2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

FDA REPRODUCTIVE HEALTH ADVISORY COMMITTEE

MEETING ON GESTIVA

Gaithersburg, Maryland
August 29, 2006

CONSULTANTS AND GUESTS

SGE Consultants (Voting)

Maria Bustillo, M.D.
Sandra Carson, M.D.
Daniel Gillen, M.D.
Julia V. Johnson, M.D.
Ezra Davidson, M.D.
Gary Hankins, M.D.
Karin B. Nelson, M.D.
Hyagriv, Simhan, M.D.
Rose Marie Viscardi, M.D.
Vivian Lewis, M.D.
Joseph Harris, M.D., FACOG
Cassandra Henderson, M.D.
Katharine Wenstrom, M.D.
James Liu, M.D.
Elizabeth Shanklin-Selby

Guest Speaker (Non-Voting)

Roberto Romero, M.D.

F.A.C.P. Acting Industry Representative

Steven Ryder, M.D.

FDA Center for Drug Evaluation and Research Participants at the Table

(Non-Voting)
Daniel Shames, M.D.
Scott Monroe, M.D.
Lisa Soule, M.D.
Lisa Kammerman, Ph.D.
Barbara Wesley, M.D., M.P.H.
Julie Beitz, M.D.

COMMITTEE MEMBERS

Teresa A. Watkins, R.PH., Designated Federal Official

Arthur L. Burnett, II, M.D.

Ronald S. Gibs, M.D. - Absent

Charles J. Lockwood, M.D. - Absent

Diane Merritt, M.D.

James R. Scott, M.D.

William D. Steers, M.D.

Jonathan A. Tobert, M.D., Ph.D. - Absent

Lorraine J. Tulman, R.N., D.N.Se.

O. Lenaine Westney, M.D.

PROCEEDINGS

DR. DAVIDSON: Good morning. It is time for us to begin business today so I would declare the committee meeting open for business. First, there is a rather large assemblege around the table here so why don't we begin by brief introductions. Give your name and position and I will await my turn when it gets around to me. Why don't we start with Doctor Beitz.

DR. BEITZ: Yes my name is Julie Beitz and I'm the acting director of the Office of Drug Evaluation three and CDER.

DR. KAMMERMAN: I'm Lisa Kammerman, FDA Statistician.

DR. MONROE: I'm Scott Monroe the Acting Director of Reproductive and Urologic drug products.

DR. WESLEY: I'm Barbara Wesley, I'm a medical officer in the division of Reproductive and Urologic products and the primary reviewer of this application.

DR. HANKINS: I'm Gary Hankins, I'm maternal fetal medicine clinician, practicing in Galveston,

Texas at the University of Texas.

DR. NELSON: Karin Nelson, I'm a child neurologist at NINDS/NIH.

DR. BURNETT: Good Morning, I'm Arthur Burnett, a urologist at Johns Hopkins and a committee member.

DR. BUSTILLO: I'm Maria Bustillo, I'm a reproductive endocrinologist at the South Florida Institute for Reproductive Medicine in Miami.

DR. MERRITT: Diane Merritt, Professor of OBGYN, Washington University, Saint Louis.

DR. JOHNSON: Thanks. Julia Johnson, I'm the Director of Reproductive endocrinology and infertility at the University of Vermont and a new member to the committee.

DR. STEERS: William Steers, Professor and Chair at the Department of Urology at the University of Virginia.

DR. LIU: Jim Liu, I'm a Reproductive endocrinologist, I'm chair at Chase Western Reserve.

DR. SINHAM: Hy Simhan. I'm a maternal fetal medicine doctor at the University of Pittsburgh, Magee Women's Hospital.

DR. LEWIS: I'm Vivian Lewis, I'm a Reproductive endocrinologist and professor of obstetrics and gynecology at the University of Rochester Medical Center.

DR. DAVIDSON: I'm Ezra Davidson, professor of obstetrics and gynecology at the Charles R. Drew University and the David Geffen School of Medicine at UCLA in Los Angeles. Also maternal fetal medicine.

MS. WATKINS: I'm Teresa Watkins, the designated federal official for this committee.

MD. WENSTROM: I'm Cathy Wenstrom, I'm a professor of OBGYN and human genetics at Vanderbilt.

DR. HARRIS: I'm Joseph Harris, I'm in maternal fetal medicine specialist in Reno Nevada.

DR. GILLEN: Daniel Gillen, I'm assistant professor in the department of statistics at the University of California, Irvine.

DR. SCOTT: Jim Scott, professor and former chair of the OBGYN department at the University of Utah, also the editor of the Green Journal, obstetrics and gynecology.

DR. CARSON: Sandra Carson, professor of obstetrics and gynecology at Baylor College of Medicine, I'm a reproductive endocrinologist.

DR. WESTNEY: Lenaine Westney, I'm associate professor, residency program director, and interim division director of University of Texas Health Science Center, division of urology.

MS. SELBY: I'm Elizabeth Shanklin-Selby and I am the patient representative.

NURSE TULMAN: Lorraine Tulman, associate professor at the school of nursing at the University of Pennsylvania. And I'm the consumer rep to the committee.

DR. RYDER: Steve Ryder and I'm a non-voting industry representative. I'm an endocrinologist in Pfzier research in Eastern Connecticut and I'm sitting in for Jonathan Tobert who could not make this meeting.

DR. DAVIDSON: Thank you. Doctor Watkins.

DR. WATKINS: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the

appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms all regulated by the Center for Drug Evaluation and Research present no potential for appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), Doctor Cassandra Henderson has been granted a full waiver for her unrelated speakers bureau activities for the sponsor for which she receives less than $10,001.00 per year.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be attained by submitting a written request to Agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

We would also like to note that Doctor Steven

Ryder has been invited to participate as a non-voting industry representative acting on behalf of regulated industry. Doctor Ryder is employed by Pfizer. In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm their product which they wish to comment upon. Thank you.

DAVIDSON: Doctor Monroe.

MONROE: Good morning and I'll just reintroduce myself briefly. I'm Scott Monroe and I'm the Acting Director of the Division of Reproductive and Urologic Drug products. On behalf of the division, I'd like to welcome all of you to this meeting of the advisory committee for reproductive health drugs. I also want to convey the division's

appreciation to the members of the advisory committee who have found time in their busy schedules to participate in this meeting.

Today, the committee will be reviewing a new drug application submitted by Adeza Biomedical for 17-hydroxy progesterone caproate with the proposed trade name Gestiva. The proposed indication is prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth. The adverse consequence of pre-term birth is a major public health problem. Approximately twelve percent of all live births in the United States are pre-term, defined as birth before thirty-seven weeks gestational age. Pre-term birth is the leading cause of neonatal death and a major cause of early childhood morbidity and mortality including pediatric neuro-developmental problems.

Currently there is no approved drug product in the United States for the prevention of pre-term birth. The medical need for an effective approved drug for prevention of pre-term birth is particularly acute because there are also no

approved drug products for pre-term labor currently marketed in the U.S. Although several drugs with tocolytic properties are used off label for pre-term labor. Randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

17-hydroxyprogesterone caproate is not a new drug and was initially approved for marketing by the FDA in 1956 largely on safety considerations. In 1956, approval for marketing for a new drug did not require substantial evidence of effectiveness. Suggested uses of 17-hydroxyprogesterone caproate also known by the trade name Delalutin included treatment of habitual, recurrent, or threatened abortion. Delalutin was withdrawn from marketing in 2000 at the request of the NDA holder. The withdrawal was not related to safety concerns. Presently 17-hydroxy progesterone caproate is available only from compounding pharmacies.

In 2003, the findings from a randomized, double blind control trail of 17-hydroxyprogesterone caproate for the prevention of pre-term birth

sponsored by the National Institutes of Child Health and Human Development, were published in the New England Journal of Medicine.

The study reported a significant reduction in the rate of pre-term births prior to 37 weeks gestational age and possibly at earlier gestational ages as well.

The new drug application that will be discussed today is based largely on this trial and a follow-up safety study of children whose mothers had participated in the earlier trial.

The application that the Committee will be reviewing and discussing today, poses several challenging issues for the division.

It is primarily because of these issues that the division is seeking guidance from the Committee.

The clinical issues that are of concern to the division include the following three items:

First: Are the clinical data adequate to support the claim of effectiveness for 17-hydroxyprogesterone caproate for prevention of pre-term birth.

Second: The pre-term birth rate in the vehicle, or control arm, of the principal study was 55 percent.

This rate was considerably higher than the expected rate of approximately 36 percent and is considerably higher than that generally reported in the literature.

Finally, there is a possible safety concern based on the increase in the percentage of second trimester miscarriages and stillbirths observed in the 17-hydroxy caproate arm compared to the control arm.

In regard to the adequacy of clinical data needed to support effectiveness of a new drug product, the FDA generally requires two adequate and well-controlled studies for substantial evidence of effectiveness.

A circumstance in which a single trial may be adequate would include a trial that has shown a meaningful effect on mortality, irreversible morbidity, or prevented a disease with a potentially serious outcome, and a situation in which

confirmation of the result in a second trial would be either logistically impossible or ethically unacceptable.

In the present application, the applicant is seeking approval of 17-hydroxyprogesterone caproate based on findings from a single clinical trial and on a surrogate endpoint for infant and neonatal morbidity and mortality; namely, reduction in the rate of pre-term births prior to 37 weeks of gestational age.

I would now like to briefly present the questions that the members of the Committee will be asked to consider.

First: Is the primary endpoint, prevention of pre-term birth prior to 37 weeks gestation, an adequate surrogate for reduction in fetal and neonatal morbidity or mortality?

If not, would prevention of pre-term birth prior to 35 weeks or prior to 32 weeks gestational age be adequate?

Second: Does the high rate of pre-term birth, approximately 55 percent in the vehicle arm of the

principal trial, indicate the need to replicate the findings in a confirmatory trial?

Third: Do the data provide substantial evidence that 17-hydroxyprogesterone caproate:

(1) Prevents pre-term birth prior to 35 or prior to 32 weeks gestational age; or,

(2) Reduces fetal and neonatal morbidity or mortality?

Is further study needed to evaluate the potential association of 17-hydroxyprogesterone caproate with increased risk of second trimester miscarriage and stillbirth?

If so, should this information be obtained prior to approval for marketing or post-approval?

And, lastly, are the overall safety data provided in the application adequate and sufficiently reassuring to support marketing approval of 17-hydroxyprogesterone caproate without the need for additional pre-approval safety data?

The agenda for the remainder of the day is listed on this slide.

In a moment, Dr. Roberto Romero, who is Chief

of Perinatology at the NICHD, will make a presentation entitled, "Causes of Premature Birth: The Premature Parturition Syndrome."

This will be followed by the applicant's presentation.

After a brief break, the FDA will make its presentation.

Following lunch, there will be an Open Public Forum, and this will be followed by discussion and questions by the Committee, concluding with Committee voting.

I think, now, Dr. Romero, I would like to turn the podium over to you.

I think there's going to be a moment here while we do an equipment swap-out.

(Long Pause.)

DR. ROMERO: Good morning, Dr. Davidson, Dr. Scott Monroe, Dr. Wesley, Distinguished Members of the Advisory Committee and the Sponsor, ladies and gentlemen.

I hope that this slide is going to work, but I would like to begin by indicating that I am here in

my official capacity as a member of NICHD, the Perinatology Research Branch, which I direct as part of the Division of Intramural Research of the Institute.

And the trial that will be subject of in- depth discussion today was conducted by the Extramural Program of our Institute, NICHD.

I did not participate in the design, execution, analysis or reporting of such trial.

Therefore, this trial has been conducted independently of the Perinatology Research Branch, and I have no conflict of interest to report with the sponsor of this application.

The editorial of the last issue of the Lancet remarked that in the United States at least one public health problem, pre-term birth, has worsened in the past decade.

However, it entitled the piece: "Pre-term Birth: Crisis and Opportunity," to stress the importance of this condition and the urgency with which the questions posed by premature labor and delivery must be addressed.

On July 28th of this year, the Institute of Medicine released a report entitled "Pre-term Birth: Causes/Consequence of Prevention." And the report is particularly timely because this Advisory Committee has been convened to consider the issue of prevention.

Pre-mature birth is defined, conventionally, as one that occurs before 37 completed weeks of gestation.

In 2004, more than 500,000 neonates were born pre-term in the United States, with a frequency of 12.5 percent.

This bar graph illustrates a cycle of trends in the frequency of pre-term birth, as a percentage of live birth in the United States between 1990 and 2004. An increase from 10.6 in 1990 to 12.5 in 2004 can be noted.

There is a large disparity in the proportion of pre-term birth among racial and ethnic groups in the United States which has persisted and remains concerning.

The frequency of pre-term birth among non-

Hispanic Americans was 17.8 percent, among American Indians and Native Alaskans 13.5 percent, Hispanics 11.9 percent, Whites 11.5, and among the Pacific Islanders, 10.5 percent.

Now the cost of pre-term birth, in medical care services, has been estimated to be $16.9 million, approximately 33.200 dollars per pre-term infant.

In maternal delivery cost, $1.9 million dollars.

The cost for special education $1.1 million dollars, and the lost household and labor market productivity is estimated at $5.7 million dollars.

So the annual society economic burden associated with pre-term birth in the United States is in excess of $26.2 million dollars, according to the estimates of the Institute of Medicine.

Now, the prognosis of pre-term birth, neonates, is a function of gestational age at birth.

And I regret that a part of these slides are not showing, so I'll do my best with the material that we have here.

This is work reported by Dr. Brian Mercer, in

the Journal of Obstetrics and Gynecology.

And in the vertical axix is percentage, and the horizontal axix is gestation.

And, as you can see, in red is mortality, in blue is survival.

And this slide is at 32 weeks of gestation, and the point of the slide is mortality changes dramatically at 32 weeks of gestation.

The magnitude of the problem, the infant mortality rate for very pre-term infants are those delivered at less 32-weeks of gestation, was 186.4 per 1,000, which is 70 times -- 75 times the rate for infants born at term, which is 2.5 per thousand weeks of gestation.

So 20 percent of all infants born at less than 32 weeks of gestation do not survive beyond the first year of life, and that is the importance of 32 weeks of gestation.

In of acute morbidity by gestational age among surviving infants, this is also data from Brian Mercer, published in 2003, in Obstetrics and Gynecology, and is a result of a community-based

evaluation of 8,523 deliveries between 1997 and 1998 in Shelby County, Tennessee.

In the horizontal axis, cut on the slide, approximately over here, 32 weeks of gestation will be approximately over here, and you can see that the rate of complications -- respiratory distress syndrome, sepsis and intra-ventricular hemorrhage -- increased dramatically before 32 weeks of gestation.

The Ailien (ph) report, in July of 2006, concluded that babies born before 32 weeks of gestation have the greatest risk for death and poor health outcomes. However, infants born between 32 and 36 weeks of gestation, which make up the greatest number of pre-term birth, are still at higher risk for health and developmental problems compared to those infants born full term.

So infants born after 32 weeks of gestation are common and also remain at high risk for health and developmental problems.

Now the frequency of pre-term birth, by gestational age, based on data from 1995 to 2000, was infants born at less than 28 weeks of gestation,

.82 percent; less than 32 weeks, 2.2 percent, between 33 and 36 weeks, 8.9 percent. And less than 37 weeks of gestation, 11.2 percent.

Now, the complications of the late-term, or near term infant, include cold stress, hypoglycemia, respiratory distress syndrome, jaundice, and sepsis.

And the clinical circumstances that result in the birth of a spontaneous pre-term birth are, fundamentally, three:

One: Is spontaneous pre-term labor with intact membranes;

The second is pre-term birth. So these two are the result of spontaneous pre-term birth; and,

The third is indicative pre-term delivery that results from maternal indications, such as pre-eclampsia or fetal indications, such as an infant that is small for gestational age or has fetal compromise.

Now, one of the key questions is whether pre-term labor is simply labor before its time. So "term" is between 38 and 42 weeks of gestation.

And the question is, whether premature labor, is simply the untimely onset of the physiologic or the phenomenon of labor.

And if you looked and you compare a patient who has term labor over here and a patient who has a pre-term gestation, there are clearly events in common.

Myometrial contractions are common in both pre-term labor and term labor, cervical dilatation and effacement occurs in both, and premature rupture of membranes, or membrane decidua activation, is also a common feature of the two conditions.

So we have defined the common uterine features of term and pre-term labor as including increased myometrial contractility, cervical ripening, which includes dilatation and effacement.

And, finally, decidua and membrane activation.

Now this common terminal pathway can be defined as the anatomic physiologic, biochemical, endocrinologic, immunologic, and clinical events in the mother and/or fetus that are shared by both term and pre-term parturition.

Now, what are the phenotypes of spontaneous pre-term parturition?

The phenotypes can be derived from understanding the activation of the common terminal pathway.

So, here, we have cervical ripening. Here, uterine contractility; and, here, membrane and decidua activation.

Now, in this part of the screen, I'm going to show you the activation, let's say, of cervical ripening over here, untimely activation of cervical ripening when you rise to cervical insufficiency. That used to be known as cervical incompetence.

Untimely activation of uterine contractility would lead to pre-term uterine contractions.

And untimely activation of the membrane and decidua would lead to premature rupture of membranes. And, of course, there is a combination of the two.

So could be synchronous activation of these components, or synchronous activation, and the

phenotypes or presentation will be different -- cervical insufficiency, pre-term uterine contractions, premature ruptured membranes, and the combination of the three.

The approaches that have been used so far for the prevention of pre-term birth have taken a uterocentric approach to the common pathway.

So investigators interested in activation of the myometrium have used the uterine monitor to test activation of this component and tocolysis to arrest uterine contractions.

Those interested in the cervix have used ultrasound to detect cervical shortening and use a cerclage to prevent dilatation of the cervix.

Those interested in membrane decidua activation have looked at fetal-fibrinectin, a marker of extracelluar metric segregation.

And these patients have a very high risk for pre-term delivery, and antibiotics have been used in an attempt to prevent pre-term delivery in patients at risk.

A positive fetal fibrinectin confers a relative

risk of approximately 60 antibiotic administrations in a randomized clinical trial conducted by the extramural program of our Institute, indicated that there was no benefit.

A similar story can be said of the uterine monitor and tocolysis. Tocolysis is able to prolong pregnancy for a short period of time but has not been demonstrated to decrease the rate of pre-term delivery.

The result of a cerclage is somewhat controversial, but most of the literature indicates that placement of a cervical cerclage is ineffective in preventing pre-term delivery, perhaps with the exception of one trial in Europe.

So the view that we propose is that normal labor at term is the result of physiologic activation of the common terminal pathway of parturition.

That will be crossed over here.

And in contrast, premature labor results from pathologic activation of this common terminal pathway.

Now, what is the evidence that the pathologic activation of the pathway is the cause of premature labor and delivery?

Well, examination of the placenta, by a number of investigators in patients who deliver pre-term, have indicated that acute chorioamnionitis, that are inflammatory lesions of the placenta, are present in 42 percent of the cases;

That vascular lesions are present in 20 percent;

Mixed inflammation of vascular lesions in 20 percent;

Chronic vellitis in .8 percent;

Velliserema, 1.7; and,

A normal placenta, in which the pathologist is not able to identify a lesion 13 percent.

Now we have coined the term, "The great obstetrical syndromes," to collectively refer to a number of conditions that are -- you know, are daily problems in obstetrics and have the following features.

First: They have multiple etiologies;

Second: They are chronic in nature, although they are generally diagnosed in the third trimester.

Often, there is fetal involvement.

Fourth: The chemical manifestations of the syndromes are adapted.

Symptomatic treatment is largely ineffective, and they result from gene and environmental interactions.

And all these postulates are met by the pre-term parturition syndrome.

So we have proposed that the pre-term parturition syndrome is defined by the presence of uterine contractility, activation of membrane and decidua, cervical dilatation, and it has multiple etiologies -- infection, vascular, uterine distention, cervical disease, hormonal disorders, immunological problems.

And we have left room for unknown mechanisms yet to be discovered.

Now, of all these potential causes for the pre-term parturition syndrome, the only one that has been causally linked to spontaneous labor is

infection.

In intra-amniotic infection that means that the presence of microorganisms in the amniotic cavity is a frequent complication of pre-term labor; is present in 25 percent at the time of presentation. That is, not endometrial by the time of presentation in the onset of labor.

These infections are subclinical in nature, may affect the fetus, may elicit a fetal inflammatory response syndrome, and this is considered a host defense mechanism.

Now, the evidence that these infections are subclinical in nature is that clinical chorioamnionitis, defined by the presence of fever and other findings, are present in 12 percent of patients with premature labor and 20 percent of patients with pre-term PROM.

Now, the fetal inflammatory response syndrome occurs because, in some instances, microbial invasion of the amniotic cavity gain access to the fetus.

The fetus mounts a systemic inflammatory

response that is very much like the adult, and this leads to three distinct outcomes:

The impending onset of premature labor and delivery;

The second: Severe neonatal mobidity and mortality that can be the most treated in the neonatal period; and,

Third: The presence of fetal multi-systemic involvement, that can be the most treated in utero.

So the fetal inflammatory response syndrome includes hematologic abnormalities, red blood cells, white blood cells, abnormalities in the endocrine system, the concentrations of cortisol are elevated.

Another form of cardiac dysfunction, in which the fetal heartbeat becomes floppy;

Pulmonary injury because the fetus aspirates bacteria and inflamed amniotic fluid.

Add to this, one can have renal dysfunction and also potentially brain injury.

Now, how common is subclinical intra-amniotic infection in a symptomatic mid-trimester pregnancies?

Because the figures that I have just given you, the 25 percent, reflects the patients who presents with a sort of premature labor and intact membranes or pre-term problem.

Well, the data that we have available here come from a study performed by a private practitioner in Ohio, published in "Prenatal Diagnostics," in 1992.

And what this private practitioner, Dr. Gray, did is to perform 2,461 myometrial amniocentesis and culture all the amniotic fluids for genital micro-plasmas.

Nine (9) patients have positive cultures with chorioplasma, relating to giving a frequency of .4 percent, in the prevalence of microbial invasion for genital micro-plasma.

One (1) patient elected to terminate the pregnancy, and eight (8) continued the pregnancy without treatment.

Six (6) patients had spontaneous abortions within four weeks of the amniocentesis, two (2) had premature labor.

All cases had histologic evidence of

inflammation, suggesting that these infections could be present in the mid-trimester.

They are relatively rare because they account for .4 percent, but once the infection is present, the prognosis of pregnancy is poor.

Now, in terms of prevention of pre-term labor and delivery, we believe, as obstetricians, that this is an important and desirable goal, that the only proven beneficial strategy so far is irradication of a symptomatic bacterurea, but this condition has a limited attributable risk.

Patients with a previous pre-term birth have an increased risk for recurrence, and this has been well established.

And the potential beneficial effect that we are considering today is progesterone administration, and this is derived from trials with 17-hydroxyprogesterone and natural volume of progesterone administration.

Now, the possibility that there is a hormonal etiology for the pre-term parturition syndrome, is something that has been seriously considered and

has been resolved for several decades.

A progesterone deficiency state has been proposed to be a mechanism of disease in premature labor for several decades.

The corpus luteum is the source of progesterone in early pregnancy.

Now, this source of progesterone is quickly shifted towards the placenta in the human.

And the studies of Arthur Shappel (ph) were key in elucidating the role of progesterone in pregnancy maintenance.

And these are the three papers published by Arthur Shappel illustrating that point.

So what is the effect of luteectomy in human pregnancy?

And this is the result of our study, or a series of studies,

In 64 pregnant women that were in very early pregnancy, less than five weeks, who desired a tubal ligation, and, after IRB approval, were allocated to three groups.

A group that underwent tubal ligation, that is,

a control group;

A group that underwent tubal ligation and luteectomy; and,

The third group that is cut in this slide: Tubal ligation, luteectomy, and progesterone supplementation.

And the results, I illustrated over here.

This is a group of patients in the vertical axis, is plasma progesterone; in the horizontal axis, at days after luteectomy, and I regret that the horizontal axis is not visible.

But here are patients who only underwent a tubal ligation with a mild drop in progesterone but no spontaneous abortion.

The second group and the third group, labeled in orange and red, includes patients who have a luteectomy and went on to have a spontaneous abortion, one within four days, the ones in red, and the other ones within seven days.

The other group is this one, who underwent a luteectomy, but then after a drop in progesterone had progesterone replacement, and these patients

continued the pregnancy, had no spontaneous abortion.

So Arthur Shapell proposed that progesterone is an indispensable hormone for normal pregnancy and that progesterone withdrawal is a prerequisite for normal pregnancy termination, be that in the mid-trimester in early pregnancy or at the time of parturition at term.

Now, the role of progesterone in pregnancy maintenance has been proposed to be to maintain myometrial quiescence, to down regulate the production of gap-junctions, and gap-junctions are important to accelerate the transmission of the electrical stimuli among myometrial cells.

And the third is to inhibit cervical ripening.

A progesterone withdrawal is thought to prepare the uterus for the action of utero-tonic agents such as oxytocin and other agents capable of stimulating myometrial contractility.

Now, the evidence that supports a suspension of progesterone action is important in human parturition, is derived from a number of studies in

which the administration of anti-progesterones, such as RU-486 or onnapreston (ph) can induce abortion and cervical ripening in patients in the mid-trimester and also at term.

Now, evidence that there could be a change in the ratio of progesterone to estrogen in human parturition, has been gathered both at term and in pre-term gestation.

And over here, in the left, is the ratio between progesterone/estradiol.

The first column represents women who are not in labor at term; the second column, women in labor at term.

Women in labor at term had a significant decrease in the progesterone to estradiol ratio.

And the same is the case for the progesterone/estriol ratio.

So progesterone is considered a key hormone for pregnancy maintenance, and, hence, its name progesterone.

A progesterone withdrawal has been proposed, and it occurs in other animal species or the

mammalian species when there is a decrease in the concentration of progesterone; however, this has not been demonstrated in humans.

So the postulated mechanism for progesterone withdrawal in humans are a change in the isoforms of the receptors from "A" to "B," and perhaps an involvement of the "C" isoform of the receptor, or a function of progesterone block.

That is, maybe a description factor, NF-kappa B.

I will now be discussing the clinical trials of meta-analysis of progesterone that will be analyzed by the FDA staff and the sponsor. And the reason for that is because our institute is one of the -- participated in the design/execution of this trial.

The interventions for the prevention of pre-term birth need to meet the standards of efficacy and safety.

The criteria for efficacy are generally prevention of pre-term birth, defined as 37 weeks, 35 weeks, and 32 weeks, prolongation of pregnancy; and, perhaps more important, neonatal morbidity and

mortality.

In terms of safety; fetal, neonatal, infant, and maternal safety.

Now, the fundamental construct is a progesterone deficiency state which may not be reflected in concentrations but simply a change in the isoforms or a suspension of progesterone action will activate the common terminal pathway of parturition, and this will result in premature labor.

To close, let me just say that the American College of Obstetrics and Gynecology, through its Committee in Obstetrical Practice, issued in November 2003, a Committee Opinion on the use of progesterone to reduce pre-term birth.

An excerpt of that Committee Opinion is that, when progesterone is used, it is important to restrict its use to only women with a documented history of previous cutaneous pre-term birth, at less than 37 weeks of gestation, because unresolved issues remain, such as the optimal drug of delivery and long-term safety of the drug.

The Committee Opinion also recognized that there were other indications for premature -- for progesterone that needed to be considered and subject of further investigation, and that included patients who have multiple gestations, and patients with a short cervix.

A trial in multiple gestations, in twins and triplets, has been conducted and sponsored by NICHD.

At trial in women who have a short cervix that have been randomized to placebo or natural volume of progesterone, will be presented next week in London, and be conducted by the Fetal Medicine Foundation (ph), but the results are not available at this time.

Thank you very much for your attention.

(Applause.)

DR. DAVIDSON: Thank you, Dr. Romero.

I think we can now proceed to the sponsor's presentation.

(Pause.)

DR. HICKOK: Give us just a moment, if you will, to see if we can get these slides lined up

correctly.

DR. DAVIDSON: While they are setting up, I've been instructed to provide the following statement, which I was going to give after this presentation and before the break, but I will take advantage of this interlude.

In the spirit of the Federal Advisory Committee Act and its Sunshine Amendment, we ask that the Committee limit their discussion of the topic to the Open Forum of the meeting.

To assist them, we also ask that the audience and press not ask them questions about the meeting during the breaks.

I also have in this instruction some suggested alternative topics, but I'll leave that to your vivid and wide imagination.

(Laughter.)

(Long Pause.)

DR. DAVIDSON: Fortunately, Dr. Romero left you some technical adjustment time here.

(Long Pause.)

DR. HICKOK: Good morning. It looks like our

audio-visual equipment is back to functioning here.

My name is Durlin Hickok, and I will be the principal speaker this morning for Adeza; and, in addition, the moderator for the question and answer session for Adeza's responses.

As way of introduction, in terms of the presentation -- in terms of the presentation today -- I'll be speaking briefly about Adeza Biomedical, and then Dr. Nageotte will be speaking on the medical need to prevent pre-term birth.

From there, we will move to a clinical review of the efficacy and safety findings from the study and then a discussion of the risks and benefits.

So, again, my name is Durlin Hickok. I'm the Vice President of Medical Affairs for Adeza.

And the person presenting the medical need will be Dr. Michael Nageotte, who is a Professor of Obstetrics and Gynecology, at the University of California at Irvine.

Other experts that we have available to the Committee today are Dr. Paul Meis, who is a Professor of Obstetrics and Gynecology at Wake

Forest University; and, indeed, was the PI of the NICHD 17-hydroxyprogesterone caproate for prevention of pre-term/premature labor trial.

Ms. Gwendolyn Norman is a Perinatal Research Nurse from Wayne State University, and she was also the active point person as the nurse coordinator for the study site at Wayne State.

Dr. Michael O'Shea is a professor of Pediatrics and a Neonatologist from Wake Forest University.

Dr. Melissa Parisi is an Assistant Professor of Pediatrics and Medical Genetics at the University of Washington.

Dr. David Savitz is a Professor of Community and Preventive Medicine at Mount Sinai School of Medicine, and his expertise is Reproductive Epidemiology.

Finally, Dr. Frank Stanczyk is a Professor of Obstetrics and Gynecology at the University of Southern California, and his expertise is progesterone chemistry.

In terms of Adeza Biomedical, Adeza is a medical technology company that is focused on

pregnancy-related and female reproductive disorders, with a special interest in pre-term birth and infertility.

We're here today because we have submitted a new drug application for FDA approval to market 17-p in the U.S. for prevention of recurrent pre-term birth.

I'd first like to describe the names that we are going to use today for the chemical entities and drug products.

17-hpc is 17-hydroxyprogesterone caproate. It is the active ingredient of 17-p, which was used in the clinical study and was the study formulation of 17-hpc for injection.

Gestiva, as mentioned before, as Adeza's proposed trade name for 17-p, and Delalutin was the trade name for the previously-marketed 17-hpc.

17-alpha hydroxyprogesterone caproate is the active pharmaceutical ingredient of 17-p.

It's created by the addition of a six (6) carbon chain at the 17 position, as you can see here.

Studies have shown that 17-hpc exhibits substantial progestational activity and a prolonged duration of action, with a half-life of approximately seven to eight days.

17-p ias provided as a sterile solution for injection containing 17-hpc, 250mgs per milliliter, in Castor Oil, along with Benzyl benzoate and Benzyl alcohol.

17-p was used in the NICHD clinical studies and is identical in composition to the previously marketed Delalutin.

As mentioned before, Delalutin was first approved by the FDA in 1956, so we actually have a long history of use in pregnancy, dating back to this time.

Its approval was for the indications of treatment of habitual and recurrent miscarriage, threatened miscarriage, postpartum after pains, and advanced uterine cancer.

Delalutin was voluntarily withdrawn from the U.S. market in 1999, for reasons not related to safety or efficacy.

There has been multiple other studies that have evaluated the safety and efficacy of 17-hpc for the prevention of pre-term birth, and I am going to describe several of these to you here now.

One of the first studies that we could find on 17-p in pre-term birth was that of Levine, that was published in the United States in 1964.

The inclusion criteria for this study was three or more miscarriages, and 17-p was initiated at less than 16 weeks and continued until 36 weeks.

A beneficial effect of 17-p was demonstrated by the odds ratio that you see here, of 0.63. However, the results were not statistically significant.

This was followed by Papiernik's (ph) study, in France, in 1970.

Papiernik and his colleagues randomized women on the basis of a high pre-term, risk labor, score.

17-hpc was initiated between 28 and 32 weeks of gestation and given for 8 doses or less.

This study also demonstrated a beneficial effect of 17-hpc, with an odds ratio of 0.24, and

this result was statistically significant

A third study was published by Johnson and was a U.S. study, again.

And the inclusion criteria in this study included two or more miscarriages, and two or more prior pre-term births.

17-hpc was initiated at the first prenatal visit and continued until 37 weeks of gestation.

This widely-quoted study exhibited an odds ratio of 0.12. Again, demonstrating substantial effectiveness and was statistically significant

A study by Dr. Hauth in 1983 took a different approach, and included women who were active in active-duty military as a high-risk group.

These were women who were randomized to 1,000 mgs per week of 17-hpc versus placebo.

The drug was instituted at 16 to 20 weeks and continued until 36 weeks of gestation or delivery.

The odds ratio for this trial was 1.11, clearly showing a non-benefit to these women that were active-duty military.

A study by Yemeni, out of Israel, published in

1985, had inclusion criteria of two prior pre-term births or two miscarriages.

17-hpc was initiated early in pregnancy in both, and in the active drug group. The mean gestational age was 12.2 weeks.

Again, this study was continued until 37 weeks, or delivery.

The odds ratio for the Yemeni study was 0.30, and the confidence intervals did not bound one, indicating a significant effect.

Finally, the last study that I would like to report is that by Sauvonna Kode (ph), out of Thailand, published in 1986.

Again, the inclusion criteria for this study were a combination of one pre-term birth or two or more prior, mid-trimester miscarriages.

The drug was initiated at 16 to 20 weeks at gestation and terminated at 37 weeks, or delivery, whichever occurred first.

This study also showed a significant benefit for 17-hpc treatment, with an odds ratio of 0.29.

In this study, we have summarized these

findings from the studies that I have just showed you, in the form of a Forrest plot.

Please note here that we did not include the NICHD 17-p study.

The overall summary suggests a 70 percent reduction in the risk of pre-term birth, as you can see here. And, again, the confidence interval suggests that this is a substantially-significant result.

Because of the promising findings of the previous studies, the NICHD decided to investigate further the 17-hpc potential in a large multi-center trial.

With the unmet need for an FDA-approved product that has standardized manufacturing and labeling, Adeza approached NICHD and was granted access to the clinical data set from the 17-p study.

The results of the NICHD study provide the primary basis for the efficacy claim of Adeza's NDA submission for 17-p.

I would like to draw attention to the fact that this was a large multi-center trial. Nineteen (19)

study sites were involved in this study.

The results were highly statistically significant for the efficacy findings.

And, also, of importance, this study was stopped early by the Data Safety and Monitoring Committee because of efficacy. In other words, it crossed efficacy bounds before the trial was completed.

And, finally, we'll show you, shortly, the results were consistent across subsets of patients, thus, leading to a conclusion that it is highly generalizable.

Lastly, we would like to note that we have proposed labeling for our formulation of 17-p, and it will be named Gestiva. And, as Dr. Monroe said, Gestiva is indicated for the prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth.

At this point, I would like to turn the podium over to Dr. Michael Nageotte, who will describe the medical need.

Again, Dr. Naggeotte is a Professor of

Obstetrics and Gynecology at the University of California-Irvine, and is the immediate past president of the Society for Maternal Fetal Medicine.

DR. NAGEOTTE: Good morning.

As has been elegantly introduced to you by Dr. Romero, pre-term birth continues to be a critical problem in this country.

Defined as any birth occurring prior to the completion of 37 weeks gestation, pre-term birth represents an ever-constant and, indeed, increasing societal challenge, which has, thus far, been resistant to multiple efforts to decrease its incidence.

Despite our having a better understanding of some of the etiologies of pre-term birth, the incidents of this serious pregnancy complication continues to increase, with the CDC reporting an increase of some 33 percent since 1981.

Pre-term birth now represents some 12.5 percent of all births in the United States, resulting in a significant cost and contributing to the

overwhelming majority of all neonatal morbidity and mortality

To place this complication into some perspective, a pre-term birth occurs in this country approximately every moment, of every hour, of every day.

Recently, the March of Dimes has launched its largest initiative in an effort to address this daunting public health problem.

However, beyond dramatic increases in mortality risk, when compared to term infants, pre-term neonates are at significantly increased risk for several important morbidities.

These include respiratory distress syndrome, a disease resulting from immature lung development, and surfactant inefficiency, intra-ventricular hemorrhage; peri-ventricular leukomalacia, which is strongly associated with adverse neurological sequelae, including cerebral palsy, necrotizing enterocolitis, a disease of the premature gut; apnea, jaundice, anemia, and infections due to presumed immaturity of the immune system, in

addition to these immediate morbidities of the neonatal period.

Long-term morbidities are also increased, including cerebral palsy, mental retardation, learning disability. and attention deficit disorders. And with the rising rate of pre-term birth, all of these morbidities are rising as well.

Now several risk factors for pre-term birth have been identified from various epidemiological studies. These include bacterial vaginosis, vaginal bleeding, and race.

Most importantly, a history of a previous pre-term birth, nearly triples the risk of pre-term birth in any subsequent pregnancy.

This slide presents the data regarding the relative risk of experiencing a pre-term birth for these various risk factors.

The population with a prior spontaneous pre-term birth represents a logical group for the testing of various intervention strategies.

This slide demonstrates the improved survival by gestational age of neonates born pre-term.

When discussing this problem with prematurity, we tend to only focus on the very small and very premature babies; those with very low birth weight or the micro-preemies. However, late pre-term birth, defined as birth between 34 and 0/7th weeks and 36-and-6/7th weeks, represents a very large and also growing cohort whose morbidity and mortality risks are unappreciated.

While all pre-term births have increased, late pre-term birth has increased as well, some 14 percent between 1992 and 2002, with the rate going from 6.9 to 7.7 percent of all births, with late pre-term birth now making up over 70 percent of all pre-term births.

These late pre-term birth newborns are often mistakenly believed to be as physiologically and metabolically mature as term infants.

As we will see, this is untrue, yet has led to an almost cavalier approach to the management of pregnancies at risk for birth between 34 and 37 weeks.

As this slide demonstrates, the length of stay

is significantly reduced with each advancing week of gestation through 37 weeks, suggesting benefit with prolongation at each week up to the 37th completed week of pregnancy.

Here is the distribution of pre-term birth at different premature gestations.

These data, from the March of Dimes, demonstrate the frequency of some 70 to 75 percent for late pre-term birth between 34 and 37 weeks. This represents over 300,000 newborns every year in this country.

Beyond 34 weeks, it is not the standard of care to administer cortical steroids to the mother nor to consider tocolysis.

So the obstetrical options are minimal to non-existent. Yet, infants born between 34 and 37th weeks have a 4.6-fold increase risk for neonatal mortality. When compared with term infants, that is, 4.1 versus 0.9 per 1,000 live births.

Further, their infant mortality is threefold greater than that of infants who are born at term.

In addition, greater risks of morbidity include

respiratory distress, apnea, temperature instability, hypoglycemia, clinical jaundice, and feeding difficulties, as well as a significant increased risk for hospital readmission.

The lack of appreciation for this issue of late pre-term infants is considered a problem by the American College of Obstetrics & Gynecology, such that they are addressing this currently through their Committee structure.

Available treatment of pre-term labor are limited and not without controversy.

The use of tocolytic therapy may, at best, prolong a gestation for 24 to 48 hours, enough time to perhaps administer corticosteroids to the mother, but without significantly lengthening the overall length of gestation.

However, no current approaches to the prevention of pre-term births have been shown to be efficacious prior to these recent reports of 17-p.

As we have heard, ACOG has recommended progesterone to be used to prevent pre-term birth in specific patient population, following the

publication of Dr. Meis' study in 2003.

Although widely appreciated by the OB-GYN community, there remains specific problems in the appropriate usage of this therapy for women, who would potentially benefit most from such treatment.

Unfortunately, due to the limited availability of this product, it is severely underutilized.

Lacking FDA approval, access to this drug has been dependent upon individual physician practices developing personal relationships with various compounding pharmacies.

Reimbursement issues are daunting, with most states not covering this cost for appropriate high-risk pregnant women, with Medicaid and various insurance plans choosing to cover or, more commonly, not cover this cost.

There is limited FDA oversight, no regulation of product consistency, and no requirement for reporting of adverse events, or even significant adverse events.

In conclusion, there is a compelling societal need to address this rising incidence of pre-term

birth and the associated costs and morbidities.

There are clear benefits with prolonging pregnancy at any pre-term gestational age, whether early or late, and, in the appropriate patient with the appropriate history, there is a need for approval of this product.

Thank you very much

DR. HICKOK: Thank you Dr. Nageotte.

We'll now move on to the clinical review.

And, as I say, we have had a history of being able to review the studies that led to the NICHD clinical study, and now we will move on specifically to the study that the NICHD conducted.

The National Institutes of Child Health and Human Development, as mentioned before, are part of the National Institutes of Health.

As such, the objectives are to identify the causes of prematurity and to evaluate safety and effectiveness of new treatments.

The Maternal Fetal Medicine Unit's Network consists of major training institutions that engage in multi-center collaborative investigations.

In the next slide you will see the Institutions that participated in the NICHD/MFMU Network sites for the 17-p study.

To be included into the Network, the clinical studies undergo a competitive selection every five years. They are chosen to participate based on leadership, number of deliveries, state of the art facilities, and the sub-specialty support that is available to them.

Study 002 was initiated in 1999 and completed in 2002. It was a randomized placebo-controlled, double-blind, multi-center clinical trial.

Weekly injections were begun between 16 weeks/zero days and 20 weeks/6 days of gestation and continued until 36 weeks/6 days of gestation or birth.

The study enrolled 463 patients in a 2-to-1 ratio of active to placebo that was pre-specified.

As I mentioned before, the Data Safety and Monitoring Committee recommended that the study be halted early.

This occurred after an interim analysis was

conducted on 351 completed patients, revealing that the boundary for test significance had been crossed and that there was a benefit for 17-p in reducing pre-term birth. And, again, these results form the primary basis for efficacy.

Study 001 is a study that was initiated in 1998, prior to the completed 002 trial. It was terminated due to a manufacture and FDA recall of the study drug.

At the time that it was terminated the study enrolled only 150 of the 500 planned patients.

Following termination of the 001 trial, NICHD made the decision to initiate a new 17-p study, and that study that we we'll describe again is Study 002.

An additional study that we'll be describing today is the follow-up study. This study was conceived by NICHD, and it was initiated following completion of the 002 Study. In this study, the design was discussed with NICHD prior to the enrollment of subjects.

And, again, the follow-up study was an

observational safety study designed to assess the long-term safety outcomes of infants exposed to 17-p in utero.

It looked at the health and development of infants born during the study. It was conducted at 15 Maternal Fetal Medicine Unit Network study centers, and it enrolled 278 children.

In terms of the efficacy and safety databases, the completed 002 Study, with its 463 enrolled patients, forms the bases of the efficacy assessment.

An overall safety assessment was generated by integrating the 002 Study with the 001 Study.

The Observational Infant Follow-Up Study is an additional component to the Safety Assessment.

We will now turn to the efficacy results.

Pregnant woman with a documented history of a previous spontaneous, previous singleton spontaneous pre-term birth, and gestational ages between 16 and 21 weeks, were randomized.

The exclusion criteria included the items that you see here in front of you:

Multi-fetal gestation, no major anomaly or fetal demise, prior progesterone treatment during the current pregnancy, prior Heparin therapy during the current pregnancy, a history of thrombo-embolic disease, or a history of several other medical or obstetrical complications that you see here listed.

A total of 463 patients were enrolled with a 2-to-1 randomization of Active 2 placebo.

This resulted in 310 patients in the 17-p group and 153 in the placebo group.

90.3 percent of patients completed injections through 36 weeks, 6 days, or birth, resulting in a 90.0 completion rate in the 17-p group and a 90.8 percent completion in the placebo group.

In examining the baseline demographic characteristics and risk factors, no differences were observed in the following characteristics:

Mean age, self-reported race or ethnic group, marital status, and years of education.

I might add that this population is relatively representative of the population of women who have experienced one or more prior pre-term

births.

Nor were there differences observed between the 17-p and placebo groups for body mass index, presence of diabetes, those who smoke cigarettes during pregnancy, had alcoholic drinks, or used street drugs during pregnancy.

In addition, the duration of gestation at the time of randomization was very similar -- 18.9 weeks in the 17-p group and 18.8 weeks in the placebo group.

However, there was a statistically significant difference in the number of previous spontaneous deliveries between the 17-p and placebo groups, as you see here.

1.3 in the 17-p group and 1.5 in the placebo group.

We'll demonstrate later to you how we adjusted for this imbalance and determined that the imbalance did not impact the interpretation of the efficacy results.

There was not a difference between the 17-p and placebo group for gestational age at the qualifying

delivery and the frequency of previous miscarriage.

The primary efficacy endpoint that was predefined was pre-term birth less than 37 weeks of gestation.

I'd like to note that miscarriages that occurred before 20 weeks of gestation were also included in the primary efficacy outcome.

The primary efficacy results that you see here are represented in two ways.

First: There's a traditional intent to treat analysis of all women who are randomized, which counted all patients lost to follow-up as treatment failures.

I'd like to note that this is a fairly conservative approach.

In the second analysis, an all-available data analysis is presented, which was published by Dr. Meis and colleagues in the New England Journal of Medicine.

This analysis excludes women who are lost to follow-up during the study.

In the second row for each analysis. we have

present a "p" value from a logistic regression, adjusting for the number of previous pre-term deliveries.

And, as you can see in these adjusted values, they do not differ in a meaningful way from the unadjusted values.

Despite whatever data analysis population we evaluated, the results were consistent with the fact that 17-p treatment significantly reduced the incidence of pre-term birth.

A sub-group analysis was also performed to further evaluate the impact of the pre-term birth imbalance.

We stratified patients, as you see in this slide, by the number of prior pre-term births, and found that 17-p treatment reduced the risk of pre-term birth.

And, again, the 17-p groups are represented in yellow, and the placebo in gray.

The data were consistent across the strata, demonstrated by a non-significant value for the Breslau Day test.

Similarly, we stratified by race, specifically, African-American versus non-African-American. In both groups, as you can see, 17-p was, again, found to reduce the risk of pre-term birth.

Again, the data were very consistent across the strata, demonstrated by a non-significant value for the Breslau Day test.

In the third stratified analysis, we examined subsets of patients with or without bacterial vaginosis, which, as Dr. Nageotte pointed out to you, is a significant risk factor for pre-term birth.

In women, both with and without bacterial vaginosis, 17-p was found to reduce the risk of pre-term birth.

Finally, we stratified by the gestational age of the qualifying pre-term birth. In this analysis, once again, you see a significant benefit that is very consistent across strata for the 17-p group versus the placebo group.

I would like to note that the implications for these four stratified analyses are very important.

They suggest that the results are highly generalizable, despite whatever patient population 17-p is administered.

We will now address the secondary endpoints.

In addition to pre-term birth, defined as less than 37 weeks, we also looked at pre-term birth less than 35 weeks, less than 32 weeks, and less than 30 weeks.

There was a similar decrease in the placenta pre-term births at less than 35, less than 32, and less than 30 weeks of gestation.

However, the reduction did not reach statistical significance for the less than 30 gestational age group.

These endpoints are important, as they demonstrate, again, the beneficial effect of 17-p applies throughout pregnancy.

This graph summarizes the key measures of efficacy and reinforces that 17-p reduces pre-term birth, however it is defined. I would like to note, again, the consistent decreases in the 17-p rate for each of the endpoints that you see.

And, again, for less than 37, the values are at 32.4 percent; for less than 35, 30.6 percent; 39.3 percent for less than 32 weeks, and 38.2 for less than 30 weeks.

We can also look at these data in terms of the gestational age intervals at which the pre-term birth occurred in each group.

For example, beginning at the 24- to 27- week interval, there was a lower percentage of patients delivering in each interval, up until term.

So, in other words, in each of these intervals here, beginning at 24 weeks, we see the percent delivering within this interval in the 17-p versus the placebo groups, all the way up until term, at this point.

An alternative measure of this effect is the hazard ratio. And the hazard ratio shows the likelihood that a woman who enters into any of the following gestational age windows will actually deliver within the window.

This can be interpreted much like a relative risk.

Again, beginning at 24 to 28 weeks, we see a consistent decrease in the hazard ratio, as shown here.

And, again, these hazard ratios can be interpreted as relative risks, and all of these, again, show protective effects.

Two important measures in looking at neonatal outcomes are the birth weight and NICU admissions.

As we can see on this slide, the incidence of birth weight less than 2,500 grams was significantly reduced in the 17-p. group.

A similar decrease was observed in the less than 1,500 grams, although, this did not reach statistical significance.

Mothers receiving 17-p were less likely to have their child admitted to a neonatal intensive care unit. And if their child was admitted, the median days in the NICU were shortened.

Although this study was not powered statistically to detect differences in these outcomes, the outcomes that you see in yellow on this slide are morbidities that occurred in a less -

- less frequently in a statistically-significant fashion.

These include necrotising enterocolitis, intra-ventricular hemorrhage -- this is any graded -- supplemental oxygen, and days of respiratory therapy.

In addition, there were decreases in the percent requiring ventilatory support, those who experienced transient kypnea, respiratory distress syndrome, and the outcomes of bronco-pulmonary dysplasia, and patent ductus arteriosis.

In general, these data suggest that infants whose mothers were treated with 17-p were generally healthy, healthier during their initial hospital experience.

A composite neonatal morbidity index was conducted as a post-hoc analysis.

Although there is not a universally- accepted standard for the components of this index, we define the index similar to other studies that were the percent of infants experiencing one or more of the following morbidities; that is, death, respiratory

distress syndrome, broncho-pulmonary dysplasia, a Grade 3 or 4 intra-ventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

The index of 11.9 for the 17-p group, compared to 17.2 in the placebo group, represents a 31 percent decrease in the morbidity index. However, this difference did not reach statistical significance.

Please recognize, however, that this study was not designed, nor was it powered, to detect a difference in these measures.

In summary of the efficacy findings, weekly administration of 17-p reduces the rate of recurrent pre-term birth at less than 37, less than 35, and less than 32 weeks of gestation.

17-p resulted in prolonged gestation, and this is very consistent with the other studies that we have previously showed you.

The neonatal outcomes were improved, resulting in a reduced percentage of infants born less than 2,500 grams, and a reduced rate of admission to the Neonatal Intensive Care Unit.

17-p was also found to reduce specific neonatal morbidities, including necrotizing enterocolitis, intra-ventricular hemorrhage, use of supplemental oxygen, and mean days of respiratory therapy.

Of the neonatal endpoints that did not reach statistical significance, the direction to the change in each case was in the favor of 17-p.

We will now move to the safety findings from the study.

As I mentioned previously to you, the completed 002 Study, with its 463 enrolled patients, formed the basis of the efficacy assessments.

The overall safety assessment was generated by integrating data from the 001 and 002 Studies, along with the observational infant follow-up study, which was an additional component. And we will describe that separately.

In the combined 001 and 002 Studies, a total of 613 patients received at least one study injection, and, again, accounting for the 2-to-1 randomization ratio, this resulted in 404 patients in the 17-p group, and 209 in the placebo group.

In evaluating the Maternal Safety Data captured in the 001 and 002 Studies, we found no differences in the occurrences of pregnancy complications.

This slide shows pregnancy-related procedures, such as admission for pre-term labor and cerclage placement.

The occurrence of these pregnancy complications was not different between the 17-p and placebo groups.

I might add that the difference you see in the denominators here, from the previous slide, represent a decrease due to patient's loss to follow-up or early withdrawals.

Similarly, when other pregnancy complications were considered, there were still no differences observed between the 17-p and placebo groups.

The most commonly reported pregnancy-related complications were pre-eclampsia, or gestational hypertension, and diabetes, as you see here.

While the rates were higher in the 17-p group, this was not a statistically significant difference between the two groups.

Other pregnancy complications occurred in similar rates between the 17-p and placebo patients, including abruption, significant antepartum bleeding, clinical chorioamnionitis, and other complications.

As shown in this slide, the percentage of subjects reporting adverse events were comparable in the 17-p and the placebo groups, 59.2 versus 56.5.

The most frequently reported AEs in the 001 and 002 Studies were injection site reactions.

Other commonly reported AEs included urticaria, puritis, contusion, and nausea. These, again, occurred at similar rates.

The percentage of patients discontinuing early and the percent in each group was very similar in the two treatment groups. 2.2 percent in the 17-p group, 3.3 percent in the placebo group.

Specifically, the types of AEs that most commonly led to early discontinuation, were injection site reactions.

However, there was no particular pattern observed to those that discontinued for other

reasons.

This is the low rate of discontinuation due to injection site reactions: 1.0 percent in the 17-p group, 1.4 percent in the placebo group.

It indicates that 17-p treatment was generally well tolerated by women in this study.

Serious adverse events were collected according to NICHD standardized procedures and included all deaths; that is, maternal, neonatal, and fetal.

And I might note, also, that this analysis included congenital anomalies.

This chart summarizes the non-fatal serious adverse events. The rates of these events was very similar between the 17-p and placebo groups, as you see here, 9.4 versus 10.5.

The greatest contribution to non-fatal SAE rate was congenital anomalies, and there did not appear to be any particular pattern that was evident for the other reported serious adverse events, as you see in this list.

SAEs due to congenital anomalies at birth were also comparable between the two groups. As you

can see, 2.2 percent in the 17-p group, 1.9 percent in the placebo group.

Overall, congenital, and not just congenital anomaly rate, is very comparable to reports in other population surveys.

There did not appear to be any particular pattern in terms of type or organ system.

The data for miscarriages, stillbirths, and neonatal deaths are shown here.

The percent of patients experiencing each of these events was generally comparable. The neonatal death rate was lower in the 17-p group compared to the placebo group. However, the miscarriage rate was higher, 1.5 percent versus 0.5 percent.

I might add that none of these differences, however, reached statistical significance.

It is also important to note that investigators were asked to evaluate each of these cases, and, in all cases, the opinion of the investigator was that no neonatal death, stillbirth, or miscarriage was considered related to the study drug.

In addition to the investigators' assessments,

we examined these cases and found that these mothers had many other risk factors, placing them at high risk for miscarriages.

In order to place the miscarriage rate in perspective, we examined miscarriage rates between 16 and 20 weeks, in similar subsets of women from other network studies, and I'd like to describe these, briefly.

Again, in the 17-p study, we found a 1.5 percent rate of miscarriage in the 17-p treated mothers versus 0.5 percent in the placebo mothers. These bars represent the 95 percent confidence intervals.

The two other studies that we examined were both NICHD, MFM Unit, network trials, that, again, had similar populations to the 17-p study.

In the pre-term birth prediction, which studied over 3,000 women, there were 485 who were multiparous and had a prior pre-term birth.

And, as we can see here, the miscarriage rate, this is between 16 and 20 weeks of gestation, was 3.1 percent.

In additional Maternal Fetal Medicine Unit's Network Study, was a Factor 5 Lydein Mutation Study (ph).

This was an observational study with no intervention being offered. And, again, of the 581 mothers that you see here, this represents a subset of mothers who are multiparous and had had a prior pre-term birth.

And what I would like to point out from this analysis that you see, first, that the numbers are fairly low, but there is great consistency between the current 17-p study, the pre-term birth prediction study, and the Factor 5 Lydein Mutation with great overlap between the 95 percent confidence intervals.

Finally, in our examination of potential causative relationships between 17-p and miscarriage, we reviewed all literature on the subject that we could find.

Oates-Whitehead published a Cochrane data base review in 2003 on the subject of progestins and prevention of miscarriage.

In the studies that examined 17-hpc for miscarriage prevention, 17-hpc compared comparably to placebo with an odds ratio of 0.77, suggesting a slight benefit that was not statistically significant.

Of importance, however, is that the results of this study do not demonstrate an increased risk for miscarriage.

In terms of the safety conclusions from the 001 and the 002 Studies, the study results demonstrate that 17-p was safe and well-tolerated by pregnant women.

It was also safe for the developing fetus and neonate with comparable rates of stillbirth, miscarriage, and neonatal death.

The rates of congenital anomalies, of 2 to 3 -- of 2 percent, were also very similar to the population rates that are often quoted in the 2 to 3 percent range.

As described previously, a follow-up study was designed and performed to examine the long-term effects of 17-p. And, as I stated previously, this

study was initiated subsequent to the completion of the 002 trial.

This study enrolled 278 children born of women enrolled in Study 002.

In the 17-p group, there were 194 patients, representing 68 percent of the eligible births, and, in the placebo group, there were 84 infants representing 59 percent of the births.

The age range at the time of the examination was 30 to 64 months.

And I might remark that this is an incredibly high percent of enrolled patients considering the time interval that followed after birth.

The demographic characteristics of the patients, including age, self-reported race, or ethnicity, and sex or gender, of the infants enrolled in the follow-up study, were comparable between the treatment groups.

The mean age of enrollment was approximately four years of age, and there were a higher percent of males in the 17-p group, as you can see here.

Note that the gestational age at birth for the

17-p infants was approximately one week higher than the placebo infants, likely due to the fact that only live-born infants, clearly, were included in the study.

None of the differences in these demographic characteristics reached statistical significance.

I'd like to go into a little bit of detail now, at this time, on the components of the 17-p follow-up study.

There were three components, and these were based on surveys and physical examinations.

The first component was the Ages and Stages Questionnaire, so-called ASQ.

The second was a set of survey questions; and,

The third, a physical examination.

I'll describe each of these separately.

The ASQ is a widely-used and validated tool to identify children who are at risk for a developmental delay.

The ASQ is comprised of multiple age- specific batteries of questions that are designed to identify children that are at risk for developmental delay in

five general areas.

And, again, as I mentioned, this questionnaire is widely used and has been validated in a number populations.

In this slide, we've presented you with random questions from different developmental areas.

For example, in the area of communication, a question would be: Does your child make sentences that are three or four words long? In the gross mortar category, does your child jump with both feet, leaving the floor at the same time, and so forth for other general areas?

The response to the ASQ question is either "Yes," "Sometimes," or "Not Yet."

The primary endpoint for the Ages and Stages Questionnaires was the percent of the infants scoring below a pre-specified cut-off in at least one developmental area.

As we can see from this table, there were no statistically significant differences between the two groups in terms of the percentages with and the occurrence of a score below the cut-off. Nor were

there differences detected for one area of development versus another.

The conclusion from this study was that there were no differences observed between the 17-p and placebo groups for the ASQ questionnaire.

A second assessment was a Survey Questionnaire that was developed specifically by NICHD for this follow-up study.

This questionnaire was comprised of questions that were selected from several validated sources, as you can see here.

These questions are used in a number of governmental and non-governmental agencies to screen for developmental abnormalities in children and have been used in some cases for several decades.

Here, we present a random sample of the questions from the Survey Questionnaire, again, with the area of interest.

Communication problem solving: Does your child pronounce words, communicate with, and understand others, in terms of motor skills and activity?

Do you have any concern about your child's

overall activity level, and so forth, for the other developmental areas?

The Survey Questionnaires results revealed no significant differences in the following areas:

Physical growth, motor skills, and activity levels, communication and problem solving, overall health, reported diagnosis by health professionals, hearing, vision, and use of special equipment, and gender-specific play, which was one of the specific questionnaires.

A third component of the follow-up study was a general physical examination. This was conducted by a pediatrician or a nurse practitioner in each one of the study sites.

A physical examination included standard measurements of the child's weight, height, head circumference, and blood pressure, as well as documentation of any abnormality in the child's history.

In addition, a part of the examination was specifically directed towards identification of genital abnormalities.

Physical examination findings were generally comparable between the 17-p and placebo groups, as you see here.

The most common abnormalities were of the skin, followed by palpable inguinal nodes.

5.3 percent of infants were described as having abnormalities on examination of the heart.

These abnormalities included murmurs and irregular rhythms.

I might note that when we examined the follow-up study reports and looked at other areas for documentation of problems, we found no evidence of any functional impairment in any of these infants in the category of heart.

Although we did not find an excess in problems, as we described to you before, we did look to the Safety literature in terms of epidemiologic studies that looked at birth defects and exposure to progestins during pregnancy.

Three (3) fairly large studies are examined and presented to you here.

First: The Michaelis Study in Germany involved

several thousand infants, of which 462 were specifically exposed to either 17-hpc or 17-hpc and other agents.

Riceggi (ph), in the Mayo Clinic, reported in 1985 a very large study that included follow-up from several thousand women in Olmsted County, Minnesota.

Of those, 649 were specifically exposed to 17-hpc.

This study is quite remarkable in that it included a follow-up, a mean follow-up, of up to 11.5 years for these infants.

So there was a lot of opportunity to capture birth defects in the Riceggi Study.

Finally, in another large study of Katz, out of Israel, 1,608 women were observed for birth defects following exposure to 17-hpc or other progestins.

The conclusion from all of these studies was that there was no association between 17-hpc exposure and congenital anomalies.

Finally, FDA itself, reviewed these studies and other information and stated in the background of the 1999 ruling on the Assessment of Progestin

Class, and I quote, "The reliable evidence, particularly from controlled studies, shows no increases in congenital anomalies, including genital anomalies, in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."

The following safety conclusions were made from the results of the NICHD studies.

First: 17-p is considered safe and well tolerated in pregnant women.

17-p administration is also safe for the developing fetus and neonate based on comparable percentage of surviving offspring and rates of congenital anomalies that were very similar to general population estimates of 2 to 3 percent.

17-p administration was also safe for the child, as evidenced by lack of any untoward effects, on the developmental milestones or physical health, determined at the follow-up safety examination.

17-p is also safe, based on literature review, as we have previously shown you. And, in fact, the

FDA assessment on the progestigen class.

In turning to the overall benefits and risks of 17-p administration for recurrent pre-term birth prevention, I believe that we would all agree on the compelling need to reduce the rising rate of pre-term birth in the U.S.

Pre-term birth is well-recognized as the leading cause of neonatal mortality and morbidity, and the incidence is increasing. In fact, there is a pre-term birth that occurs every minute in this country.

The financial costs are staggering, as well as the emotional costs, from both early and late pre-term birth.

17-p has been shown to be remarkably effective against this unmet medical need. It reduces pre-term birth, regardless of how it is defined and, on average, increases gestation by about a week.

This is translated to fewer low birth-weight infants.

As we've shown you also in stratified analysis, these results are applicable, irrespective

of the race of the mother, the number of previous pre-term births, the gestational age at the previous pre-term birth, or the presence of bacterial vaginosis.

In addition, 17-p led to reduced admissions to the NICU and fewer morbidities.

17-p also leads to healthier neonates.

Again, treatment lengthens the mean gestational age at birth and results in fewer infants under 2,500 grams. Specifically, we showed a 34 percent reduction. It also reduces admissions to the NICU by approximately 24 percent.

Specific neonatal morbidities were reduced, including the need for respiratory therapy and the incidence of necrotizing enterocolitis or any grade of intra-ventricular hemorrhage.

17-p treatment has been shown to be safe for the mother, the developing fetus, and the child.

No identifiable risks were found to the fetus and neonate, with comparable rates of neonatal deaths, miscarriages, and stillbirths.

In addition, there was no evidence that 17-p

is a teratogen.

Congenital anomalies occurred at similar rates and 17-p exposed in placebo mothers, and this was also confirmed by the 1999 FDA assessment.

I might add, also, that if one is concerned about 17-p administration during pregnancy, recall that all of the patients in the study began their administration in the second trimester of pregnancy.

In addition, there were no unidentified risks for the child.

There was no association with developmental delays or other issues in children between 30 and 64 months of age.

In closing, 17-p is both safe and effective, and the benefits clearly outweigh the risk.

As a result, we believe that 17-p merits approval for this indication as proposed, and we would like to thank you for your attention this morning.

DR. DAVIDSON: Thank you.

Since we have a break scheduled at 10:30, you

have given us some additional time, perhaps for -- Dr. Hickok? Not quite, not quite.

(Laughter.)

DR. DAVIDSON: Perhaps we can use a part of this time, if there are questions or comments, from the Committee to the Sponsor, or maybe even to Dr. Romero, in terms of constructively using this time.

DR. DAVIDSON: Yes?

DR. JOHNSON: When you talked about the physical exam for the follow-up on the children, you said you specifically identified whether or not there were genital abnormalities.

Can you tell me what the percentage of genital abnormalities were for the 17-p group and the placebo?

DR. HICKOK: Yes. Let me actually show you those specific cases, as I can. There is very few of them, and we'll run through them. We'll run through them quickly.

(Pause.)

DR. HICKOK: We're pulling up specific case history slides for you, and we'll go through these

in detail, and I apologize for -- just for the delay here.

DR, DAVIDSON: While you're on that question, on the physical examinations, I see there were five or so heart abnormalities in the 17-p group and none in the placebo group.

Could you characterize those? Were they similar or dissimilar abnormalities?

DR. HICKOK: Yes, Dr. Davidson.

Let me turn to the genital abnormalities, first, and then I'll get back to discussing the heart abnormalities, as you requested.

In terms of the physical examination and the genital abnormalities, in the 17-p group, there was 1.5 percent; in the placebo group, 1.2 percent.

And let me go over just with you, you know, what those abnormalities were.

DR. JOHNSON: I'm sorry. Were these at birth, or were these at the follow-up visit?

This is Dr. Johnson asking.

DR. HICKOK: Okay. These, were the abnormalities that were at the follow-up study.

Would you like me to start with birth first?

DR. JOHNSON: Oh, no. No. I just wanted to make sure because this doesn't quite match with the information I have. But go ahead.

DR. HICKOK: Yes.

And let me explain, first, if you're looking at the Adeza briefing package -- and there were two additional cases that we listed in there -- one of those cases was a child who was initially classified as having labial-scrotal fusion, and a second one was a child that was originally described as having clitoral hypertrophy.

NICHD went back on these individual cases and actually examined a lot of pieces of evidence because of, of, again, a concern and a real focus on their part to, you know, try to get an idea, you know, was this a teratogen in terms of genital abnormalities.

They went back, and, for example, looked at a lot of data from examination at the time of birth.

In many cases, there was evidence from multiple well- child visits.

In one case, a child had --and let me give you an example of one such infant.

And this is the child that was originally classified as having labial-scrotal fusion. This child, again, was age five at the time of the follow-up study.

The labia was described as being fused together at the follow-up study examination.

But, again, when NICHD went back, and they looked at kind of all-available evidence, they found that, for example, the genital exam at the time of birth was normal and that this young child had multiple-infant exams between one week and three years of age, where, repeatedly, the genital examination was reported as normal.

And, again, they felt that this mitigated, you know, against this being a true case of labial scrotum fusion, and it probably represented benign labial adhesions rather true labial scrotal fusion.

And, again, other evidence that NICHD took from the literature was, for example, good data showing that the urogenital sinus fuses at 12 weeks

of gestation, so that if you have a drug exposure, or other exposure after that, you really can't develop labial scrotal fusion after the 12th week of pregnancy.

If I can move on to the case of clitoral hypertrophy next, which I think is the next slide.

(Pause.)

This was a child, again, that was age four at the time of the follow-up study examination, and the genital examination was reported at the time of birth of being completely normal.

This infant, because of the concern, the original examiner that said, gee, I think that, you know, this child may have clitoral hypertrophy, was brought back in by the same follow-up study investigator and reexamined four months later and, at that exam, the investigator said, hey, you know, this child is completely normal, and actually described a measurement of the transverse diameter of the clitoral shaft being less than 5mms at that time.

Does that cover your question, then, on the

genital abnormalities or?

DR. JOHNSON: Let's go ahead and look at the four cases that you then considered true abnormalities.

DR. HICKOK: Okay. Great.

We'll go back to that prior slide on abnormalities identified.

And, again, your question was that -- to clarify and give you what you need, at the time of the follow-up examination?

DR. JOHNSON: Correct.

DR. HICKOK: Okay. Great.

Here are the other -- let me just precede that by saying, so, you know, in the spirit of full disclosure on the part of Adeza, we wanted to put that in our briefing package to make sure that everybody on the Committee was aware that these were identified and then considered to be reclassified by NICHD.

So the other cases in terms of genital and reproductive track abnormalities notes there were noted was one child, where there was a question of

early puberty in the 17-p group.

And this child, again, was age 3.6 years at the time of the follow-up examination, and there was a question as to whether or not there were breast buds observed without other signs of precocious puberty.

One of the things that was felt to be a confounding factor by NICHD in their review of this child is that was -- this young girl, unfortunately, weighed 66 pounds at the time of her follow-up at 3.6 years of age. So she was quite obese and was actually in the 100th percentile of BMI at that time.

The second case that was a question of precocious puberty, was a young child that was examined at 3.5 years of age, who had been born at 25 weeks of gestation, and had a fairly stormy neonatal course.

On her examination, she had quote, "Four or five long pubic hairs at the time of the follow-up study," but, again, no other indications that this was precocious puberty.

DR. JOHNSON: And then there were two boys with

-- DR. HICKOK: There were two boys, and we'll show those to you here shortly.

(Pause.)

DR. HICKOK: I apologize. We're having a little technical difficulties here.

Let me describe them to you even without the slide.

There were two cases of micro-penis that were identified, you know, at the time -- here we go -- two cases of micro-penis that were identified, and I'll go through those two cases with you shortly here.

That was the slide I wanted. Here we go. Okay.

The first was a case of a child born at 38 weeks of gestation and was age 4.5 at the time of follow-up study.

This child was described as having micro-penis, which, as you know, can be a very difficult diagnosis to make. And, in fact, there's often times not good diagnostic criteria for this.

NICHD went back and identified, again, all the records they could find and felt that it was especially significant that the genital examination at the time of birth was completely normal. And that's a time where it would be very sensitive.

In addition, there was a second case of micro-penis identified in a child who was three-and-a-half years at the time of follow-up study.

This infant had Down's Syndrome, and micro-penis is also a commonly associated finding in children with Down's Syndrome.

I'd also like to just invite Dr. Melissa Parisi to the podium very briefly.

She is a pediatric geneticist who is head of the Gender Assignment team at University of Washington.

So this is something she does, you know, everyday, every week, and she'll remark a little bit about genital exams on children, and variability, and all.

DR. PARISI: Melissa Parisi, University of Washington, in Seattle.

First of all, I'd like to comment that in my role as a geneticist and with a particular interest in urogenital anomalies, that these can be challenging examinations.

And I also think it is important to note that, in the context of the follow-up study, the physicians and the nurse practitioners were directed to look specifically at the genitalia, whereas most pediatricians do not routinely measure clitoral diameters nor phallic lengths in children, particularly at this age range.

So I think there may have been a little bit of an ascertainment by us on that account.

I also had the opportunity to review these five to six cases in great detail, and I feel that the evidence is fairly compelling that these are not likely to be related to exposure to the medication in utero, particularly during the time period of the drug exposure, which is well beyond the first trimester.

And, finally, I'd like to point out that when you look at the development of the external

genitalia, that prior to seven weeks gestation the appearance of the genitalia is identical in males and females.

However, starting at about eight weeks gestation under the influence of the testosterone produced in the fetal male testes, you start to see differentiation at about nine weeks gestation.

And then subsequent fusion of the urogenital folds in male to form the penis and in the female forms the labia menorrha, with final closure of the labial scrotal swellings in the male by 12 weeks gestation, to form the scrotum, and that is retained in the female labia majora.

So, in conclusion, I think the combination of the nature of the follow-up study and the attention to the genitalia provided in the directions to the providers, as well as the careful review of these case reports and the period of drug exposure, means that these genital anomalies are unlikely to be related to the actual exposure to the drug during a later time of gestation.

DR. JOHNSON: Thank you very much.