DR. WESTNEY: Lenaine Westney. No.

DR. SHANKLIN-SELBY: Elizabeth Shanklin-Selby. No.

DR. DAVIDSON: No?

DR. SHANKLIN-SELBY: No.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. No.

MS. WATKINS: If the committee members will kindly turn their mikes off after voting. Thank you.

DR. DAVIDSON: Thank you. The next question has a B and a C, B being 35 weeks and C being 32 weeks. Let's start with Dr. Tulman on B. If not, would prevention of preterm birth prior to 35 weeks gestation be an adequate surrogate?

DR. TULMAN: Yes.

DR. SELBY: No.

DR. DAVIDSON: No?

DR. SELBY: No.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandra Carson. Yes.

DR. HENDERSON: Cassandra Henderson. I said yes

for 37, so --

DR. DAVIDSON: Hold just a second. That's not an option. This is yes. Selby is no. And Westney is no? Is that right? Two yes. That's -- Tulman is no.

MS. WATKINS: Dr. Tulman?

DR. DAVIDSON: Tulman is yes.

MS. WATKINS: Dr. Tulman, please restate your vote.

DR. TULMAN: Yes.

MS. WATKINS: Yes.

DR. DAVIDSON: Okay. And Shanklin-Selby is no, and Westney is no, and Carson is yes. Okay.

DR. HENDERSON: I voted yes for 37 weeks, and I think either -- I think 37, 35, 32 --

DR. DAVIDSON: You can't change the question now.

DR. HENDERSON: Well, but I'm -- yes, but -- okay. Yes for both.

DR. SCOTT: What do we do if we voted yes the first time?

DR. HENDERSON: Then say yes the second time

too.

DR. DAVIDSON: You can say yes both times.

DR. SCOTT: 35 weeks better, yes.

DR. DAVIDSON: Dr. Henderson, would you restate your vote?

DR. HENDERSON: Yes.

DR. VISCARDI: No.

DR. GILLEN: Daniel Gillen. No.

DR. HARRIS: Joseph Harris. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. SIMHAN: Hy Simhan. Yes.

DR. LIU: James Liu. Yes.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. DAVIDSON: What are the totals? Oh, 21? Well, we didn't -- maybe we should read the totals

for the first one. For the record, we are reading the totals -- I'm going -- you've already done this. This is 1-A. The yes votes are -- I'm doing the first one now. The yes voted are five and the no votes -- it couldn't be. Have to be 16. The no votes are 16.

DR. DAVIDSON: On Question 1-B, Ezra Davidson votes yes. So 1-B, the yes votes are 13, the no votes, eight. Question 1-C, if not, would prevention of preterm births prior to 32 weeks gestation be an adequate surrogate? Let's start with Dr. Harris and go back around. Oh, I'm sorry. I intended to do the first one here, Dr. Wenstrom.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: Jim Liu. Yes.

DR. STEERS: William Steers --

DR. DAVIDSON: Wait, hold, hold -- hold just a minute. Hold just a minute. My multi-tasking here isn't -- what do you have for Harris? I mean, so far, all yeses. Okay. Dr. Liu? Yes?

DR. LIU: Yes.

DR. DAVIDSON: Okay.

DR. STEERS: William Steers. Yes.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. Yes.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. DAVIDSON: No?

DR. BURNETT: No. No.

DR. DAVIDSON: Okay.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. DAVIDSON: Tulman?

DR. TULMAN: Lorraine Tulman. Yes.

DR. SHANKLIN-SELBY: Elizabeth SHANKLIN-SELBY. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. CARSON: Sandra Carson. Yes.

DR. HENDERSON: Sandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. DAVIDSON: Ezra Davidson. Yes. So there is 20 yes and one no. Question 2. Do the differences in the incidence of preterm birth in Study 02 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%, in Study 17IF01, 36%, evaluating similar high-risk populations, indicate the need to replicate the findings of Study 17B02 in a confirmatory trial? Dr. Lewis, why don't we start with you and go around the table?

DR. LEWIS: No. Vivian Lewis.

DR. Simhan: Dr. Davidson, can I append my vote with a little comment? Was I allowed to do that?

DR. DAVIDSON: Sure.

DR. Simhan: Okay. Hy Simhan, no. I'm reassured that the frequency of preterm birth in the control arm, in fact, represents an expected frequency of preterm birth in a population with a risk profile that was actually enrolled in the

study.

DR. LIU: I also vote no. Jim Liu.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. No.

DR. MERRITT: Diane Merritt. Yes.

DR. DAVIDSON: Yes?

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. No.

DR. HANKINS: Gary Hankins. No. And I would like to also note that if you drop down to the 35-week and lower categories, those huge changes disappear and look much more close to the other trial data that exists.

DR. DAVIDSON: Tulman?

DR. TULMAN: Lorraine Tulman. No.

DR. SHANKLIN-SELBY: Elizabeth SHANKLIN-SELBY. Yes.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandra Carson. Yes.

DR. HENDERSON: Cassandra Henderson. No.

DR. SCOTT: Jim Scott. No.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. No.

DR. DAVIDSON: Ezra Davidson. Yes. I have nine yes and 12 no. Question 3-A. Now remember, again, we have a 3-B and C, so A and B are separated, A being 35 weeks and B being 32 weeks.

Okay. Why don't we start with you again, Dr. Hankins? And the question is, do the data reviewed by the committee provide substantial evidence that 17HPC prevents preterm birth prior to 35 weeks gestation age?

DR. HANKINS: Yes.

DR. DAVIDSON: Yes, this way.

DR. NELSON: Karin Nelson. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. MERRITT: Diane Merritt. No.

DR. DAVIDSON: No?

DR. JOHNSON: Julia Johnson. Yes.

DR. STEERS: William Steers. No.

DR. LIU: James Liu. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LEWIS: Vivian Lewis. Yes.

DR. WENSTROM: Kathy 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: Sandy Carson. No.

DR. WESTNEY: Lenaine Westney. No.

DR. SHANKLIN-SELBY: Elizabeth Shanklin-Selby. Yes.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. Yes. And the tally: yes, 12; no, nine. Question 3-B. Do the data reviewed by the committee provide substantial evidence that 17HPC prevents preterm birth prior to 32 weeks gestation? Let's start with Dr. Tulman.

DR. TULMAN: No.

DR. SELBY: Yes.

DR. WESTNEY: Lenaine Westney. No.

DR. CARSON: Sandy Carson. No.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. No.

DR. GILLEN: Daniel Gillen. No.

DR. HARRIS: Joseph Harris. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. LEWIS: Vivian Lewis. No.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: Yes.

DR. DAVIDSON: Wait a minute, I think I have -- let me just confirm. Okay.

DR. LIU: Jim Liu. Yes.

DR. STEERS: William Steers. No.

DR. JOHNSON: Julia Johnson. No.

DR. MERRITT: Diane Merritt. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. BURNETT: Arthur Burnett. No.

DR. NELSON: Karin Nelson. No.

DR. HANKINS: Gary Hankins. Yes.

DR. DAVIDSON: That it? Ezra Davidson. No. Okay, what's your tally? Yes, six; 15 no. Question

-- which is now 3-C. Do the data reviewed by the committee provide substantial evidence that 17HPC reduces fetal and neonatal mortality or morbidity? Start with Dr. Wenstrom.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. DAVIDSON: And let's go around.

DR. HARRIS: Joseph Harris. No.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No.

DR. SCOTT: Jim Scott. No.

DR. HENDERSON: Cassandra Henderson. No.

DR. CARSON: Sandy Carson. No.

DR. WESTNEY: Lenaine Westney. Yes, but an addendum; only in relation to morbidity, not mortality.

DR. SHANKLIN-SELBY: Liz Selby. No.

DR. TULMAN: Lorraine Tulman. No.

DR. HANKINS: Gary Hankins. No. And I would again like to state that's why I asked for if it's either/or versus both, and it was clarified, so the answer is no.

DR. NELSON: Karin Nelson. No.

DR. DAVIDSON: That was no, Dr. Nelson?

DR. NELSON: Correct.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. No.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. No.

DR. STEERS: William Steers. No.

DR. LIU: Jim Liu. No.

DR. Simhan: Hy Simhan. No.

DR. LEWIS: Vivian Lewis. No.

DR. DAVIDSON: Ezra Davidson. No. I have two yes, 19 no. Question 4. Well, let me read the preface. 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 in 17HPC group, and two of 153 subjects, 1.3 in the vehicle group, had a second trimester miscarriage or stillbirth.

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

stillbirth? Dr. Lewis, why don't we start with you and go around?

DR. LEWIS: Vivian Lewis. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LIU: James Liu. Yes.

DR. STEERS: William Steers. Yes.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. Yes.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. TULMAN: Lorraine Tulman. Yes.

DR. SHANKLIN-SELBY: Liz Selby. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. Yes

DR. DAVIDSON: Ezra Davidson. Yes. Twenty-one yes, zero no. Question 4-B. If so, should this information be obtained prior to approval for marketing or post-approval? Dr. Tulman, let's start with you.

DR. TULMAN: Clarification, so the vote is either pre or post; is that the two choices?

DR. DAVIDSON: Your vote is to be pre or post.

DR. TULMAN: Okay. Pre.

DR. SHANKLIN-SELBY: Liz Selby. Pre.

DR. WESTNEY: Lenaine Westney. Post.

DR. CARSON: Sandy Carson. Post.

DR. HENDERSON: Cassandra Henderson. Post.

DR. SCOTT: Jim Scott. Post.

DR. VISCARDI: Rose Viscardi. Pre.

DR. GILLEN: Daniel Gillen. Post.

DR. HARRIS: Joseph Harris. Pre.

DR. WENSTROM: Kathy Wenstrom. Post.

DR. LEWIS: Vivian Lewis. Pre.

DR. Simhan: Hy Simhan. Post.

DR. LIU: Jim Liu. Post.

DR. STEERS: William Steers. Post.

DR. DAVIDSON: Post?

DR. STEERS: William is post.

DR. DAVIDSON: I'm sorry?

DR. STEERS: Post.

DR. DAVIDSON: Post? Okay.

DR. JOHNSON: Julia Johnson. Pre.

DR. MERRITT: Diane Merritt. Post-approval.

DR. BUSTILLO: Maria Bustillo. Pre.

DR. BURNETT: Arthur Burnett. Pre.

DR. NELSON: Karin Nelson. Post.

DR. HANKINS: Gary Hankins. Post.

DR. DAVIDSON: Ezra Davidson. Post. Eight yes -- I mean, eight pre-approval, 13 post-approval.

Question 5, yes or no. Are the overall safety data obtained in Study 1701, 02, and long-term follow-up adequate and sufficiently reassuring to support marketing approval of 17HPC without need for additional pre-approval safety data? Dr. Hankins, why don't we start with you?

DR. HANKINS: Yes. Gary Hankins. Yes.

DR. DAVIDSON: Let's go this way.

DR. NELSON: Karin Nelson. Yes.

DR. BURNETT: Arthur Burnett. No.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. MERRITT: Diane Merritt. No.

DR. JOHNSON: Julia Johnson. No.

DR. STEERS: William Steers. Yes.

DR. LIU: Jim Liu. Yes.

DR. Simhan: Hy Simhan. Yes.

DR. LEWIS: Vivian Lewis. No.

DR. WENSTROM: Kathy Wenstrom. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. GILLEN: Daniel Gillen. No.

DR. VISCARDI: Rose Viscardi. No. And I would just comment that the follow-up study was inadequate because of the methods used to identify all children with disabilities.

DR. SCOTT: Jim Scott. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. SHANKLIN-SELBY: Liz Selby. No.

DR. TULMAN: Lorraine Tulman. No.

DR. DAVIDSON: Ezra Davidson. Yes. Thirteen

yes, eight 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 trial to investigate further safety or effectiveness? Dr. Lewis, why don't we start with you?

DR. LEWIS: Yes.

DR. Simhan: Hy Simhan. Yes.

DR. STEERS: William Steers. Yes.

DR. JOHNSON: Julia Johnson. Yes.

DR. MERRITT: Diane Merritt. Yes.

DR. BUSTILLO: Maria Bustillo. Yes.

DR. BURNETT: Arthur Burnett. Yes.

DR. NELSON: Karin Nelson. Yes.

DR. HANKINS: Gary Hankins. Yes.

DR. TULMAN: Lorraine Tulman. Yes.

DR. SHANKLIN-SELBY: Liz Selby. Yes.

DR. WESTNEY: Lenaine Westney. Yes.

DR. CARSON: Sandy Carson. Yes.

DR. HENDERSON: Cassandra Henderson. Yes.

DR. SCOTT: Jim Scott. Yes.

DR. VISCARDI: Rose Viscardi. Yes.

DR. GILLEN: Daniel Gillen. Yes.

DR. HARRIS: Joseph Harris. Yes.

DR. WENSTROM: Kathy Wenstrom. Yes

DR. DAVIDSON: Ezra Davidson. Yes. Twenty-one yes, zero -- oh, I'm sorry.

DR. LIU: Jim Liu. Yes.

DR. DAVIDSON: Oh. Twenty-one yes, zero no. Okay. I hear you have a chance at a narrative. Should we put a time limit on these? If so, what would be the primary objective of the trials? What unanswered questions would the study investigate? Since we started with you, Gary, let's end with you.

DR. HANKINS: Since I think every one of us voted that the issue of stillbirth and early loss needs to be looked at, I think that's certainly a part of the surveillance that we would hope, even post-marketing of the drug. That's one issue.

The second issue is I would like to see more long-term follow-up of the children in a more formalized testing fashion. I understand how this study was conducted, that was never the goal of it,

etc., but post-marketing, I think there should be a leveled requirement to follow at least a cohort of these children in a prospective fashion for neural development.

DR. NELSON: Karin Nelson. Maternal gestational diabetes, fetal death, neonatal death, days in hospital, days on ventilator, abnormal neonatal neuron-imaging, I'd love to see a lengthy late testing, but I think the numbers -- unless you get really -- it just doesn't seem clearly realistic.

DR. BURNETT: This is going to sound a little bit like a broken record, but I echo their comments. I think we need long-term follow-up on the children, and I do think that there are some concerns raised in the mother with regard to gestational diabetes and some of the other co-morbidities, and I think follow-up on that side is required, as well.

DR. BUSTILLO: Being an endocrinologist, I'm very interested in pubertal development, so I certainly would like long-term studies looking at the children in terms of their genital development

and their internal general structures, etc.

DR. MERRITT: Being a pediatric gynecologist, internal structures on children are very difficult to assess, short ultrasound. So I would vote for more immediate neonatal data that is already being -- started to be looked at, as well as maternal data, and post-marketing stillbirth and first trimester data, second trimester -- the post-marketing is second trimester pregnancy loss data, sorry.

DR. JOHNSON: Yes, Julia Johnson. I hear Dr. Nelson's argument about not following patients long-term, but I would like to see the effect on reproductive health, fertility, because of the issue about sperm production, on reproductive health for both men and women who were exposed to this in utero.

DR. STEERS: William Steers. Based on the spermatogenesis, or sperm count data, and the lack of long-term data, I'd like to recommend a more practical approach, and not necessarily a study, but a registry of all children exposed to this with

fertility, rather than a strict study, per say, but at least they're registered and they can be tracked.

DR. LIU: I haven't expressed my views on this, but judging from the way that this compound is handled in the body, I think we should consider this a new type of progestogen as opposed to thinking that this is progesterone or 17-hydroxyprogesterone, because the caproate moiety is not broken down.

I am concerned that we may be dealing with a different steroidal exposure, even though it does bind to progesterone receptors, and I think a registry is the minimum I would recommend, if nothing else, as well as long-term pubertal development follow-up. Because I'm afraid that we may be forced to use this compound for preterm labor prevention, but yet, we don't know what the downstream side effects are.

DR. Simhan: I echo the support for surveillance for mid trimester loss, whether that be stillbirth or birth prior to 24 weeks. I think a practical methodology for surveying some of these other issues is a registry, so I echo support for that, as well.

DR. LEWIS: I concur with a registry. That's certainly a good idea. It's true that there are -- I think valid concerns have been raised about potential pubertal or reproductive effects downstream in both sexes. As well, of course, I'm concerned about the incidence of very early stillbirth and/or second trimester loss.

Some of these questions can be answered through a registry. Also, I would wonder whether there aren't data available by studying European populations which are easier to track the -- after all, this compound has been available for many, many years and in wide use, and perhaps a study, even a case control study, could be designed on populations who are already out there, rather than thinking that we have to wait another 20 years to get some of this information.

DR. WENSTROM: I would like to see all future losses evaluated by a fetal pathologist with a complete protocol. Several studies have shown that with a complete evaluation, you can determine the cause of a loss in over 90% of cases. And then,

because this drug is already being used for all sorts of perceived or imagined risk factors, I think we should start looking at it in other kinds of high-risk women.

DR. HARRIS: Yes, I'd like to agree with the increased examination of second trimester miscarriages and stillbirths that's already been mentioned on the safety side, and on the efficacy and effective side, better data on neonatal outcome.

And under maternal complications, perhaps at least screening women for depression to make sure that this drug is not increasing their risk of depression in the postpartum period for this population. And maybe be more user-specific, since we now have described at least four etiologies or four pathways for preterm labor, some which are contraindications to even preventative therapy, to look at that to see how that holds up in a post-marketing evaluation.

DR. GILLEN: I think it's pretty hard to argue with days in the hospital following birth and long-term follow-up being clinically relevant, and

so I would like to see both of those evaluated, with penalties taken for some sort of penalization for miscarriages and stillbirths in that way.

DR. VISCARDI: I second that about hospital days as being probably an appropriate thing to track, as well as, for long-term follow-up, probably an appropriate comparison would be comparing these children that were exposed to the progesterone to their siblings who were born preterm, since the indication is going to be a prior preterm birth, to see whether, in fact, there is any difference as a result of being exposed to that drug.

DR. SCOTT: Even though I voted for it, I'm still skeptical. I think that premature labor and preterm birth is such a huge and devastating problem that the potential benefits way outweigh the risks of non-approval, but I still think that there are potential problems with the control group that was presented.

And so I'd like to see longer and additional studies that really do prove the efficacy. I think that that's necessary. I think that it should be

possible to get much better data on the exact risk of premature labor in the next pregnancy by week of gestation, and I think that's a crucial thing.

I'd like to see more biologic data to prove that it really works. In other words, why not just even do simple 17-hydroxyprogesterone levels in mothers in which it worked -- in other words, premature labor was prevented -- versus those that were a failure? In other words, I think that those things are important.

I pretty much second the March of Dimes' recommendations, in which they outlined how this ought to be done and followed up.

DR. HENDERSON: I'd like to see investigation for the losses, the stillbirths and the spontaneous abortions, looking for infectious etiologies that could potentially be treated. And I'd also like to -- well, I think a clinical trial to really prove that this works would be useful.

I think it would also be helpful to just even go back and survey all the networks to see what their rate of preterm delivery has been,

understanding that this drug is so widespread now -- urologists are using it if they have a complicated pregnancy; they don't tell the GYN to give it.

So, I mean, understanding that it's out there and people are using it, that it would be nice to know what the networks preterm delivery rates were now. Because if they were approaching 50%, then it would make sense that the control group had a 50% incidence of preterm delivery.

DR. CARSON: Well, I'm very concerned about how much we don't know about just regular pharmacokinetics and dynamics of this drug. The studies that we've read in preparation to this gave 25 milligrams to a rodent model. That's about -- it seems to me, doing the math, that that's probably, on a per-kilogram basis, about 25 times larger than the dose that was administered.

The axle (phonetic) study gave 1000 milligrams to squirrel monkeys. I don't know how big they are, but I guess they're about like this. And so I would think you're getting four times the dose in that

model at -- which is maybe about a fifth the size of an adult non-pregnant woman. And we don't have -- and in those studies, it's very variable about efficacy and drug levels are not that high.

We don't have any idea about what kind of drug levels we have in women who have BMIs all over the board who have at least a 30% increase in their blood volume. I'm very concerned about exactly whether any of these women really did have an effective drug in their circulation. And when one -- so I think that we need to ask for, (1) some dose ranging studies and (2) some concentrations of drugs.

I did ask for a repeat study because I think when you look at the data, again, not -- at least as presented, not controlled to BMI -- you see that one site had a huge efficacy, but every other site had maybe five patients. I'm not at all sure that this is -- that we can really say it's efficacious.

And along those lines, the -- when -- it would be nice to have larger numbers at what sites. If you really look at the data and rather than call it

drug and placebo, call it Drug A and Drug B, you can actually say B was a very potent stimulator of labor, because the Drug A, which was the 17-hydroxy B, has the same background risk of preterm delivery as the population studies presented by Dr. Romero, and Drug B, which we call placebo, has a higher than background risk. So I'm quite concerned about efficacy and I think we need to have at least those parameters.

DR. WESTNEY: I would agree in whole with what Dr. Carson said. I think we really should have some rigorous pharmacokinetic studies to allow for dose adjustment and in addition to that, I would advocate also an extension of the current follow-up, and that would decrease the -- that would give us a lead time in those children to really evaluate them in the late teen and early adult years.

DR. SELBY: Yes. I'm a preemie mom and I had delivered my son at 30 weeks, and he died five months later due to complications of sepsis. That said, I still don't feel that the efficacy data is strong enough to me. I would not want to be -- I

would not want to trade -- I would not be ready, based on this data, to trade one set of problems for another. I don't feel comfortable enough with the efficacy data.

Because I would be afraid, looking down the road -- some of the -- I would be concerned about long-term, about a possible -- that 17P might have a potential carcinogenic potential in the adult children of these moms who have been treated with Delalutin, and I was -- I didn't hear anything about whether they had looked at that or there was any increased incidence of reproductive cancers. So I would be concerned about that.

I didn't see enough to convince me that -- I mean, gaining a week didn't seem to make any difference, as far as the long-term neuro-developmental outcomes, and that would be something that would be very important to me, but I didn't see enough proof with that to take the risk with 17P.

I would also want them to evaluate more studies on mortality and morbidity and repeat studies on stillbirth and miscarriage. And I was

also wondering if they've been looking at these patients who are being treated currently, if there's any data coming in from those patients, as far as efficacy and safety. They said that, what, 67% of maternal-fetal specialists were using this -- using the compound, and I was wondering if any data had come in from them. So I would want that looked at, too.

DR. TULMAN: Lorraine Tulman. I agree, it seems like there's two types of things that have been proposed. One is a registry for follow-up on mothers and infants who would be getting the medication in terms of stillbirth, miscarriages, gestational diabetes for the mother, neonatal morbidity, pubertal development, reproductive health problems in the generation of children born. And I agree with the notion of a registry.

No one has addressed -- and I don't know if this is a procedural matter that should be addressed or not -- but exactly who is going to keep that registry. If it is the pharmaceutical company, they have a -- if the drug is approved, they have a

patent on the drug, the patent runs out, what is their responsibility after that? Does that revert to the FDA or some other government agency? How does that work exactly?

And I think we need the mechanisms for that registry spelled out very clearly. And I think we need the notion of -- rather than just saying we need a registry, but I think we need the mechanisms put in place; otherwise, it won't get done.

The other things that have been proposed that I'm in agreement with is we know very little about how this thing actually works, in terms of the basic biology, and some of the pharmacokinetics, and what does it mean in women of different weights and how exactly is it working?

And again, I'm concerned about the mechanism for getting that done. Are we saying this is what the sponsor should be doing? Is that what other drug companies should be doing? But if so, they don't have the incentive if we have a patent -- they have a patent on it.

Is it something that the NIH would pose as an

RFA request for applications and proposals? Would it be contract work? My concern is that's not the FDA's purview, but it becomes an NIH, perhaps, purview.

So I'm very concerned that we can voice all these concerns, but it won't happen. So I'd like that sort of for the record, that -- I'd like to hear more from, I guess, the FDA on how this works.

DR. SHAMES: Well, we can facilitate these issues. I mean, we can't -- we don't have the appropriate funds or -- to address the monetary issues, but we can facilitate and bring together partners to come up with a group of ideas or partners that will allow us to do some of these things, once we go back and decide exactly what we want to do.

So we can sort of leverage and facilitate with the company, with NIH, with we talked about epi studies, things like that, so -- we see ourselves as having a more facilitative role more than just a regulatory body. So we can -- we do try to be more aggressive in this area in more recent

years, I would say.

DR. SHAMES: We would try to stimulate the appropriate studies, if that's what we decide, what we decide to do. Okay?

DR. DAVIDSON: I tend to agree with the recommendations about post-marketing studies that's in the March of Dimes testimony. I think it is very important in the short term to answer this miscarriage/stillbirth question, because that has -- and it probably could be answered in the shorter term.

I don't have very much faith, I think, in the long-term follow-up being done by a pharmaceutical company, but I hope that NICHD understands that all of the definitive work around this has not been completed, and they probably would be in the best position to either do or fund long-term studies into the reproductive lives of these kids.

Because if there are some adverse effects, it ought to be found as soon as possible. And I think those are two of the really large things that ought to be done and encouraged, one on the shorter term

and one on the longer term.

Well, did anybody miss saying or proposing something?

DR. LEWIS: Adjournment.

DR. DAVIDSON: There is a motion and a second to adjourn. All in favor, say I. Oppose? Well, you've done a lot of work. Thank you for everybody.

(Off the record and adjourned at 4:40 p.m.)