, and

self-sufficiency compared with their unexposed siblings, and lower scores for insecurity.

The personality profile has been associated with having a significant relationship with school achievement and success. So at any rate, they didn't really find any deleterious results in these studies of the teenaged children.

DR. DAVIDSON: Okay. Dr. Tulman?

DR. TULMAN: Yes, thank you. I was wondering if you could show us the -- I'm still troubled about the high rate of prematurity in the control group. Were there any differences by site?

DR. HICKOK: Let me address this, Dr. Das. We don't have a slide prepared for you on this. We can probably look this up fairly quickly for you on prematurity rates by site. Oh, we do have -- I'm sorry, we do have a slide.

DR. DAS: Yes, we -- I'm sorry. We have looked at preterm less than 37 weeks by site, and you'll see a relatively consistent treatment effect across sites. Some of the sites with lower enrollment won't have as stable estimates, and so

there may be some differences there.

We also did do a site by treatment interaction analysis, and there was no significance on this analysis, except for the top site, which is Pittsburgh, where that was significant interaction, but you'll see that the number of patients enrolled there is not that high and would not be driving the overall treatment effect.

DR. TULMAN: Could I ask a follow-up question on that?

DR. HICKOK: Yes.

DR. TULMAN: Were there differences in the -- because it does -- there is quite a variation there. Do you have data on the other management of the patients who are at risk -- they all were at risk -- for premature delivery, in terms of other interventions that were done during the pregnancy, whether it was things such as cerclage or bedrest or hospitalization or some such other things? Were there differences in how they were managed?

DR. HICKOK: We do have information, for example, that directly addresses your question on

the use of tocolytics and corticosteroids and would that help you? First, we do have a limitation on the information on tocolytic use because the way the case report forms were created, we have information only on tocolytic use prior to the birth hospitalization; so, for example, as information on tocolytic use, if a mother got admitted one or more times and then discharged, but not for her ultimate hospitalization that led to the birth.

I might add though, too, that this was difficult to summarize because there were no specific guidelines given to the site investigators regarding tocolytic use, and just -- there's various opinions amongst the maternal-fetal medicine unit centers regarding how you should use that. For example, one site used no tocolytic agents whatsoever, and they do that by policy at that institution.

But in terms of giving you the rates of tocolytic use between the 17P and the placebo group, these are very similar at 12.9% in the 17P group and 11.8% in the placebo group.

If we can turn now, though, and talk about corticosteroids -- that should be Slide 544 -- I can give you more information on corticosteroid use. Again, corticosteroids were -- that information was taken at several times during the course of the pregnancy, first at baseline, did you use corticosteroids and for what reason, then weekly during the prenatal visits, and then also, for preterm labor admissions.

But once again, corticosteroid use was collected only prior to the final birth hospitalization.

Again, regarding the same comment that I used about tocolytics, is that there wasn't any guidelines given by the network on that, and people did, just, I'm sure, as people do in the room here, use corticosteroids in various different ways in terms of when to stop administering it, what the dose is, and things like that.

But if we actually turn to the corticosteroid use during the 17P study itself, we can first look at information on any corticosteroid use before

randomization, and in the 17P group, there were five women, or 1.6%; in the placebo group, eight women, or 5.2%.

If we look at that in terms of the type of steroid that was used, we see that inhaled corticosteroids accounted for the great proportion of this 1.6 and -- or at least of the 5.2. The great proportion in the placebo group was due to inhaled corticosteroids, which were presumably because of asthma.

So the difference in corticosteroid use between the 17P and the placebo group was primarily due to the use of -- the lower use of corticosteroids in the 17P group and the higher use of corticosteroids in the placebo is likely due to a high rate of asthma. So in other words, of this difference that we observe, it's most likely due primarily to a high use of an inhaled corticosteroid use for asthma.

We didn't make an adjustment for this in the analysis because recently, there's been two large studies that have failed to identify asthma as a prognostic risk factor for preterm birth. Another

network study by Dembrasky (phonetic) and another study out of the epidemiology literature by Bracken (phonetic) failed to identify asthma as a predictor of preterm birth. Therefore, we felt justified not to adjust for this in the analysis.

DR. DAVIDSON: Dr. Scott?

DR. SCOTT: I guess the efficacy really comes down to are the two groups truly comparable, and we've spent a lot of time on that and the statistics and so on. But aside from that, I just wonder about the biologic plausibility. 17- hydroxyprogesterone is a pretty week progestin, and the endocrinology of pregnancy, of course, is very complicated, but the last half of pregnancy, there are tremendous amounts of hormones being produced by the placenta, including progesterone.

So how do you -- what is the mechanism of action? Why would it work to give a small amount -- 250 milligrams of Delalutin, or 17-hydroxyprogesterone IM, that diffuses into the maternal circulation at a low rate, when you have all these high levels of progesterone and other

hormones -- why would it prevent premature labor?

DR. HICKOK: Your point is a very good one, Dr. Scott, as 20 or 30 years ago, the progesterone supplementation theory was the predominant one. We knew that progesterone levels fell preceding the onset of parturition; hence, if we give progesterone, we prevent -- we supplement with progesterone and prevent preterm birth.

That clearly is not the case, as we know now, and there are mechanisms of action that have been proposed, and I'd like to ask Dr. Singh to again give us brief presentation on some of the mechanisms that have been proposed so far.

DR. DAVIDSON: Dr. Henderson?

DR. HENDERSON: I'd just like to explore -- we talked a little bit earlier about using the animal data, looking -- talking about the effect on the neonate when -- after exposure. And looking at the sexual function and how mature the offspring is, could we talk a little bit about the animal data again? How long did these animals live? I mean, did they have a normal life after they were born?

Did they do all the normal things that they would be expected to do as lab animals, or -- I mean, how can we look at what happened to them after they were exposed to this in utero?

DR. HICKOK: Yes. Mr. Chairman, I'm sorry to ask the question, should we -- I felt like we didn't complete the last answer on mechanism of action, but I'd be pleased to go on to animals and sexual function, if you feel that's most appropriate now. I'm sorry, Dr. Davidson, at your preference, whether you'd like me to finish up the question on mechanism of action or to go on to animal studies and sexual function.

DR. DAVIDSON: Which one would you rather do?

DR. SCOTT: I'd rather the answer to my questions.

DR. HICKOK: Let's defer to Dr. Scott, then -- you're putting me on the spot here -- and have Dr. Singh give us a very brief rundown of some of the proposed mechanisms of action.

DR. SINGH: Actually, Dr. Hickok, since I'm going to be answering both of those questions, it

doesn't really matter which order I take them in. Okay, I'll start with mechanisms of action. Thank you.

Several today have already discussed the proposed mechanisms of action of progesterone, and so forgive me for being repetitive here, but the mechanism of action of 17HPC is unknown. Multiple pathways are possible, if not likely.

The pharmacological activity of 17HPC is similar to that of progesterone; however, their mechanisms of action may be distinct. There are proposed mechanisms of action of progesterone and I'll summarize them briefly on the next slide. They've been generally categorized into non-genomic and genomic mechanisms.

So on this next slide, which briefly summarizes these proposed mechanisms that are out in the open literature, it's been shown that progesterone modulates progesterone receptor activity. It also reduces estrogen receptor activity by either direct interaction with the estrogen receptor or potentially proposed genomic

type mechanism.

Also, it's been shown to inhibit oxytocin-induced uterine contractility, most likely through inhibition of prostaglandin synthesis. It's been shown to enhance tocolytic responses associated with adrenergic receptor responses, and specifically, the beta adrenergic preceptor.

Also, it's been shown to have local anti-inflammatory effects that touch on some of the mechanisms that were mentioned earlier today, such as the -- perhaps the interference with NF kappa beta, transcription of various genes that lead to pro-inflammatory effects. Also, it's been shown to inhibit myometrial gap junctions, and again, leading to uterine quiescence.

So these, again, are the proposed mechanisms, a summary of them that are out and available open literature for progesterone. However, as I mentioned in the beginning, 17HPC, there's very little known on that. Recently, at the SGI conference back in March of this year, it was shown on two different abstracts a couple of in

vitro binding assays with 17HPC that kind of bring to light a little bit of the mechanistic activity of this compound in particular, and how it may be different from progesterone itself.

First, Zaleznic (phonetic) and colleagues presented that actually 17HPC is better at inducing progesterone-responsive genes than progesterone itself or 17 alpha-hydroxyprogesterone. Secondly, Atardi (phonetic) and colleagues showed, in the same conference, that the 17HPC actually exhibits selectivity for the beta isoform of the progesterone receptor, which is associated with transcriptional activity, as opposed to the alpha isoform, which is associated with repressor effects.

So that sort of brings to light some selectivity and differences with respect to 17HPC and how the activity might be different from progesterone, even though they may be very similar, in general.

DR. SCOTT: Are those in vivo studies or in vitro studies?

DR. SINGH: No, those two that were presented,

these abstracts are in vitro receptor binding studies.

DR. SCOTT: Do you have any hard data in the actual patients? Any differences in anything; serum levels or --

DR. SINGH: Dr. Meis will respond.

DR. Yes, Dr. Meis will address that, if we can, Dr. Scott.

DR. MEIS: Dr. Scott, one of this is very recent information which we intend to present at the SMFM next year. We collected salivary samples weekly on these women throughout their gestation, and the early results from a serial sampling of a group of women, both in the 17P and the placebo group who delivered at term and who delivered preterm, basically showed that the treatment did not alter salivary levels of progesterone.

However, it did alter salivary levels of estriol. It lowered salivary levels of estriol and in fact, shifted the estrogen -- the progesterone ratio. Now, we don't know what the mechanism of that is, but it clearly had some effect.

DR. DAVIDSON: Satisfied, Dr. Scott?

DR. SCOTT: Yes.

DR. DAVIDSON: Dr. Carson?

DR. CARSON: Did any of your side effects -- I'm glad that it had such low side effects --

DR. DAVIDSON: Just one he had two questions to answer.

DR. HICKOK: Oh, Dr. Scott asked about -- I'm sorry -- about sexual functions later on in life. Now --

DR. HENDERSON: I asked -- we started when Dr. Steers asked about sexual function, and as adolescents, would you expect or have we noticed that there was any change in puberty. Did fetuses who were exposed to this, when they got to be in puberty age, were they different? And we don't have the answers to that.

So I was asking about the -- and you then suggested looking at the animal studies. The animals -- as the animals went into puberty, or adolescence, what ever the phase would be comparable -- were there -- one, was it any different, and then

two, their length of life, did -- throughout life, were the animals any different after having been exposed to the progesterone in utero?

DR. HICKOK: Yes. I'm sorry we got interspersed questions, and Dr. Singh was ready to address that question.

DR. SINGH: Yes. Unfortunately, I don't have a study to cite for you because that was not actually looked at in the broad range of animal data that is out there and published on 17HPC. The studies that were done only looked at the fetuses upon caesarean section, upon removal from the mother. So they did not look at -- apart from that one study that I mentioned earlier in rats where an F-1 generation was looked at, and the males actually exhibited a suppression in spermatogenesis.

A follow-up study was done by the same team, and it was felt that this might be due to inhibition of testosterone production in those males. And I can tell you that on that subject, though, as far as -- there have been sort of sex-specific differences to your question, as far as

what's been seen in the animal data.

There is no evidence whatsoever of verilization due to the exposures to 17HPC. So in terms of androgenic effects in females, there's nothing, there's no activity there. However, the only signal that there has been in all of the animal data that I have seen is this one study. It was the follow-up study in rats that showed an effect on spermatogenesis.

DR. HICKOK: If I can perhaps turn this a little bit to the molecular level to try to answer your question, it may be helpful. I'd like to remind everybody that the length of exposure to 17P is fairly limited during the pregnancy time. But we have Dr. Frank Stanczyk here, who is a progesterone chemist, who I think could give us some very interesting and worthwhile information on 17HPC as a chemical entity and what its steroid hormone effects are and what we might anticipate in that.

DR. STANCZYK: Frank Stanczyk, University of Southern California in Los Angeles.

DR.HICKOK: Bare with us here as we get a slide

ready. We're pretty close

DR. STANCZYK: I'd like to point out that the 17HPC molecule is very different from the progesterone molecule, and it's the caproic acid side chain that makes it very different.

There is no evidence at all that 17HPC is converted to 17-hydroxyprogesterone. That's what would happen if you had hydrolysis of the caproic acid group. Nor is there any evidence that it's converted to progesterone. Both the 17-hydroxyprogesterone and progesterone assays are readily available. They've been around for many years now, and there is not one study that has shown the conversion of 17HPC to either of these molecules, and this is using both radio-amino assay methodology and mass spectrometry methodology.

Since 17-hydroxyprogesterone, and progesterone, of course, are important precursors for the formation of androgens, estrogens, and corticosteroids, you don't have any conversion of 17HPC to these compounds.

DR. DAVIDSON: Thank you. Dr. Carson?

DR. CARSON: But does 17HPC displace those from albumin or SHBG, to then make them more biologically available?

DR. STANCZYK: 17HPC does not bind to SHBG, but it would bind weakly to albumin. So it would be just like all steroids. It would bind very loosely and would be available to target cells and for metabolism.

DR. CARSON: So it would make those -- the endogenous steroids available then? You would have -- it could --

DR. STANCZYK: The endogenous? Yes.

DR. CARSON: You could, in effect, increase your endogenous bioavailable androgens, estrogens, and progestins.

DR. STANCZYK: You mean by displacing --

DR. CARSON: By --

DR. STANCZYK: From albumin? Well, albumin is a -- like a sponge. It carries all steroids. So it's possible that you would because you get that differentiation between, for example, the sulfates and the glucaronites (phonetic), where the albumin

likes the sulfates a little better than the glucaronites. So this is why you see mostly glucaronites in urine, in addition to the faster glomerular filtration rate. But albumin prefers the sulfates, so -- a little bit, so --

DR. BUSTILLO: But that would also explain the elevated salivary estrogen.

DR. STANCZYK: Yes, that, I don't know how to explain. Of course, it wouldn't be by conversion to estrogens, but it could be that some enzyme is induced somehow, and I think that would be interesting to find out how this occurs.

DR. DAVIDSON: Okay. Dr. Wenstrom?

DR. WENSTROM: I had a comment about an earlier issue and that's the high rate of preterm delivery in the placebo group, which still seems to still be a concern for people around the table. I would think it would be possible to figure out exactly what that preterm delivery rate should have been based on the women's previous preterm delivery, using the data from Brian Mercer that I believe that Dr. Romero presented earlier.

So, for example, a previous delivery between 24 and 28 weeks has, I think, a 50% recurrence risk. If half the patients in this study had a preterm delivery in that range, that would indicate a higher risk of recurrence.

And so couldn't we go back and look at the previous -- what proportion of women were in each of those categories of gestational age at preterm birth, and sort of use that to predict what the preterm birth rate should have been in the placebo group? Because I'm guessing if we did that, we'd find out that it is pretty close to what we'd expect, based on the fact that they were very early -- many of the women had very early preterm births in their previous pregnancies.

DR. HICKOK: Dr. Savitz, can you -- I believe Dr. Wenstrom may be referring to maybe direct standardization technique or something like that. Would you comment to that, Dr. Savitz?

DR. SAVITZ: The sort of -- the general comment is that when we took a look at that, the question was whether -- and specifically comparing the rate

in the placebos in the 17P trial with some of the previous maternal and fetal medicine network trials. In other words, that's the comparison to make. And we're not talking about -- we're not worried at this point about the placebo arm versus the treatment arm; we're worried about why is that baseline rate so high?

That fact alone accounts for a fraction -- I don't remember the exact figure, but it's not by any means the complete explanation. It doesn't go from 37 to 51% when you make that adjustment. It goes up some in that direction.

I think -- I'm afraid that when you look at the results across the centers and so on, I think what we are probably getting is an accurate reflection of the population served in the network centers. In other words, this is the baseline risk in the calendar years of the study, and again, one of the reasons in this case was their recruitment that seemed to more effectively or preferentially recruit those with a more severe history of adverse outcome.

But I really think it's this combination of

medically indicated preterm deliveries, of course, are going up fairly rapidly. If the demographic constitution of the MFM centers changes over time -- and I know I've done work at North Carolina over 10 years. With nothing else changing, we would watch the preterm rates go up. Nothing else changed, the same institution and just over calendar time, not accounted for by demographics.

So this combination of who you're recruiting, clinician inclination, in terms of medically indicated preterm delivery, and I think also just the recruitment into the trial, all of those are part of it. It is also part of it, the most severe adverse outcome history, but not all of it.

DR. DAVIDSON: Dr. Bustillo?

DR. BUSTILLO: I had a question about this last slide that was just handed again, which I think is sort of an amplification of a previous slide that was shown by Dr. Wesley, which was Slide 9, about the graphs of the patients that were still pregnant at certain gestational ages.

MS. WATKINS: For clarification, was that an

open public hearing statement submission?

DR. BUSTILLO: I'm sorry?

MS. WATKINS: For clarification purposes, the slide you are referring to, is it an open public hearing statement submission?

DR. BUSTILLO: No, I'm talking about Dr. Wesley's presentation this morning with the two live table analyses --

MS. WATKINS: Okay. Thank you.

DR. BUSTILLO: -- of the patients that are still pregnant between 20 weeks and 24 weeks being much lower in the treatment group versus the placebo group. So I don't understand that, but my question relevant to that actually is, how was it decided to give drug prior to 20 weeks? Was there any data on -- for the initial trial? Was there a reason that we thought might be more efficacious starting it earlier than 20 weeks, as opposed to 20 weeks? Because the --

DR. HICKOK: Dr. Meis? I'm sorry. Dr. Meis, would you comment on the rationale, as the principal investigator?

DR. MEIS: It seemed that some of the trials of progesterone which had not shown efficacious started the drug rather late in gestation, and we felt that the efficacy would -- may be enhanced by starting it at an earlier time.

We wanted to wait until after 16 weeks to reduce any possible teratogenic effects. We felt that we might prejudice the outcome if we waited until after 21 weeks, that it may not be as effective after that time. The slide presented here shows that the -- I'm sorry, this doesn't really help. That's -- the study in Finland that studied women with the twin gestation started their drug at 28 weeks, and it was totally ineffective, and we thought that might be part of it.

DR. KAMMERMAN: Oh, excuse me. I just had a comment on that. I actually did that analysis for this dataset, and I stratified -- I looked at women who started studies beyond 20 weeks, and the two curves pretty much are identical and they overlap.

It would appear that most of the effect is

coming from women who are started on study drug prior to 20 weeks gestational age, so that would be pretty much consistent with what you were saying.

DR. DAVIDSON: Okay. Dr. Johnson?

DR. JOHNSON: Actually, don't sit down, Dr. Meis. I was going to ask you another question. Addressing back to my original question this morning, when you looked at the Delalutin data, did you find anything in regards to examining children for genital abnormalities? Now, you talked about the effect on their cognitive and behavioral changes, but did you look at any effect on their reproductive tracts?

DR. MEIS: There were no effects found on their reproductive tracts. I didn't go into that, but there was nothing there compared with controls.

DR. JOHNSON: So they did do exams and compare controls to the children that got the 17-hydroxyprogesterone?

DR. HICKOK: Yes.

DR. JOHNSON: Thanks.

DR. HICKOK: And again, that was reinforced by the three large trials that I showed you this morning that looked specifically at 17HPC, exposed infants with controls for the most part, and then FDA's -- also the FDA assessment in 1999 on the progestin class here that I showed you also.

Again, the FDA has done this periodically over time in assessing risks of progestins being -- and estrogens being given during pregnancy.

DR. DAVIDSON: Dr. Nelson, did you have a question?

DR. NELSON: I was -- had been going to comment on the issue that has been raised repeatedly about the high rate of preterm birth in the control arm, and the answer that was given was why there was a high rate of preterm birth in all the entrants to the study. I think the answer to why that's different in the placebo and the active drug recipients had to be -- just has to be the randomization failed, and given -- and that certainly can happen.

I think if we're going to do this study again, one would lock randomize it at admission for number of preterm births.

While I have the microphone, may I make one other comment? That is that the justification for studying an agent to prevent preterm birth has been significantly for the prevention of long-term disabilities, and we have been shown no evidence whatever that that was achieved here. The one week of benefit in gestational age was not in the data we've seen on follow-up associated with any benefit in any of the categories examined.

In fact, it doesn't rule out that there could've been a sharp increase in cerebral palsy, for example, in the children who received active drug, because so few children were examined.

DR. DAVIDSON: Just to comment. Dr. Carson?

DR. CARSON: It's reassuring to see there weren't very many side effects to the drug, and I'm glad about that. But I wonder if you looked at any of the side effects that did occur and see if they were a predictor of preterm labor, particularly like

the local site reaction and the GI side effects.

DR. HICKOK: We looked at the timing of the injection site reactions and found interestingly that they were fairly unpredictable. They would happen in some cases early on and in some cases later on. But it wasn't really an indication that it was a true allergic reaction, with somebody receiving an injection and then later -- or subsequently, getting a more severe reaction.

We don't -- I -- we looked at the relationship between -- I believe we looked at the relationship between onset of premature labor and did not find a result, but I don't have those data to give to you.

DR. CARSON: So you're saying that if they had a reaction, they were not more likely to have preterm labor? Or do you --

DR. HICKOK: I don't believe our -- we had such a low rate of adverse reactions also --

DR. CARSON: I realize --

DR. HICKOK: -- that those -- now, those -- the women -- and I don't have it to show you, but the

women that had injection site reactions, no, were not more likely to have preterm delivery.

DR. CARSON: How about GI side effects?

DR. HICKOK: Gastrointestinal side effects?

DR. CARSON: Yes.

DR. HICKOK: We had very low rates of those also, and that's generally confounded by the pregnancy condition itself and when the -- and a lot of gastrointestinal complications also.

Dr. Davison, could I address -- there's one question of Dr. Nelson's -- she had a two-part question -- that I did not get a chance to answer, which was regarding pre-eclampsia, and then I think she just raised another issue about the value of prolonging pregnancy one week and what might that result.

Because again, the follow-up study was designed as a safety study. It wasn't designed as an efficacy study to say that 17P babies did better than placebo babies. It was really just looking for safety signals up until five years of age. So I wanted to make that point clear. But we do have

other data about the value of prolonging pregnancy. And if I can, we have a neonatologist with us, Dr. Michael O'Shea, that can speak to that issue, and he's trained in public health and epidemiology also, in addition to being a professor and a person who cares for sick neonates.

DR. O'SHEA: I'm going to pull up a slide to try to tie together a number of concepts that several people have spoken about, and it relates to the issue of the surrogate outcome measure. As Dr. Nelson mentioned, there seemed to have been an average prolongation of gestation. Excuse me just a minute. Well, to give you some framework of --

DR. DAVIDSON: How long do you think this is going to take?

DR. O'SHEA: One minute.

DR. DAVIDSON: Okay.

DR. O'SHEA: We can think in terms of the sequela of prematurity as being very prevalent short-terms effects, such as an admission to the neonatal intensive care unit. We can think in terms of somewhat less prevalent, but more severe

problems as one of the -- several of the speakers have spoken about; necrotizing enterocolitis, for example.

Even less prevalent, but more important, would be long-term effects like cerebral palsy. And most important, but least prevalent, would be mortality.

I think the data that were provided to you from the study show an effect on necrotizing enterocolitis and NICU admission. In terms of the latter two events, which are much less prevalent, cerebral palsy and mortality, we would have to use external data which indicate that there is a gradient of risk that extends all the way from 23 to 37 weeks.

DR. DAVIDSON: Okay. Dr. Simhan, you have the last shot at this.

DR. Simhan: Thanks. That's a big responsibility. I have a caution regarding the value of prolonging pregnancy in this setting of what might be a pathological process. If infection is, in fact, the etiology of preterm labor, preterm PROM, that having the fetus remain in utero may, in

fact, have undesired long-term consequences, whether those are neuron-inflammatory or otherwise.

However, with respect to these data, I was -- am I correct in being reassured that the chorioamnionitis frequency in the 17P treated population and the placebo treated population was in fact similar?

DR. HICKOK: That's correct. We were -- it was -- the rate of confirmed clinical chorioamnionitis was very similar between the two groups, and again, that also reassured us, because as you know, you certainly don't want to prolong a gestation where there's an active infection going. But again, this rate was 3.3% in the 17P group, 2.4% in the placebo group, and investigators didn't know which group women were in, so there shouldn't be any biases introduced by that.

DR. DAVIDSON: Let's take -- I know it's impossible, but let's do it. Let's take a 10-minute break, and when we return, we will go over the list of questions from the standpoint of making sure that the committee has clarity about each one of these

questions before we go to the voting at the end of the day, so that if we need to find out additional information from the agency or et cetera so that we're all on the same page when we get ready to vote. Let's take a short break.

(Off the record at 3:05 p.m.)

(On the record at 3:15 p.m.)

DR. DAVIDSON: Okay. Let's reassemble, please. Let's turn our attention to the page -- do you have a -- in your folder a sheet of questions for the Advisory Committee for Reproductive Health Drugs that are numbered? Everyone has this sheet? Is there anyone without a sheet? Okay.

This is not for voting; this is for clarity and making sure we understand the questions. So why don't we just go through these in order and see whether or not any clarification is requested by anyone? I have been advised that maybe I should read the introductory paragraph that's at the top of this page.

In general, the FDA requires an applicant for a new drug product to submit two adequate and

well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable.

The applicant is seeking marketing approval for 17HP based primarily on: (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal infant morbidity and mortality; i.e., reduction of the incidence of preterm birth at less than 37 weeks gestation. Any questions or comments about that?

Question 1-A. Is the primary endpoint for 17P CT002 prevention of preterm birth prior to 37 weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity? Understandable? Any questions about

that?

DR. VISCARDI: Actually, I guess I have a comment. Again, as a neonatologist, I'm a little concerned about that being a surrogate for fetal and neonatal mortality and morbidity, because when you actually look at the mortality data and the morbidity data, both -- at least the short-term NICU morbidity, there really were not any important differences, yet there was a reduction in the incidence of preterm birth less than 37 weeks.

But the more important outcome is how do those pregnancies do, and I think that I'm not entirely convinced that that is an appropriate surrogate.

DR. DAVIDSON: Let me get this. You understand the question, but you are questioning its appropriateness?

DR. VISCARDI: Well, the question is, is it an adequate surrogate? And I would state that it is not an adequate surrogate.

DR. DAVIDSON: Yes, we are now just clarifying the question. All of those other things may go into how you answer it --

DR. VISCARDI: Okay.

DR. DAVIDSON: -- but you do understand the question?

DR. VISCARDI: I do understand the question. I was --

DR. DAVIDSON: Okay.

PARTICIPANT: She was answering it for us.

DR. DAVIDSON: Yes.

PARTICIPANT: As a neonatologist, she answered the question.

DR. VISCARDI: Jumped ahead there.

DR. DAVIDSON: Dr. Hankins?

DR. HANKINS: Is it and, or is it or? Fetal and neonatal, or fetal or neonatal? I hate to be picky, but which is it? The same thing is going to come up in (inaudible).

DR. DAVIDSON: Okay. An adequate surrogate for a reduction in fetal and neonatal mortality. I'll ask the FDA. They put the and here. I can't hear you.

DR. MONROE: Can you hear me?

DR. DAVIDSON: Yes.

DR. MONROE: Yes, we would prefer that to be an and, because we're looking at the whole pregnancy as a continuum. So if, for instance, you had a negative impact on fetal outcomes, but you had a gain on neonatal, and the outcome was zero, we wouldn't consider that a benefit. So I think we would like it to be fetal and neonatal as a continuum. Is that hopefully clear?

DR. DAVIDSON: 1-B. If not, would prevention of preterm birth prior to 35 weeks or prior to 32 weeks gestation be an adequate surrogate? Any questions? Like -- yes?

DR. JOHNSON: Yes. When answering that, would it be -- if we need to answer that question, should we state 35 or 32? I presume we should let you know which of those two is acceptable.

DR. MONROE: Yes, we would like to know which of those two, or if both are acceptable.

DR. DAVIDSON: Now, I have a list -- the Chair would like a clarification. I have a list of yes, no, or abstain as an answer to all of these questions. You're telling me that there is another

option here in 1-B, that if one votes one way or the other, they say both or 35 or 32 weeks?

DR. MONROE: I guess in retrospect, that should be a B and a C, perhaps. We would like the differentiation. That would helpful in our deliberations.

DR. DAVIDSON: Okay. Any questions about that? Question 2. Do the differences in the incidence of preterm birth in Study -- I'm just -- 002 prior to 37 weeks in the vehicle control group, 55% compared to those in the control arms of another maternal-fetal medicine unit network trial, approximately 37%, and (b) Study 1701, 36%, evaluating similar high-risk populations, indicate the need to replicate the Study 002 in a confirmatory trial? Any questions about that? Understandable and clear?

Question 3-A. Do the data reviewed by the committee provide substantial evidence that 17PC prevents preterm birth prior to 35 weeks or 32 weeks gestation age? Do you want a specific week after this question?

DR. MONROE: Yes. Once again, the differentiation between 35 and 32 is important.

DR. DAVIDSON: Okay. Any question about that? You answer with either both, or a differentiation between these weeks of gestation.

Question 3-B. No, no, we're not voting. No. I will ask you to vote, and your vote will be public and we are -- we're just going through to make sure when we do this when you're voting, that there is understanding of the questions. If you leave the starting blocks before the gun, it's a foul.

3-B. Do the data reviewed by the committee provide substantial evidence that 17HPC reduces fetal and neonatal mortality or morbidity? Any question about that? Potential safety concerns and adequacy of safety data, there was a numeric increase in the percentage of second trimester miscarriages, pregnancy loss prior to week 20 of gestation, and stillbirths in the 17HPC group.

Overall, 11 of 306 subjects, 3.6% 17HPC group, and two of 153 subjects, 1.3 in the vehicle or control group, had a second trimester miscarriage or

stillbirth.

Question 4-A. Is further study needed to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth?

DR. WESTNEY: Sorry, I just had a question, and I hate to subdivide things unnecessarily, but the question is, when you're speaking about morbidity or mortality, it's conceivable that you might say there's a different threshold, depending on whether you're talking about morbidity versus mortality.

DR. DAVIDSON: Would you say that over again?

DR. WESTNEY: I'm saying you may say, for instance, for morbidity, that would be sufficient 35 weeks -- less than 35 weeks, and in mortality, you may say that it's 32 weeks.

DR. DAVIDSON: Dr. Monroe, did you understand that?

DR. WESTNEY: Or just group them together, but I just want a clarification.

DR. MONROE: I understand the concept. Are you referring to a specific question, and which subpart?

DR. WESTNEY: I'm sorry?

DR. MONROE: I understand the concept of your question --

DR. WESTNEY: Right.

DR. MONROE: -- but are you referring to a specific question, and --

DR. WESTNEY: Yes, either 1B or 3B. Where you were asking for either 32 or 35 weeks, is it just both together, morbidity and mortality, or one or the other, or is there a specific week that you should look at for mortality versus morbidity, if that's different to you? And that maybe something that's more critical to the people who are actually MFM. I mean, we're all --

DR. MONROE: We were not really differentiating between that. If you wish to comment, that would be up to you. I guess you could discuss that during your discussion about it.

DR. WESTNEY: Okay.

DR. DAVIDSON: Are you clear? Any other questions? Speak now, or -- I'll read Question B, anyway, although it's been discussed. If so, should

this information be obtained prior to approval for marketing or post-approval? So that's kind of two parts to that question. I guess you want specific help in that regard?

DR. Simhan: So again, just to clarify, that's -- if the three options are yes, no, or abstain, there's actually two options there that -- so prior to approval for marketing would be one option, and then post-approval would be option two?

DR. DAVIDSON: Right, right. Any further questions? I know some of you thought this was unnecessary. Question 5. Are the overall safety data obtained in studies 17PCT02 and 01 and studies 17PFU long-term follow-up adequate and sufficiently reassuring to support marketing approval of 17HPC without the need for additional pre-approval safety data? Any question about that? No?

Post-approval clinical studies. Question 6-A. If 17HPC were to be approved for marketing without additional pre-approval clinical studies, would you recommend that the applicant conduct a

post- approval clinical trials to investigate further safety or effectiveness? Any question about that and its options? Yes?

DR. TULMAN: There might be an overlap of potential conflicting results that can lead to some ambiguity here. For example, if we were to say that we think we need some more -- if we were to say that we don't believe that we need more second trimester miscarriage and stillbirth info post-approval, but we still might want post-approval studies for long-term effects after the child is born alive.

So I think we could get into a situation of having an -- of not being able to vote on what we wanted to vote on because of the way it's phrased. I'm not sure how to fix it, so --

DR. DAVIDSON: I -- okay, let me read 6-B and see if that helps. If so, what would be the primary objective of the trials? What unanswered questions would this study investigate?

DR. TULMAN: Okay. So then you could -- okay.

DR. DAVIDSON: Does that help?

DR. TULMAN: Probably.

DR. DAVIDSON: I've been assured these questions have been gone over carefully in the Agency, and if there are internal issues to resolve, they will have to resolve them. Yes, sir?

DR. MONROE: To perhaps reduce some of the ambiguity and make voting easier, where you correctly identified that we didn't fully differentiate between weeks 35 and 32, would it be helpful if, for Question 1-B, we make it a B, as far as 35 weeks, and then call that C for 32, just to keep track of bookkeeping.

So it would be -- for instance, 1-B would read, "If not, would prevention of preterm birth prior to (B) 35 weeks or prior to (C) 32 weeks," just for the purposes of answering and keeping track of this score?

DR. DAVIDSON: Wait a minute.

DR. MONROE: I'm going back to 1-B, where you had identified --

DR. DAVIDSON: You're going back to 1-B?

DR. MONROE: Yes. I thought you had finished everything, and I just wanted to clarify before you

go on to voting, to make that perhaps --

DR. DAVIDSON: Well, okay. Well, then go over that again?

DR. MONROE: Yes. For Question 1-B, says, would prevention of preterm birth prior to 35 weeks or prior to 32 weeks gestation be an adequate surrogate? Perhaps it would just be easier to call that a B and a C, or I don't know how you will keep track of the vote. I just --

DR. DAVIDSON: You want to make a C and put 35 weeks, B; 32 weeks, C?

DR. MONROE: yes. I think it would just allow people to answer yes or no very simply. If you feel that will further confound everybody, I'll defer to your judgment. And then the same would apply to Question 3, Dr. Davidson. A would have to be -- A would apply up through 35 weeks, then B could apply through 32 weeks, and then what is now B would become a C. If that hasn't confused everybody, I'll --

DR. DAVIDSON: So you want to make B, C?

DR. MONROE: Yes. And I think then it'll be

very easy to keep track of the votes.

DR. DAVIDSON: Okay.

DR. MONROE: All right.

DR. DAVIDSON: You're challenging our bookkeeper here. A would be 35 weeks, Question 3-B would be 32 weeks, and C stands as it is, and --

DR. NELSON: To help us in answering that first question, we all know that the risk per baby is much greater in under 32-weekers. On the other hand, there are a lot more babies in the less severely preterm children. Is any information available about attributable risks in those groups that would help us answer that question; that is, how much of the morbidity and mortality come from these different niches, or is such data available?

DR. DAVIDSON: Well, I think, unless someone wants to answer that, you'll have to go from whatever available information that's been provided.

DR. HANKINS: Well, Karin asks a very interesting question, and the NIH convened a task force on the late preterm infant, and that data is generally available --

DR. DAVIDSON: Would you speak a little closer into the microphone?

DR. HANKINS: The question that Karin asked is very, very important, and the NIH, within the last few months, convened a task force on the late preterm delivery. And it was alluded to earlier, ACOG has a practice bulletin that's coming out. One of the astounding things that would probably surprise very people is there are more ventilator days in America between 34 and 37 weeks than in all the rest of the babies going into units.

Now, I'm in a tertiary care center and I'm biased. I would've never believed that if I hadn't seen the data that came from the pediatrics group, etc. So the data is available, the task force met, and I think that is important information, perhaps, that people that are just giving input might need to look at to give the best-informed input.

DR. HENDERSON: It's also available on the March of Dimes web site. They do a very nice graph for each gestational age and what the contribution is to the preterm delivery population.

DR. DAVIDSON: Dr. Steers?

DR. STEERS: Yes, clarification for Question 6. If you don't believe that the mechanism for any concerned safety is a clinical trial, but let's say a registry, are we allowed to kind of have that trial registry, or is it strictly within the confines that the FDA wants us to specify a clinical trial, which may not actually answer or be impractical?

DR. MONROE: We would like it answered in the broader context, where -- a trial we would lump under the general request to you, yes. I mean, a registry could be considered a trial in the context of the question.

DR. DAVIDSON: Dr. Monroe, did you have any answer for Dr. Hankins and Dr. Nelson?

DR. MONROE: No, I don't have a specific answer. I think if I understood their comments is that there is new information that would be nice if everybody, I guess, on the panel had access to, to help them in their answering our questions, but I think the reality of the moment is that everyone

will have to go with whatever information they have, and I guess those individuals that have access to that data, in terms of their response to the questions, it's up to your prerogative, Dr. Davidson, but frequently, an individual has the opportunity to explain their vote, and perhaps in that context, they might explain something that which to some people, may not appear to be -- the logical answer be based on some new information that have privy to. Does that perhaps help?

DR. DAVIDSON: I am -- I have been advised -- I don't know if this answers it -- that if you wanted to make a comment or a statement at the time of your vote, I guess that also will be registered on the -- so that may help.

I think I see a collective nod from the Agency. So that -- if that provides any comfort to yes or no and then making a statement about it, it will be a part of the record that they will have for review. Is that acceptable? Any other questions? Are there any other questions? Oh, you do? Okay.

Well, let's see if we can go through this and keep all of the new Bs and Cs separated, so let's be careful about that. So let's begin at Question 1. I will not start with the same person on each question, so that there will be no bias here, at least as much as possible.

I think Dr. Hankins is the first voting member on this side. Is that correct? We'll start with you, Gary, with the first question.

DR. WATKINS: Just -- I'm sorry, just a reminder to the committee members. Please identify yourself prior to casting your vote so that the transcriber is able to easily identify you.

DR. DAVIDSON: Is the -- I won't read this question each time for each person, so we're going on Question 1-A. Is the primary input for Study 02, prevention of preterm birth prior to 37 weeks gestation, an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

DR. HANKINS: Gary Hankins. No.

DR. DAVIDSON: Next?

DR. NELSON: Karin Nelson. No.

DR. DAVIDSON: Speak -- was that --

DR. NELSON: No.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. Yes.

DR. DAVIDSON: Yes?

DR. JOHNSON: Yes.

DR. STEERS: William Steers. No.

DR. LIU: James Liu. No.

DR. Simhan: Hy Simhan. Yes.

DR. DAVIDSON: Yes?

DR. LEWIS: Vivian Lewis. No.

DR. DAVIDSON: I've been advised not to vote until the end.

DR. WENSTROM: Katharine Wenstrom. Yes.

DR. HARRIS: Joseph Harris. No.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No.

DR. SCOTT: Jim Scott. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. CARSON: Sandra Carson. No.