

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

1 CONSULTANTS AND GUESTS

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SGE Consultants (Voting)

3

Maria Bustillo, M.D.

4 Sandra Carson, M.D.

Daniel Gillen, M.D.

5 Julia V. Johnson, M.D.

Ezra Davidson, M.D.

6 Gary Hankins, M.D.

Karin B. Nelson, M.D.

7 Hyagriv, Simhan, M.D.

Rose Marie Viscardi, M.D.

8 Vivian Lewis, M.D.

Joseph Harris, M.D., FACOG

9 Cassandra Henderson, M.D.

Katharine Wenstrom, M.D.

10 James Liu, M.D.

Elizabeth Shanklin-Selby

11

Guest Speaker (Non-Voting)

12

Roberto Romero, M.D.

13

F.A.C.P. Acting Industry Representative

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Steven Ryder, M.D.

15

16 FDA Center for Drug Evaluation and Research
Participants at the Table

17

(Non-Voting)

18 Daniel Shames, M.D.

Scott Monroe, M.D.

19 Lisa Soule, M.D.

Lisa Kammerman, Ph.D.

20 Barbara Wesley, M.D., M.P.H.

21 Julie Beitz, M.D.

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COMMITTEE MEMBERS

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

3 Official

4 Arthur L. Burnett, II, M.D.

5 Ronald S. Gibs, M.D. - Absent

6 Charles J. Lockwood, M.D. - Absent

7 Diane Merritt, M.D.

8 James R. Scott, M.D.

9 William D. Steers, M.D.

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

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

12 O. Lenaine Westney, M.D.

13

1 P R O C E E D I N G S

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

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

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

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

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

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

1 Texas at the University of Texas.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. DAVIDSON: Thank you. Doctor Watkins.

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

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

9 In accordance with 18 U.S.C. Section 208(b)(3),
10 Doctor Cassandra Henderson has been granted a full
11 waiver for her unrelated speakers bureau activities
12 for the sponsor for which she receives less than
13 \$10,001.00 per year.

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

22 We would also like to note that Doctor Steven

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

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

15 DAVIDSON: Doctor Monroe.

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

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

4 Today, the committee will be reviewing a new
5 drug application submitted by Adeza Biomedical for
6 17-hydroxy progesterone caproate with the proposed
7 trade name Gestiva. The proposed indication is
8 prevention of pre-term birth in pregnant women with
9 a history of at least one spontaneous pre-term
10 birth. The adverse consequence of pre-term birth is
11 a major public health problem. Approximately twelve
12 percent of all live births in the United States are
13 pre-term, defined as birth before thirty-seven weeks
14 gestational age. Pre-term birth is the leading
15 cause of neonatal death and a major cause of early
16 childhood morbidity and mortality including
17 pediatric neuro-developmental problems.

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

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

7 17-hydroxyprogesterone caproate is not a new
8 drug and was initially approved for marketing by the
9 FDA in 1956 largely on safety considerations. In
10 1956, approval for marketing for a new drug did not
11 require substantial evidence of effectiveness.
12 Suggested uses of 17-hydroxyprogesterone caproate
13 also known by the trade name Delalutin included
14 treatment of habitual, recurrent, or threatened
15 abortion. Delalutin was withdrawn from marketing in
16 2000 at the request of the NDA holder. The
17 withdrawal was not related to safety concerns.
18 Presently 17-hydroxy progesterone caproate is
19 available only from compounding pharmacies.

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

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

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

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

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

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

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

19 First: Are the clinical data adequate to
20 support the claim of effectiveness for
21 17-hydroxyprogesterone caproate for prevention of
22 pre-term birth.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 (2) Reduces fetal and neonatal morbidity or
8 mortality?

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

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

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

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

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

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

4 This will be followed by the applicant's
5 presentation.

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

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

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

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

16 (Long Pause.)

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

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

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

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

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

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

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

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

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

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

10 In 2004, more than 500,000 neonates were born
11 pre-term in the United States, with a frequency of
12 12.5 percent.

13 This bar graph illustrates a cycle of
14 trends in the frequency of pre-term birth, as a
15 percentage of live birth in the United States
16 between 1990 and 2004. An increase from 10.6 in
17 1990 to 12.5 in 2004 can be noted.

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

22 The frequency of pre-term birth among non-

1 Hispanic Americans was 17.8 percent, among American
2 Indians and Native Alaskans 13.5 percent, Hispanics
3 11.9 percent, Whites 11.5, and among the Pacific
4 Islanders, 10.5 percent.

5 Now the cost of pre-term birth, in medical care
6 services, has been estimated to be \$16.9 million,
7 approximately 33,200 dollars per pre-term infant.

8 In maternal delivery cost, \$1.9 million
9 dollars.

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

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

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

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

22 This is work reported by Dr. Brian Mercer, in

1 the Journal of Obstetrics and Gynecology.

2 And in the vertical axis is percentage, and the
3 horizontal axis is gestation.

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

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

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

15 So 20 percent of all infants born at less than
16 32 weeks of gestation do not survive beyond the
17 first year of life, and that is the importance of 32
18 weeks of gestation.

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

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

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

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

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

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

1 .82 percent; less than 32 weeks, 2.2 percent,
2 between 33 and 36 weeks, 8.9 percent. And less than
3 37 weeks of gestation, 11.2 percent.

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

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

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

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

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

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

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

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

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

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

17 And, finally, decidua and membrane activation.

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

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

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

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

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

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

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

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

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

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

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

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

15 Those interested in membrane decidua
16 activation have looked at fetal-fibrinectin, a
17 marker of extracellular matrix segregation.

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

22 A positive fetal fibrinectin confers a relative

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

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

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

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

19 That will be crossed over here.

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

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

4 Well, examination of the placenta, by a number
5 of investigators in patients who deliver pre-term,
6 have indicated that acute chorioamnionitis, that are
7 inflammatory lesions of the placenta, are present in
8 42 percent of the cases;

9 That vascular lesions are present in 20
10 percent;

11 Mixed inflammation of vascular lesions in 20
12 percent;

13 Chronic vellitis in .8 percent;

14 Velliseraema, 1.7; and,

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

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

22 First: They have multiple etiologies;

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

3 Often, there is fetal involvement.

4 Fourth: The chemical manifestations of the
5 syndromes are adapted.

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

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

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

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

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

1 infection.

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

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

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

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

22 The fetus mounts a systemic inflammatory

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

3 The impending onset of premature labor and
4 delivery;

5 The second: Severe neonatal morbidity and
6 mortality that can be the most treated in the
7 neonatal period; and,

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

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

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

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

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

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

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

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

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

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

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

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

22 All cases had histologic evidence of

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

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

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

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

15 And the potential beneficial effect that we are
16 considering today is progesterone administration,
17 and this is derived from trials with
18 17-hydroxyprogesterone and natural volume of
19 progesterone administration.

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

1 has been resolved for several decades.

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

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

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

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

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

14 So what is the effect of luteectomy in human
15 pregnancy?

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

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

22 A group that underwent tubal ligation, that is,

1 a control group;

2 A group that underwent tubal ligation and
3 luteectomy; and,

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

7 And the results, I illustrated over here.

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

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

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

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

1 continued the pregnancy, had no spontaneous
2 abortion.

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

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

15 And the third is to inhibit cervical ripening.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 The criteria for efficacy are generally
20 prevention of pre-term birth, defined as 37 weeks,
21 35 weeks, and 32 weeks, prolongation of pregnancy;
22 and, perhaps more important, neonatal morbidity and

1 mortality.

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

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

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

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

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

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

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

15 Thank you very much for your attention.

16 (Applause.)

17 DR. DAVIDSON: Thank you, Dr. Romero.

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

20 (Pause.)

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

1 correctly.

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

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

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

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

17 (Laughter.)

18 (Long Pause.)

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

21 (Long Pause.)

22 DR. HICKOK: Good morning. It looks like our

1 audio-visual equipment is back to functioning here.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 17-hpc is 17-hydroxyprogesterone caproate. It
12 is the active ingredient of 17-p, which was used in
13 the clinical study and was the study formulation of
14 17-hpc for injection.

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

18 17-alpha hydroxyprogesterone caproate is the
19 active pharmaceutical ingredient of 17-p.

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

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

5 17-p is provided as a sterile solution for
6 injection containing 17-hpc, 250mgs per milliliter,
7 in Castor Oil, along with Benzyl benzoate and Benzyl
8 alcohol.

9 17-p was used in the NICHD clinical studies and
10 is identical in composition to the previously
11 marketed Delalutin.

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

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

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

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

5 One of the first studies that we could find on
6 17-p in pre-term birth was that of Levine, that was
7 published in the United States in 1964.

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

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

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

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

19 17-hpc was initiated between 28 and 32 weeks
20 of gestation and given for 8 doses or less.

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

1 this result was statistically significant

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

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

7 17-hpc was initiated at the first prenatal
8 visit and continued until 37 weeks of gestation.

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

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

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

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

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

22 A study by Yemeni, out of Israel, published in

1 1985, had inclusion criteria of two prior pre-term
2 births or two miscarriages.

3 17-hpc was initiated early in pregnancy in
4 both, and in the active drug group. The mean
5 gestational age was 12.2 weeks.

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

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

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

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

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

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

22 In this study, we have summarized these

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

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

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

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

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

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

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

1 study sites were involved in this study.

2 The results were highly statistically
3 significant for the efficacy findings.

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

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

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

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

22 Again, Dr. Nageotte is a Professor of

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

5 DR. NAGEOTTE: Good morning.

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

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

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

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

1 overwhelming majority of all neonatal morbidity and
2 mortality

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

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

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

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

1 addition to these immediate morbidities of the
2 neonatal period.

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

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

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

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

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

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

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

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

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

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

22 As this slide demonstrates, the length of stay

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

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

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

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

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

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

22 In addition, greater risks of morbidity include

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

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

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

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

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

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

1 publication of Dr. Meis' study in 2003.

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

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

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

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

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

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

1 birth and the associated costs and morbidities.

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

7 Thank you very much

8 DR. HICKOK: Thank you Dr. Nageotte.

9 We'll now move on to the clinical review.

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

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

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

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

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

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

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

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

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

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

22 This occurred after an interim analysis was

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

6 Study 001 is a study that was initiated in
7 1998, prior to the completed 002 trial. It was
8 terminated due to a manufacture and FDA recall of
9 the study drug.

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

12 Following termination of the 001 trial, NICHD
13 made the decision to initiate a new 17-p study, and
14 that study that we we'll describe again is Study
15 002.

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

22 And, again, the follow-up study was an

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

4 It looked at the health and development of
5 infants born during the study. It was conducted at
6 15 Maternal Fetal Medicine Unit Network study
7 centers, and it enrolled 278 children.

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

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

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

16 We will now turn to the efficacy results.

17 Pregnant woman with a documented history of a
18 previous spontaneous, previous singleton spontaneous
19 pre-term birth, and gestational ages between 16 and
20 21 weeks, were randomized.

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

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

7 A total of 463 patients were enrolled with a
8 2-to-1 randomization of Active 2 placebo.

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

11 90.3 percent of patients completed injections
12 through 36 weeks, 6 days, or birth, resulting in a
13 90.0 completion rate in the 17-p group and a 90.8
14 percent completion in the placebo group.

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

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

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

1 births.

2 Nor were there differences observed between the
3 17-p and placebo groups for body mass index,
4 presence of diabetes, those who smoke cigarettes
5 during pregnancy, had alcoholic drinks, or used
6 street drugs during pregnancy.

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

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

15 1.3 in the 17-p group and 1.5 in the placebo
16 group.

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

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

1 delivery and the frequency of previous miscarriage.

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

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

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

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

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

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

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

22 In the second row for each analysis. we have

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

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

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

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

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

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

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

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

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

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

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

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

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

1 They suggest that the results are highly
2 generalizable, despite whatever patient population
3 17-p is administered.

4 We will now address the secondary endpoints.

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

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

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

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

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

1 And, again, for less than 37, the values are at
2 32.4 percent; for less than 35, 30.6 percent; 39.3
3 percent for less than 32 weeks, and 38.2 for less
4 than 30 weeks.

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

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

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

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

21 This can be interpreted much like a relative
22 risk.

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

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

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

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

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

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

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

1 - less frequently in a statistically-significant
2 fashion.

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

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

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

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

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

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

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

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

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

16 17-p resulted in prolonged gestation, and this
17 is very consistent with the other studies that we
18 have previously showed you.

19 The neonatal outcomes were improved, resulting
20 in a reduced percentage of infants born less than
21 2,500 grams, and a reduced rate of admission to the
22 Neonatal Intensive Care Unit.

1 17-p was also found to reduce specific neonatal
2 morbidities, including necrotizing enterocolitis,
3 intra-ventricular hemorrhage, use of supplemental
4 oxygen, and mean days of respiratory therapy.

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

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

10 As I mentioned previously to you, the completed
11 002 Study, with its 463 enrolled patients, formed
12 the basis of the efficacy assessments.

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

18 In the combined 001 and 002 Studies, a total of
19 613 patients received at least one study injection,
20 and, again, accounting for the 2-to-1 randomization
21 ratio, this resulted in 404 patients in the 17-p
22 group, and 209 in the placebo group.

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

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

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

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

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

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

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

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

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

9 The most frequently reported AEs in the 001 and
10 002 Studies were injection site reactions.

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

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

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

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

1 reasons.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 In addition to the investigators' assessments,

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

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

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

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

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

20 And, as we can see here, the miscarriage rate,
21 this is between 16 and 20 weeks of gestation, was
22 3.1 percent.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Note that the gestational age at birth for the

1 17-p infants was approximately one week higher than
2 the placebo infants, likely due to the fact that
3 only live-born infants, clearly, were included in
4 the study.

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

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

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

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

14 The second was a set of survey questions; and,
15 The third, a physical examination.

16 I'll describe each of these separately.

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

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

1 five general areas.

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

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

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

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

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

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

1 there differences detected for one area of
2 development versus another.

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

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

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

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

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

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

22 Do you have any concern about your child's

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

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

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

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

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

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

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

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

6 5.3 percent of infants were described as
7 having abnormalities on examination of the heart.

8 These abnormalities included murmurs and
9 irregular rhythms.

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

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

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

22 First: The Michaelis Study in Germany involved

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

4 Riceggi (ph), in the Mayo Clinic, reported in
5 1985 a very large study that included follow-up from
6 several thousand women in Olmsted County, Minnesota.

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

9 This study is quite remarkable in that it
10 included a follow-up, a mean follow-up, of up to
11 11.5 years for these infants.

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

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

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

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

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

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

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

11 17-p administration is also safe for the
12 developing fetus and neonate based on comparable
13 percentage of surviving offspring and rates of
14 congenital anomalies that were very similar to
15 general population estimates of 2 to 3 percent.

16 17-p administration was also safe for the
17 child, as evidenced by lack of any untoward effects,
18 on the developmental milestones or physical
19 health, determined at the follow-up safety
20 examination.

21 17-p is also safe, based on literature review,
22 as we have previously shown you. And, in fact, the

1 FDA assessment on the progestigen class.

2 In turning to the overall benefits and risks of
3 17-p administration for recurrent pre-term birth
4 prevention, I believe that we would all agree on the
5 compelling need to reduce the rising rate of
6 pre-term birth in the U.S.

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

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

15 17-p has been shown to be remarkably effective
16 against this unmet medical need. It reduces
17 pre-term birth, regardless of how it is defined and,
18 on average, increases gestation by about a week.

19 This is translated to fewer low birth-weight
20 infants.

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

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

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

7 17-p also leads to healthier neonates.

8 Again, treatment lengthens the mean gestational
9 age at birth and results in fewer infants under
10 2,500 grams. Specifically, we showed a 34 percent
11 reduction. It also reduces admissions to the NICU
12 by approximately 24 percent.

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

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

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

22 In addition, there was no evidence that 17-p

1 is a teratogen.

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

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

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

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

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

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

21 DR. DAVIDSON: Thank you.

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

1 have given us some additional time, perhaps for --

2 Dr. Hickok? Not quite, not quite.

3 (Laughter.)

4 DR. DAVIDSON: Perhaps we can use a part of this

5 time, if there are questions or comments, from the

6 Committee to the Sponsor, or maybe even to Dr.

7 Romero, in terms of constructively using this time.

8 DR. DAVIDSON: Yes?

9 DR. JOHNSON: When you talked about the physical

10 exam for the follow-up on the children, you said

11 you specifically identified whether or not there

12 were genital abnormalities.

13 Can you tell me what the percentage of genital

14 abnormalities were for the 17-p group and the

15 placebo?

16 DR. HICKOK: Yes. Let me actually show you

17 those specific cases, as I can. There is very few

18 of them, and we'll run through them. We'll run

19 through them quickly.

20 (Pause.)

21 DR. HICKOK: We're pulling up specific case

22 history slides for you, and we'll go through these

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

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

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

9 DR. HICKOK: Yes, Dr. Davidson.

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

13 In terms of the physical examination and the
14 genital abnormalities, in the 17-p group, there was
15 1.5 percent; in the placebo group, 1.2 percent.

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

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

20 This is Dr. Johnson asking.

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

1 Would you like me to start with birth first?

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

5 DR. HICKOK: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

7 (Pause.)

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

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

22 Does that cover your question, then, on the

1 genital abnormalities or?

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

5 DR. HICKOK: Okay. Great.

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

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

11 DR. JOHNSON: Correct.

12 DR. HICKOK: Okay. Great.

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

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

1 early puberty in the 17-p group.

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

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

13 The second case that was a question of
14 precocious puberty, was a young child that was
15 examined at 3.5 years of age, who had been born at
16 25 weeks of gestation, and had a fairly stormy
17 neonatal course.

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

22 DR. JOHNSON: And then there were two boys with

1 --

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

4 (Pause.)

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

7 Let me describe them to you even without the
8 slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. JOHNSON: Thank you very much.