

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE

Friday, January 20, 2012

8:00 a.m. to 4:00 p.m.

FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room
Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER

(Non-Voting)

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Office of Executive Programs Center for Drug Evaluation and
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P R O C E E D I N G S

(7:59 a.m.)

Call to Order and Opening Remarks

Introduction of Committee

DR. JOHNSON: So good morning, let's go ahead and get started. I'd first like to remind everyone present to please silence your cellphones, BlackBerries or any device if you have not done so already.

I would like to identify the FDA press contact, Morgan Liscinsky. Thank you for introducing yourself. She will be present throughout the day.

Now let us start off with introductions. Good morning again. I'm Julia Johnson. I am the acting chair of the advisory committee for reproductive health drugs. I'll now the call meeting of the Advisory Committee for Reproductive Drugs to order. We will go around the room. Let me first introduce myself, and then we will start with the FDA and Julie Bietz on my left.

Again, I'm Julia Johnson. I'm professor and

1 chair of obstetrics and gynecology at the
2 University of Massachusetts.

3 DR. BIETZ: Good morning. I'm Julie Bietz,
4 the director of the Office of Drug Evaluation III.

5 DR. SOULE: I'm Lisa Soule, the clinical
6 team leader in the division of reproductive and
7 urologic drugs.

8 DR. WESLEY: I'm Barbara Wesley. I'm the
9 reviewing medical officer.

10 DR. SOBHAN: I'm Mahboob Sobhan, a
11 statistician in the Office of Biostatistics.

12 DR. DWYER: I'm Kate Dwyer, statistical
13 reviewer, Division of Biostatistics III.

14 DR. WEINSTEIN: Lou Weinstein, maternal
15 fetal medicine.

16 DR. SICALLI: I'm Tony Sicalli. I'm an
17 obstetrician gynecologist and reproductive
18 toxicologist at George Washington University and at
19 a consulting company called Tetra Tech Sciences.

20 DR. SCHWARZ: Eleanor Bimla Schwarz from the
21 University of Pittsburgh.

22 DR. ROSEN: Cliff Rosen, endocrinologist at

1 Maine Medical Center.

2 DR. HARRIS: Joseph L. Harris at
3 St. Joseph's Hospital and Medical Center in Phoenix
4 and clinical associate professor at the University
5 of Arizona.

6 MS. BHATT: Good morning. I'm Kalyani
7 Bhatt. I'm the designated federal officer with the
8 Division Advisory Committee and Consultants
9 Management.

10 DR. MONTGOMERY RICE: Valerie Montgomery
11 Rice, reproductive endocrinologist, dean and EVP,
12 Morehouse School of Medicine.

13 DR. CLARKE: Bart Clarke, endocrinologist,
14 Mayo Clinic, Rochester, Minnesota.

15 DR. ORZA: Michele Orza, National Health
16 Policy Forum in Washington, D.C.

17 DR. HOEGER: Kathleen Hoeger, professor of
18 obstetrics and gynecology and reproductive
19 endocrinologist.

20 DR. BOCKMAN: Richard Bockman,
21 endocrinologist, professor of medicine at Weill
22 Medical College, Cornell in New York City.

1 MS. ARONSON: Diane Aronson, patient
2 representative, Cambridge, Massachusetts.

3 DR. EMERSON: Scott Emerson, professor of
4 biostatistics, University of Washington, Seattle.

5 DR. GILLEN: Daniel Gillen, associate
6 professor of statistics, UC Irvine.

7 DR. GREENE: Mike Greene, director of
8 obstetrics at Massachusetts General Hospital and
9 professor at Harvard Medical School.

10 DR. DAVIDSON: Ezra Davidson, professor of
11 obstetrics and gynecology at Drew University and
12 UCLA in Los Angeles.

13 DR. GUT: Good morning. Robert Gut, vice
14 president, clinical development, medical affairs at
15 Novo Nordisk, Inc.

16 DR. JOHNSON: Thank you, everyone.

17 For topics such as those being discussed at
18 today's meeting, there are often a variety of
19 opinions, some of which can be quite strongly held.
20 Our goal is that today's meeting will be a fair and
21 open forum for discussion of these issues and that
22 individuals can express their views without

1 interruption. Thus, as a gentle reminder,
2 individuals will be allowed to speak into the
3 record only if recognized by the chair. We look
4 forward to a very productive meeting.

5 In the spirit of the Federal Advisory
6 Committee Act and the Government in the Sunshine
7 Act, we ask that the advisory committee members
8 take care that their conversations about the topic
9 at hand take place only in the open forum for the
10 meeting.

11 We're aware that members of the media are
12 anxious to talk with the FDA about these
13 proceedings. However, the FDA will refrain from
14 discussion on the topics of this meeting with the
15 media until its conclusion. So, the committee is
16 reminded to please refrain from discussing the
17 meeting topics at breaks or at lunch.

18 Thank you very much.

19 Now, I would like to refer to Ms. Bhatt to
20 read the conflict of interest statement.

21 **Conflict of Interest Statement**

22 MS. BHATT: Good morning. Before I start

1 the conflict of interest statement, could
2 Dr. Greene please introduce yourself again for the
3 mic? Thank you.

4 DR. GREENE: I'm sorry. I'm Mike Greene.
5 I'm director of obstetrics at Massachusetts General
6 Hospital and professor at Harvard Medical School.

7 MS. BHATT: Thank you.

8 The Food and Drug Administration is
9 convening today's meeting of the Advisory Committee
10 for Reproductive Health Drugs under the authority
11 of the Federal Advisory Committee Act of 1972.
12 With the exception of the industry representative,
13 all members and temporary voting members of the
14 committee are special government employees or
15 regular federal employees from other agencies and
16 are subject to federal conflict of interest laws
17 and regulations.

18 The following information on the status of
19 the committee's compliance with federal ethics and
20 conflict of interest laws, covered by but not
21 limited to those found at 18 U.S.C. Section 208 and
22 Section 712 of the Federal Food, Drug and Cosmetic

1 Act, is being provided to participants in today's
2 meeting and to the public.

3 FDA's determined that members and temporary
4 voting members of this committee are in compliance
5 with federal ethics and conflict of interest laws.
6 Under 18 U.S.C. Section 208, Congress has
7 authorized FDA to grant waivers to special
8 government employees and regular federal employees
9 who have potential financial conflicts when it's
10 determined that the agency's need for a particular
11 individual's service outweighs his or her potential
12 financial conflict of interest.

13 Under Section 712 of the FD&C Act, Congress
14 has authorized FDA to grant waivers to special
15 government employees and regular federal employees
16 with potential financial conflicts when necessary
17 to afford the committee essential expertise.

18 Related to the discussion of today's
19 meeting, members and temporary voting members of
20 this committee have been screened for potential
21 financial conflicts of interest of their own as
22 well as those imputed to them, including those of

1 their spouses or minor children and for purposes of
2 18 U.S.C. Section 208, their employers. These
3 interests may include investments, consulting,
4 expert witness testimony, contracts, grants,
5 CRADAs, teaching, speaking, writing, patents and
6 royalties and primary employment.

7 The agenda for today's meeting involves the
8 discussion of the benefits and risk of new drug
9 application, NDA 22-139, progesterone gel 8%,
10 Columbia Laboratories, Incorporated for the
11 proposed indication of reduction of risk of preterm
12 birth in women with singleton gestation and a short
13 uterine cervical length in the mid-trimester of
14 pregnancy.

15 The uterine cervix is the mouth of the
16 uterus leading into the vagina or birth canal. The
17 benefit-risk discussion will focus on the adequacy
18 of the demonstration of efficacy in the U.S.
19 population.

20 This is a particular matter meeting during
21 which specific matters relating to Columbia
22 Laboratories progesterone gel 8% will be discussed.

1 Based on the agenda for today's meeting and all
2 financial interests reported by the committee
3 members and temporary voting members, no conflict
4 of interest waivers have been issued in connection
5 with this meeting.

6 To ensure transparency, we encourage all
7 standing committee members and temporary voting
8 members to disclose any public statements that they
9 have made concerning the product at issue.

10 With respect to FDA's invited industry
11 representative, we'd like to disclose that
12 Dr. Robert Gut is participating in this meeting as
13 a nonvoting industry representative acting on
14 behalf of regulated industry. His role at this
15 meeting is to represent industry in general and not
16 any particular company. Dr. Gut is currently
17 employed by Novo Nordisk.

18 We'd like to remind members and temporary
19 voting members that if the discussions involve any
20 other products or firms not already on the agenda
21 for which an FDA participant has personal or
22 imputed financial interest, the participants need

1 to exclude themselves from such involvement, and
2 their exclusion will be noted for the record. FDA
3 encourages all participants to advise the committee
4 of any financial relationship that they may have
5 with the firm at issue. Thank you.

6 DR. JOHNSON: Thank you.

7 Now we'll proceed with FDA opening remarks
8 from Dr. Lisa Soule.

9 **Opening Remarks - Lisa Soule**

10 DR. SOULE: Good morning. My name is Lisa
11 Soule, and I'm the clinical team leader in the
12 division of reproductive and urologic products.
13 I'd like to welcome you and thank the committee for
14 their deliberations today as we discuss this new
15 drug application.

16 The drug we are discussing today is
17 progesterone gel 8%. It is to be self-administered
18 using a vaginal applicator once daily from the
19 second trimester of pregnancy until the end of
20 36 weeks of gestation or delivery. This same drug
21 in formulation has already been approved for two
22 different OB/GYN indications, as shown on the

1 slide, and it remains on the market for these
2 indications.

3 As you've heard, the proposed indication is
4 to reduce the risk of preterm birth in women who
5 are pregnant with a single fetus and who have a
6 short uterine cervical length in the mid-trimester
7 of pregnancy. There are no products approved to
8 reduce the risk of preterm birth in women with this
9 specific risk factor. However, there are other
10 risk factors for preterm birth.

11 FDA approved a different progesterone
12 product, hydroxyprogesterone caproate, in 2011, to
13 reduce the risk of preterm birth in women who were
14 at high risk because they had a history of a prior
15 spontaneous preterm birth.

16 The applicant has provided data from the
17 following studies in support of approval of this
18 NDA. First, a single randomized placebo-controlled
19 trial that enrolled women with short cervixes,
20 defined as 1 to 2 centimeters as measured by
21 vaginal ultrasound in the second trimester of
22 pregnancy; an earlier randomized placebo-controlled

1 study that enrolled women who were at risk due to a
2 different risk factor, that is, women who had a
3 prior spontaneous preterm birth; a two-year
4 follow-up study of the health and development of
5 babies born in the earlier trial; and finally, the
6 applicant also conducted a pharmacokinetic study,
7 but that won't be discussed further by FDA today.

8 Although the usual regulatory standard for
9 drug approval is two adequate and well controlled
10 trials, FDA is sometimes asked to approve a drug on
11 the basis of a single study. In these cases, we
12 look for features that allow a single study to
13 provide convincing evidence of efficacy. These
14 include a well-designed study in which the
15 demonstration of efficacy is very convincing from a
16 statistical perspective; a lack of contradictory
17 efficacy findings; no evidence that a few sites
18 drive the efficacy results; and a consistent
19 demonstration of efficacy.

20 In this case, the FDA and the applicant
21 discussed reliance on a single trial because the
22 initial trial, that is, the one done in women with

1 a prior preterm birth, had failed to show efficacy.
2 The applicant believed that the drug worked in
3 women with a short cervix and proposed a single
4 additional trial to study this population. The
5 applicant anticipated that data from the failed
6 trial for the small subgroup of women who had short
7 cervixes would be supportive.

8 FDA and the applicant agreed on the major
9 endpoints of preterm birth at less than 33 weeks
10 and a zero to 4-point scale that measured neonatal
11 mortality and morbidity. These were agreed to
12 represent clinically important outcomes.

13 We bring this NDA to the advisory committee
14 because there are several aspects that raise
15 questions. The primary issue relates to the
16 demonstration of efficacy. The population of the
17 study was multinational, about half U.S. and half
18 non-U.S., and there were notable differences in
19 efficacy in the U.S. and non-U.S. populations.

20 We are concerned as to whether a true
21 treatment benefit has been demonstrated. For both
22 of the major endpoints, the applicant's analysis

1 shows marginal significance overall, and the FDA's
2 analysis shows no significance overall. In the
3 U.S. population, both the applicant's and the FDA's
4 analysis show no significance. In addition, we
5 will show you evidence that a few non-U.S.
6 countries are driving the overall efficacy results.
7 Finally, the treatment benefit is inconsistent over
8 different patient subgroups, in one case even
9 favoring treatment with placebo.

10 We are particularly interested in hearing
11 your thoughts on the following issues: Do you
12 believe that progesterone gel reduces the risk of
13 preterm birth in women with a single gestation and
14 a short uterine cervix given that statistically
15 significant efficacy was not demonstrated in the
16 pivotal trial, particularly in U.S. subjects? And
17 do you believe that there is any clinical
18 explanation, based on the data provided in the NDA,
19 for the difference in efficacy results in the U.S.
20 and foreign populations? If yes, could this
21 explanation be adequately addressed in labeling so
22 that progesterone gel could be used safely and

1 effectively in the U.S. population?

2 Here is an overview of today's agenda. The
3 applicant will present first, followed by FDA with
4 time for questions from the committee to the
5 presenters. Following lunch, we will have an open
6 public hearing, and then we'll have time for
7 additional questions from the committee before we
8 move into committee discussion and deliberations.
9 I thank you again for your interest and attention.

10 DR. JOHNSON: Thank you very much.

11 Now we will proceed with the sponsor's
12 presentations.

13 **Sponsor Presentation - George Creasy**

14 DR. CREASY: Madam Chair, distinguished
15 panelists, members of the FDA and guests, my name
16 is George Creasy, and I am vice president of
17 clinical research for Columbia Laboratories and an
18 obstetrician by training. My colleagues and I are
19 delighted to present to you data in support of NDA
20 22-139, progesterone gel 8%, for the treatment of
21 uterine short cervix in pregnancy.

22 Note that I am joined today in presenting by

1 Dr. Amy Murtha, a perinatologist from Duke
2 University; Dr. Sonia Hassan who is the lead
3 investigator in this PREGNANT trial; Dr. Philip
4 Darney is an OB/GYN who is also an experienced
5 trialist; and Professor Stuart Campbell, a pioneer
6 in the application of ultrasound in obstetrics and
7 gynecology and honorary fellow of the American
8 College of Obstetricians and Gynecologists. Our
9 presentations will focus on the data that supports
10 the proposed new indication.

11 The proposed new indication we seek today is
12 for the reduction of risk of preterm birth in women
13 with a singleton gestation and short uterine
14 cervical length in the mid-trimester of pregnancy.
15 Data from several studies support this new use.

16 Specifically, the data in the NDA for this
17 new use comes from three vaginal gel studies and a
18 study of a different formulation that provides
19 independent substantiation for the efficacy of
20 vaginal progesterone. Our primary safety and
21 efficacy data come from a large randomized clinical
22 trial we will refer to as Study 302.

1 Supportive safety data from a two-year
2 infant follow-up are from a large randomized
3 clinical trial that we will refer to as Study 300.
4 Study 300 also provided the initial hypothesis
5 generating efficacy data in women with a short
6 cervical length. In Study 301, we measured serum
7 progesterone levels.

8 Finally, the randomized clinical trial of
9 Fonseca and Nicolaides provide an independent
10 substantiation of the use of vaginal progesterone
11 from a different formulation in women with a short
12 cervical length in the mid-trimester.

13 Progesterone gel 8%, or Crinone, has been
14 approved for use in pregnant women worldwide for
15 14 years in the first trimester of pregnancy. It
16 is prescribed for support in the achievement of
17 pregnancy and continued in the maintenance of early
18 pregnancy for women worldwide. This formulation
19 consists of a unique bioadhesive delivery system
20 marketed in more than 60 countries.

21 Here you see the single dose intravaginal
22 application accompanied by the detached removal end

1 tab and the standard dose of gel with 90 milligrams
2 of natural progesterone in about a gram of gel. As
3 mentioned, Crinone is currently approved for use in
4 pregnancy as once daily progesterone
5 supplementation or twice daily for progesterone
6 replacement as part of an assisted reproductive
7 technology treatment for infertile women. These
8 doses are the same worldwide. Crinone is also
9 approved for use in secondary amenorrhea. These
10 indications have been approved since 1997.

11 The regulatory history of this new NDA began
12 with a submission of the first version of the
13 Study 300 protocol and an IND for the prevention of
14 preterm birth in the fourth quarter of 2003. We
15 had three meetings with the division on Study 300
16 to discuss the protocol and the statistical
17 analysis plan. Once this multinational study was
18 completed, we met with the division to discuss the
19 findings of delayed cervical shortening and the
20 delay in delivery of women with a short cervix at
21 baseline.

22 To follow up on those short cervix findings,

1 we began multinational Study 302 in 2008. We again
2 met with the division to discuss and agree on the
3 protocol design. Before the study was completed,
4 we agreed on the statistical analysis plan.

5 In 2011, we reviewed the results at the pre-
6 NDA meeting. During this period in 2006, this
7 committee agreed that the primary endpoint for a
8 preterm birth prevention trial is the frequency of
9 preterm birth less than 35 weeks gestational age or
10 earlier. From meetings such as these, key
11 agreements are determined.

12 Our discussions with the division did result
13 in several key agreements. The division agreed
14 that one trial such as 300 could be adequate if it
15 showed a robust reduction in preterm births of less
16 than or equal to 32 weeks gestation and no
17 suggestion of an increase in intrauterine deaths or
18 in neonatal morbidity.

19 Further, the division asked for adequate
20 postnatal safety follow-up of the infants as well
21 as strong supportive data from the literature
22 attesting to the safety and effectiveness of

1 progesterone in the proposed indication. Due to an
2 unexpected results in Study 300, a second trial,
3 Study 302, was eventually needed, as will be
4 discussed momentarily.

5 Please note that we were never asked to plan
6 for a statistically significant result in any
7 subgroup in the protocol or in the analysis plan
8 for Study 302.

9 Let us now spend a few moments reviewing
10 this history of the use of progesterone to prevent
11 preterm birth, our focus today.

12 Clinical evaluation began in the 1960s when
13 a trial was published on an unsuccessful attempt to
14 use a progesterone infusion to stop preterm labor.
15 By the 1970s, the focus shifted to the use of
16 progesterone in women with a history of preterm
17 birth where studies suggested that injections of a
18 synthetic progesterone would delay delivery in
19 women with a history of preterm birth. The full
20 evaluation of this earlier finding led to a number
21 of studies, including studies with vaginal
22 progesterone. In the 1990s, a short cervix was

1 identified as a powerful risk factor for preterm
2 birth.

3 In 2007, data from the randomized trial of
4 Fonseca, et al., demonstrated the efficacy of
5 vaginal progesterone in the reduction of preterm
6 birth in women with a short cervix. Later that
7 same year, O'Brien, et al., published the results
8 of Study 300 showing that vaginal progesterone
9 delayed cervical shortening, and at the same time,
10 DeFranco, et al., published the results of
11 Study 300 demonstrating that in a short cervix
12 subgroup, there was a delay in delivery.

13 In 2011, Hassan, et al., published the 302
14 study results and demonstrated a reduction in
15 preterm birth in women with a short cervix.
16 Finally, Romero, et al., published a meta-analysis
17 of individual patients' data, concluding that
18 vaginal progesterone leads to a reduction in
19 preterm birth in women with a short cervix.

20 Let's take a closer look at the two
21 progesterone gel studies that form the basis of our
22 submission.

1 Both of the progesterone studies were
2 randomized, double-blind, placebo-controlled
3 studies conducted worldwide. In Study 300, women
4 with a history of preterm birth were randomized.
5 The data collected included a baseline measurement
6 of cervical length by transvaginal ultrasound on
7 all subjects. In Study 302, meanwhile, women with
8 a short cervix as determined by transvaginal
9 ultrasound were randomized.

10 Study 300 revealed some unexpected and
11 interesting findings. In Study 300, the efficacy
12 of vaginal progesterone gel 8% in women with a
13 history of preterm birth was far less than expected
14 when the analysis of the primary endpoint was
15 completed. We are often asked why Study 300 did
16 not demonstrate efficacy in women with a history of
17 preterm birth, and honestly, we don't know for
18 sure. However, in Study 300, we measured cervical
19 length at baseline, and we excluded subjects with
20 cerclage. Some centers elected to place a cerclage
21 in the subjects diagnosed to have a short cervix.

22 Based on published frequency distribution of

1 cervical length, we would have expected many more
2 subjects with a cervical length of less than
3 30 millimeters that we actually observed. The
4 absence of these short cervix subjects may have had
5 an impact on the trial result.

6 With the analysis of the secondary
7 endpoints, more specifically the data on cervical
8 length, there was an interesting finding.
9 According to the protocol, Study 300 patients had a
10 cervical length measurement at both baseline and
11 28 weeks gestation. There was an observed delay in
12 cervical shortening after analysis of the cervical
13 length data between baseline and 28 weeks gestation
14 in the planned secondary objective of the trial.
15 This delay was interesting and appeared to be a
16 relevant pharmacodynamic finding.

17 In the subgroup of women with a cervical
18 length of 30 millimeters or less, we observed a
19 delay in gestational age at delivery as shown on
20 this Kaplan-Meier plot. The data for the
21 progesterone-treated short cervix patient shows a
22 clear delay in delivery relative to placebo. With

1 this data, we formed the hypothesis for the next
2 study.

3 The short cervix data from Study 300 coupled
4 with the results of the Fonseca trial in short
5 cervix patients helped us to design the follow-up
6 study, 302. Study 302 was designed and conducted
7 under a clinical trials agreement with the National
8 Institutes of Health. It was designed to identify
9 and randomize women with a short cervical length in
10 the mid-trimester. The primary endpoint was a
11 reduction in the frequency of preterm birth at less
12 than 33 weeks gestation with secondary endpoints
13 that included a reduction in infant morbidity and
14 mortality. A predefined statistical analysis plan
15 with multiple sensitivity analyses was developed to
16 demonstrate the robustness of the trial result for
17 the primary endpoint.

18 Study 302 demonstrated a significant
19 reduction in preterm birth at less than 33 weeks
20 gestation, the primary endpoint of the trial. In
21 addition, planned sensitivity analyses supported
22 this finding, and there was no evidence of harm to

1 the mother, fetus or infant, as you will see in the
2 later presentation.

3 In the upcoming presentations, my colleagues
4 and I will be explaining that a short cervix is the
5 best predictor of preterm birth and a large unmet
6 medical need given that our perinatal mortality
7 rate in the United States is among the worst in
8 industrialized nations. We will show that
9 Study 302 demonstrated efficacy in reducing preterm
10 birth in women with a short cervix, that the
11 efficacy is supported by the breadth and depth of
12 preplanned supportive analyses for the primary
13 endpoint, along with evidence of improvement in
14 infant outcome, as well as evidence of benefit in
15 subgroups.

16 We will also demonstrate that there is a
17 favorable safety profile with the use of
18 progesterone gel 8% in the second and third
19 trimesters for the mother, fetus and infant. You
20 will see that there is support for this approach
21 from other studies and analyses and that there is a
22 favorable risk-benefit assessment.

1 I would like to turn the presentation over
2 to Dr. Amy Murtha, who will discuss the medical
3 need for this product. Dr. Amy Murtha is vice
4 chair for the office of research support in the
5 department of obstetrics and gynecology and
6 associate professor of obstetrics and gynecology
7 and pediatrics at Duke University.

8 Dr. Murtha is a certified maternal fetal
9 medicine specialist, and her research interests
10 include progesterone and preterm birth prevention.
11 Dr. Murtha is a practicing MFM physician.

12 Dr. Murtha was not an investigator in this program.

13 Following Dr. Murtha, Dr. Sonia Hassan will
14 present the Study 302 efficacy. She is associate
15 dean for maternal perinatal and child health at
16 Wayne State University and a professor in the
17 department of obstetrics and gynecology.

18 Dr. Hassan is a practicing MFM physician and was
19 the lead investigator in Study 302.

20 Dr. Murtha.

21 DR. JOHNSON: But, Dr. Murtha, welcome.

22 Before you proceed, I would like to do two items.

1 Dr. Henderson, if you would turn on your
2 microphone and introduce yourself, please.

3 DR. HENDERSON: Hi, I'm Cassandra Henderson.
4 I'm a medical director of New York Diabetes Care in
5 the Bronx, and I'm also associate professor of
6 obstetrics and gynecology at Albert Einstein
7 College of Medicine also in the Bronx. Thank you.

8 DR. JOHNSON: Thank you.

9 And, also, as we proceed on with the
10 sponsor's presentations, I wanted to remind the
11 sponsors that both FDA and the public believe in a
12 transparent process of information gathering and
13 decision making. To ensure such transparency at an
14 advisory committee meeting, FDA believes that it's
15 important to understand the context of each
16 individual's presentations. And for this reason,
17 we do encourage all of the participants, including
18 the sponsor's nonemployee presenters, to advise the
19 committee of any financial relationship they may
20 have with the firm at issue such as consulting
21 fees, travel expenses, honoraria, interest in the
22 sponsor, including equity interest and those based

1 on the outcome of this meeting.

2 Likewise, the FDA encourages you at the
3 beginning of your presentation to also advise the
4 committee if you have any such financial
5 relationships. If you choose not to address these
6 financial relationships at the beginning of the
7 presentation, it will not preclude you speaking.

8 So, Dr. Murtha.

9 **Sponsor Presentation - Amy Murtha**

10 DR. MURTHA: Thank you, and good morning. I
11 am Amy Murtha, and I am a paid consultant to
12 Columbia Laboratories for today's meeting. I do
13 not have any financial interest in its outcome.

14 I plan to spend the next few minutes
15 reviewing for you the importance of preterm births
16 in the U.S. and its contribution to infant
17 mortality. As well, I will discuss opportunities
18 to reduce preterm birth rates both from a
19 historical perspective as well as the potential for
20 the future.

21 Specifically, an improved understanding of
22 the pathophysiologic mechanisms leading to preterm

1 birth has advanced our ability to identify at-risk
2 individuals early in the process by measuring
3 cervical length in the mid-trimester.

4 Identification of short cervix even in first
5 pregnancies offers an important opportunity to
6 intervene. Unfortunately, identification without
7 improved therapy offers little hope for impacting
8 preterm birth rates.

9 Preterm birth or delivery less than 37 weeks
10 gestation has continued to rise in the U.S. over
11 the last 20 years with a slight decline in recent
12 years. Importantly, preterm birth prior to 34
13 weeks gestation has not changed despite efforts
14 specifically directed at reducing those rates. As
15 you will see, it is this group that contributes
16 most significantly to major morbidity and mortality
17 in newborns.

18 According to the World Health Organization,
19 North America has one of the highest preterm birth
20 rates worldwide, second only to Africa. It is
21 imperative that we work aggressively to fix this
22 problem.

1 Unfortunately, despite the objectives of
2 Healthy People 2010, the U.S. also has one of the
3 highest infant mortality rates, ranking 48th in the
4 world, far below most other industrialized nations.
5 Importantly, preterm birth accounts for 34 percent
6 of infant mortality, and 95 percent of those are
7 born less than 32 weeks gestation. In order to
8 address the issue of infant mortality in the U.S.,
9 we must work aggressively to reduce preterm birth
10 rates, especially in those born less than 32 weeks.

11 Short-term consequences of preterm birth
12 include diminished survival and respiratory
13 distress syndrome. In addition, sepsis,
14 intraventricular hemorrhage and necrotizing
15 enterocolitis are common complications, and the
16 vast majority occur in patients that deliver prior
17 to 32 weeks.

18 Preterm birth is costly in many ways, both
19 for the individual and for society. Infants born
20 preterm are more likely to have chronic lung
21 disease, visual or hearing impairments, cerebral
22 palsy and developmental delay. While we all know

1 that this is true, it is also important to
2 understand the more subtle but substantial
3 consequences of prematurity.

4 In the Norwegian national registry, infants
5 born preterm but did not have the physical
6 disabilities listed above had a lower education
7 level attained, lower income, receipt of social
8 security benefits, and lower rates of establishment
9 of a family. Thus the consequences of preterm
10 birth are numerous and difficult to measure.

11 Understanding the etiology of preterm birth
12 is complicated by the multifactorial nature of the
13 disease. About 70 percent of all preterm births
14 are categorized as spontaneous preterm birth and
15 are the result of infection, ruptured membranes,
16 preterm contractions, and idiopathic cervical
17 shortening. The remaining 30 percent of preterm
18 births are the result of either maternal or fetal
19 complications, including preeclampsia and fetal
20 growth restriction, for example.

21 As mentioned earlier, the rates of preterm
22 birth in the U.S. remain high despite significant

1 efforts to reduce these rates. The historical
2 approach to reducing preterm birth has focused on
3 the treatment of preterm contractions with
4 evaluation of tocolytics such as alcohol,
5 terbutaline, nonsteroidal anti-inflammatory drugs,
6 and calcium channel blockers. This approach has
7 not been successful and likely reflects the fact
8 that the process resulting in preterm contractions
9 is the end stage of the disease.

10 Well established, non-modifiable risk
11 factors for preterm birth include maternal race,
12 socioeconomic status, and extremes of maternal age.
13 More recently, attempts have been made to identify
14 individuals at greatest risk for preterm delivery
15 with targeted interventions directed to reduce the
16 risk.

17 While the initial focus on history of
18 preterm birth as a risk factor has met with some
19 success, it unfortunately does not address
20 individuals having their first pregnancy or those
21 with a prior term delivery. Cervical length is
22 recognized as an important risk factor that may, in

1 fact, identify the disease process early enough
2 that intervention is effective.

3 Attempts at identifying women at risk for
4 preterm birth by cervical length have been the
5 subject of much research for the past 20 years. It
6 is now established that cervical length by
7 transvaginal ultrasound is an effective screening
8 tool when performed with adequate technique and is
9 predictive of preterm birth.

10 While evidence has existed that cervical
11 length can identify women at risk for a preterm
12 birth for years, without an appropriate therapeutic
13 intervention, its clinical utility has been
14 limited.

15 The landmark study by Iams in 1996 clearly
16 defined that cervical length is an important
17 predictor of preterm birth. When this cervix
18 measured less than 3 centimeters, the relative risk
19 for preterm birth was nearly 4. This relative risk
20 increases with decreasing cervical length with a
21 14-fold increased risk for preterm birth when the
22 cervix measures less than 1.3 centimeters.

1 Utilizing the observational data by Iams and
2 Berghella, we can estimate the preterm birth rates
3 less than 35 weeks in the U.S. for several cervical
4 lengths. As you can see, in the group of women
5 with a cervical length less than 2 centimeters or
6 20 millimeters, there are an estimated 60,000
7 births less than 35 weeks gestation. As the length
8 of the cervix approaches 3 centimeters, the
9 estimated number of preterm births less than
10 35 weeks increases threefold to 180,000. Many of
11 these infants will have chronic diseases related to
12 prematurity.

13 The cervix is composed of abundant
14 extracellular matrix, including collagen and
15 elastins. Understanding the mechanisms that result
16 in a short cervix provides an opportunity for
17 therapeutic intervention. Cervical shortening or
18 remodeling is a clinical observation of a
19 pathophysiologic process occurring over an extended
20 period of time.

21 In term pregnancies, cervical ripening or
22 shortening occurs as a result of decreased collagen

1 content, increased collagen solubility, and
2 increased collagenolytic activity. In women at
3 risk for preterm birth, these same cervical changes
4 occur over weeks. There's often an increase in
5 inflammatory cells in the cervical stroma with
6 production of cytokines, prostaglandins and matrix
7 metalloproteinases that disrupt the extracellular
8 matrix.

9 It is well established that blocking the
10 progesterone receptor leads to cervical ripening or
11 remodeling. This demonstrates the importance of
12 progesterone in maintaining cervical integrity.
13 Importantly, steroid hormones, including
14 progesterone, can inhibit the degradation of the
15 extracellular matrix associated with cervical
16 ripening.

17 Understanding the mechanisms resulting in a
18 short cervix is critical to the identification of
19 effective therapeutic interventions. Extracellular
20 matrix degradation or destruction of collagen,
21 which can result from an inflammatory process, both
22 of which can be chronic in nature, and finally,

1 uterine contractility result in a short cervix.

2 Importantly, progesterone diminishes extracellular
3 matrix degradation, reduces inflammation, and
4 reduces uterine contractility.

5 With a clear understanding of the processes
6 resulting in cervical shortening and preterm birth
7 and the effect of progesterone, it is biologically
8 plausible that application of progesterone directly
9 on the cervix would be an effective therapeutic
10 tool.

11 In conclusion, we understand that preterm
12 birth is an important contributor to infant
13 mortality in the U.S. We also understand that
14 consequences of preterm birth are significant and
15 include both short- and long-term devastating
16 effects. In short, we've known for years that
17 having a short cervix puts pregnant women and their
18 babies at risk for preterm birth, but we've had no
19 approved or efficacious treatment.

20 As a physician-scientist who's spent her
21 career caring for and researching preterm birth,
22 it's incredibly frustrating to have nothing to

1 offer this group of women. In summary, what is
2 needed to resolve this serious health issue is for
3 the approval of a safe, effective and readily
4 available treatment.

5 Thank you, and I'd now like to invite
6 Dr. Sonia Hassan to the podium to present efficacy
7 of Study 302.

8 **Sponsor Presentation - Sonia Hassan**

9 DR. HASSAN: Madam Chair, members of the FDA
10 and distinguished guests, good morning. On behalf
11 of my co-investigators, I am pleased to be here to
12 present Study 302, also called the PREGNANT trial.

13 I was the lead investigator at Wayne State
14 University. We were the coordinating center of the
15 perinatology research branch, NICHD, NIH network.
16 And our network worked in collaboration with
17 Columbia Laboratories through a clinical trial
18 agreement. I received no funding from Columbia
19 Laboratories or Watson for my participation in the
20 trial. I have no financial interest in the outcome
21 of this meeting, and I am not a paid consultant to
22 Columbia or Watson.

1 As Dr. Murtha mentioned, the problem of
2 preterm birth is substantial. The problem is so
3 substantial that we continue to ask is there a
4 solution. We certainly have a method to identify
5 patients at risk. A short cervix is the most
6 powerful predictor of preterm birth. However, the
7 challenge is that preterm birth is a syndrome with
8 multiple causes.

9 Our group has focused a large part of its
10 research on two major causes of preterm birth,
11 cervical disease and progesterone deficiency. The
12 findings of our group and others were the basis for
13 the design of the PREGNANT trial. Some of you have
14 seen the exciting results of the PREGNANT trial
15 after the publication in April of last year.
16 Today, I will review with you the study design, the
17 predetermined analysis plan, and the results of the
18 trial.

19 The objective of this study was to determine
20 if vaginal progesterone administration to women
21 with a sonographic short cervix can reduce the risk
22 of preterm birth. The PREGNANT trial was

1 cosponsored by the perinatology research branch of
2 the NICHD/NIH and Columbia Laboratories. The
3 protocol was developed in collaboration with the
4 perinatology research branch, Columbia Laboratories
5 and leading experts in the study of preterm labor.
6 The study was conducted at 44 centers worldwide.
7 Thirty-seven were university centers.

8 The participating centers in the trial are
9 shown here. As you can see, most of the centers
10 were in the U.S. where 45 percent of the subjects
11 were enrolled. Additional centers were distributed
12 worldwide.

13 Centers were selected for inclusion in this
14 trial if, number one, the site had the
15 infrastructure to conduct a research study and,
16 number two, the site was a tertiary care center
17 with a high-risk obstetrics unit and neonatology
18 unit. Although not a requirement, several centers
19 in the trial outside the U.S. either had physicians
20 that were trained in the U.S. or followed U.S.
21 guidelines for perinatal care.

22 This was a randomized double-masked,

1 placebo-controlled trial. The study was conducted
2 in compliance with good clinical practice,
3 including extensive onsite monitoring visits. The
4 statistical analysis plan was developed prior to
5 unblinding of the trial by statisticians of the
6 perinatology research branch of NICHD and NIH and
7 Columbia Laboratories and was agreed upon by the
8 FDA. This analysis plan was followed when the
9 trial was unblinded.

10 The key inclusion criteria were a singleton
11 gestation between 19 and 23 and six-sevenths weeks
12 with a cervical length of 10 to 20 millimeters.
13 Subjects were excluded if they met any of the
14 criteria listed here.

15 The range of 10 to 20 millimeters of
16 cervical length was selected after a thorough
17 review of the available data. The lower limit of
18 10 millimeters was selected after a review of the
19 data of the study by Fonseca which demonstrated
20 that the effect of vaginal progesterone decreased
21 as the cervical length decreased from
22 10 millimeters to zero. We know that women with a

1 cervix less than 10 millimeters have a higher rate
2 of intraamniotic infection and inflammation. And
3 unfortunately, often these women have likely
4 entered a terminal likely irreversible phase of the
5 parturitional process.

6 The upper limit of 20 millimeters was
7 selected after a review of previous observational
8 studies. As cervical length increases beyond
9 20 millimeters, the risk of preterm birth
10 decreases. Therefore, the selection of 10 to
11 20 millimeters represented a range in which the
12 potential efficacy of vaginal progesterone could be
13 demonstrated in a trial with a reasonable sample
14 size.

15 Subjects were stratified by the presence or
16 absence of a prior preterm birth. The study drug
17 was the vaginal progesterone gel formulation
18 containing 90 milligrams of natural progesterone.
19 The planned sample size was 450. The sample size
20 calculation was based on assumptions from both
21 previous trial experience and the existing
22 literature.

1 The assumptions were the following: a 22
2 percent placebo, a planned 55 percent reduction in
3 the risk of preterm birth with the use of
4 progesterone. Given a two-sided alpha of .05, this
5 yielded a power of 93 percent. The primary
6 endpoint of this study was the reduction in the
7 frequency of preterm birth at less than 33 weeks of
8 gestation.

9 A prespecified key secondary outcome was a
10 reduction in the frequency of neonatal morbidity
11 and mortality. In addition, we evaluated the
12 reduction in the frequency of preterm birth at
13 other gestational ages. The intent of the
14 secondary endpoints was to support the findings of
15 the primary endpoint. The study was not powered
16 for any of the secondary endpoints.

17 The planned secondary assessments of infant
18 outcome included the frequency of morbidity and
19 mortality as measured individually as well as
20 through composite scores. The composite score
21 consisted of the following seven components:
22 respiratory distress syndrome, bronchopulmonary

1 dysplasia, and other morbidities that are listed
2 here.

3 The four composite scores were described in
4 the analysis plan. Zero to 4 point morbidity and
5 mortality score was considered the key composite
6 analysis for this secondary endpoint. The seven
7 morbidities on the previous slide were used to
8 calculate the weighted zero to 4-point composite
9 score. In the zero to 4-point scale: no morbidity
10 or mortality; 1, one morbidity event; 2, two
11 morbidity events; 3, three or more morbidity
12 events, and 4, perinatal death. We also included
13 planned assessments of other birth parameters that
14 are shown on this slide, including infant length,
15 weight and head circumference as well as NICU
16 admission.

17 Our publication of April 2011 presented
18 results from three trial analysis sets. Today, I
19 will present data from one of these sets which
20 represents the primary analysis from the
21 statistical analysis plan submitted to the FDA, the
22 intent to treat or safety analysis set, which in

1 the publication was the treated subject analysis
2 set.

3 This dataset also includes all subjects who
4 were randomized and received at least one dose of
5 study drug. Importantly, missing delivery dates
6 were imputed in a conservative manner. All placebo
7 subjects with a missing delivery date were
8 considered to have delivered at term while
9 progesterone gel subjects with missing dates were
10 considered to have delivered as of their last date
11 of contact.

12 This is a worst-case analysis scenario for
13 the vaginal progesterone gel. Of note, there were
14 four placebo subjects with missing delivery dates.
15 They were treated as term deliveries, and no
16 progesterone subjects had missing delivery dates.

17 Four hundred and sixty-five subjects with a
18 cervical length of 10 to 20 millimeters were
19 randomized, 236 to vaginal progesterone and 229 to
20 placebo. Only six subjects did not take study
21 drug, one in the progesterone gel group and five in
22 the placebo group, leaving 235 in treatment and 224

1 in the placebo for a total population of 459. In
2 this analysis set, all subjects were considered to
3 have completed the study.

4 The demographics and baseline
5 characteristics at first dose were similar between
6 groups. There was an equal distribution between
7 Asian, black and white subjects. The mean cervical
8 length was 17 millimeters, and the mean gestational
9 age at the initial dose was almost 22 weeks.
10 Approximately 16 percent of subjects had a previous
11 preterm birth at less than 35 weeks of gestation.

12 The overall duration of treatment was about
13 13 weeks with a maximum of 18 weeks in both groups.
14 Calculated compliance was similar between
15 treatments at 90 percent.

16 Next, I will review the key aspects of the
17 statistical analysis plan for this study. The
18 focus of the plan was in the evaluation of the
19 primary endpoint of the trial. All other secondary
20 analyses were planned as supportive of the primary
21 analysis. The trial was not powered for any
22 secondary endpoint or subgroup analysis.

1 Nine pooled study sites were prespecified.
2 Centers were pooled in order to account for
3 geographic location and small sample size in some
4 study centers. The goal of pooling was to have an
5 equal number of subjects in each pooled study
6 center to have a large enough sample size to
7 accommodate statistical testing. All U.S. centers
8 were grouped into four pooled centers.

9 The Cochran-Mantel-Haenszel test was the
10 prespecified analysis for the primary endpoint. I
11 will briefly review this test and its
12 appropriateness in the next two slides.

13 The Cochran-Mantel-Haenszel test, or CMH
14 test, compares the effect of two treatments and can
15 be used to adjust for stratification factors or
16 potential confounders. In the PREGNANT trial, the
17 CMH test was used to compare the proportion of
18 preterm birth at less than 33 weeks between placebo
19 and progesterone. The test adjusted for two
20 prespecified stratification factors, a history of
21 preterm birth in the previous pregnancy also called
22 risk strata. In addition, since results will vary

1 from center to center, the nine primary pooled
2 study sites defined before unmasking were also
3 included as a stratification in the prespecified
4 analysis plan for the Cochran-Mantel-Haenszel test.
5 These stratifications in the CMH were included to
6 improve the internal and external validity of the
7 result.

8 So is this test appropriate for the
9 evaluation for the primary endpoint of this study?
10 The validity of the use of the Cochran-Mantel-
11 Haenszel test is verified by applying the
12 Mantel-Fleiss criterion. This criterion is used to
13 determine if the normal approximation for this test
14 is adequate. This criterion requires a test
15 statistic of more than 5. In other words, if the
16 Mantel-Fleiss is more than 5, it means that the use
17 of this CMH test is appropriate. The result for
18 the Mantel-Fleiss test for the PREGNANT trial data
19 was 26.2, demonstrating that the use of the
20 Cochran-Mantel-Haenszel test was appropriate.

21 According to the analysis plan, there were
22 three criteria to be met in order to establish the

1 efficacy of progesterone gel 8% over placebo:
2 First, the 95 percent confidence interval for the
3 risk difference should not cross zero; second, the
4 95 percent confidence interval for the relative
5 risk should not cross unity; and third, the
6 direction of the difference should favor
7 progesterone gel.

8 Next, to the results. Using the primary
9 prespecified analysis, the use of progesterone gel
10 reduced the frequency of preterm birth before
11 33 weeks by a statistically significant risk
12 difference of 6.2 percent which translates into a
13 44 percent reduction in the risk of preterm birth.
14 This p-value of .022 was derived from the
15 prespecified Cochran-Mantel-Haenszel test adjusting
16 for stratified factors, as I described in the
17 previous slides. In addition, the 95 percent
18 confidence interval for the risk difference and the
19 relative risk are displayed.

20 So the results of the trial met the
21 prespecified criteria in order to claim a reduction
22 in the risk of preterm delivery at less than

1 33 weeks of gestation. One of the criteria, as I
2 mentioned, was that the 95 percent confidence
3 interval for the risk difference would not cross
4 zero. This criterion was met. Another of the
5 criterion was that the 95 percent confidence
6 interval for the relative risk would not cross
7 unity. This criteria was also met. Finally, the
8 direction of the difference in risk was to favor
9 progesterone gel. This criterion was also met.
10 Clearly, Study 302 met all of the criteria to
11 establish efficacy of progesterone gel 8% over a
12 placebo.

13 In support of the Cochran-Mantel-Haenszel
14 test for the primary endpoint, there were also
15 several prespecified sensitivity analyses that were
16 intended to evaluate the robustness of the result
17 at the primary endpoint by testing sensitivity of
18 results in alternate study site pooling paradigms.

19 First, the Cochran-Mantel-Haenszel test was
20 conducted using 16 prespecified pooled study
21 centers rather than the nine while maintaining the
22 risk strata of a history of a prior preterm birth.

1 This result remained significant. Second, the
2 Cochran-Mantel-Haenszel test was conducted using
3 two pooled study sites rather than nine, U.S. and
4 non-U.S., while maintaining the history of a
5 preterm birth risk strata. This result was also
6 significant.

7 If the strata sizes for the Cochran-Mantel-
8 Haenszel test were too small, the statistical
9 analysis plan specified a backup exact test in the
10 event that the requirement for a normal
11 approximation had not been met by the Mantel-Fleiss
12 test. In that case, an exact test was to be used.
13 However, please remember that the criterion of the
14 Mantel-Fleiss was met. Nevertheless, the exact CMH
15 test was performed, and it was also significant.

16 Another prespecified secondary analysis was
17 the logistic regression analysis using seven
18 covariates: age, race, cervical length,
19 gestational age at study start, history of preterm
20 birth, primary pooled study center, and treatment.
21 The result of the logistic regression for treatment
22 was also significant and provides further support

1 for the robustness of the primary endpoint,
2 efficacy.

3 Thus, regardless of the tests that were
4 applied, the PREGNANT trial established the
5 efficacy for vaginal progesterone gel 8% for the
6 reduction of preterm birth at less than 33 weeks.

7 In addition, we conducted some planned
8 analyses of the secondary endpoints of other
9 gestational ages using the prespecified
10 Cochran-Mantel-Haenszel test stratified for nine
11 pooled study sites and risk strata. The results
12 demonstrated a consistency of effect across the
13 prespecified gestational age cut points of less
14 than 28 weeks and less than 35 weeks of gestation.
15 The point estimate for the secondary endpoint of
16 less than 35 weeks was also nominally significant.

17 By 37 weeks, the effect of vaginal
18 progesterone is near placebo. Vaginal progesterone
19 appears to have its greatest effect in the lower
20 gestational ages at which neonatal morbidity is
21 most significant.

22 We additionally evaluated the robustness of

1 the finding of the primary endpoint by the
2 preplanned use of a time-to-event analysis for each
3 treatment. Shown here is a Kaplan-Meier plot for
4 gestational age at delivery for both vaginal
5 progesterone and placebo. The Y axis is the
6 cumulative percent of subjects that are
7 undelivered, and the X axis is gestational age.
8 The vertical lines represent the points on the
9 curve where gestational age at delivery would be at
10 less than 28, less than 33, less than 35 and less
11 than 37 weeks. The curves start together since all
12 subjects are undelivered at randomization.

13 Note that we see that the progesterone gel
14 curve here in blue separates from placebo in gray
15 before 28 weeks and remains separated from placebo
16 until term. The separation of the curve shows the
17 effect of vaginal progesterone in delaying
18 delivery. Since all pregnant women will eventually
19 deliver, as expected, the curves of progesterone
20 and placebo will come together at term. Also note
21 that the Sensern (indiscernible) log-rank test for
22 gestational age cut points of less than 33 and less

1 than 35 weeks both reach a level of nominal
2 significance.

3 A number of subgroup analyses were
4 performed, although this trial, as most trials, was
5 not powered for any subgroup analysis. Subgroup
6 analyses are expected to display some variability
7 around the overall results, but the majority of
8 subgroups should follow the overall results in
9 treatment effect.

10 Note that the subgroup estimates on this
11 slide all favor progesterone with one exception,
12 and this pattern of results for subgroups support
13 the finding of the primary endpoint.

14 Moving now to neonatal outcomes, recall that
15 our preplanned key secondary endpoint was the
16 neonatal morbidity mortality score evaluation.
17 Prior to the calculation of the composite scores,
18 the individual morbidities and mortality were
19 assessed. Consistent with the use of surfactant,
20 even the most frequent of these events, respiratory
21 distress syndrome, occurred at a frequency of
22 7 percent in the placebo group. Still, the use of

1 progesterone was associated with a clinically
2 significant further reduction in the frequency of
3 respiratory distress syndrome, reaching a nominal
4 level of significance. This is the only preterm
5 prevention trial since the introduction of
6 surfactant in which the reduction in the rate of
7 respiratory distress syndrome reached a nominal
8 level of significance.

9 The results of the key zero to 4 composite
10 score is shown in the upper part of this slide. In
11 addition, any morbidity or mortality score for each
12 subject is only counted once without adjusting for
13 the number of events or for death as also shown.

14 The results of the other two ordinal
15 composite scores are very similar to the zero to 4
16 score shown here. Overall, these composite scores
17 show a trend for improvement in infant outcome as
18 would be expected from progesterone gel's efficacy
19 in extending gestational age.

20 Other measures of neonatal outcome also
21 improve with progesterone gel treatment. Please
22 note that the percentage of infants with a birth

1 weight of less than 1500 grams was cut in half from
2 13.3 to 6.4 percent. Treatment also reduced the
3 mean number and median duration of NICU admissions,
4 although these did not achieve statistical
5 significance.

6 In summary, Study 302 demonstrates that
7 vaginal progesterone gel significantly reduces the
8 risk of preterm birth. It is associated with a
9 statistically significant 44 percent reduction in
10 the risk for preterm birth at less than 33 weeks of
11 gestation, the study's primary endpoint.

12 The finding of the primary endpoint was
13 supported by a number of sensitivity and secondary
14 analyses, including that the benefit of
15 progesterone gel treatment was consistent from less
16 than 28 weeks to less than 35 weeks of gestation.
17 The progesterone was favored over placebo in
18 subgroup analyses. All of these analyses speak to
19 the robustness of the finding at the primary
20 endpoint.

21 Finally, this reduction in preterm birth is
22 associated with an improvement in infant outcomes

1 with a reduction in the rate of respiratory
2 distress syndrome, a reduction in the birth weight
3 of less than 1500 grams and trends for a reduction
4 in composite neonatal morbidity and mortality
5 scores.

6 We have provided compelling evidence for the
7 efficacy of vaginal progesterone for the prevention
8 of preterm birth in women with a short cervix. The
9 results of this study are so compelling that our
10 group and others have implemented the use of
11 cervical length and progesterone for the prevention
12 of preterm birth. This study has and will continue
13 to change the practice of obstetrics.

14 Thank you for your attention. I will now
15 turn the presentation back to Dr. Creasy.

16 **Sponsor Presentation - George Creasy**

17 DR. CREASY: Thank you, Dr. Hassan.

18 While the sponsor briefing book and the FDA
19 briefing book appear to come to different
20 conclusions regarding the efficacy of progesterone
21 gel 8% in the prevention of preterm birth, in the
22 next few slides, I would like to offer some

1 clarifications and show some important similarities
2 in the statistical results between the prespecified
3 analysis and the FDA analysis.

4 As mentioned by Dr. Hassan, we followed the
5 prespecified analysis plan in evaluating the
6 results from Trial 302. It is important to note
7 that the statistical analysis plan was reviewed
8 with the FDA and that the agency found it
9 acceptable as long as Kaplan-Meier analyses with
10 left truncation were also provided. The analysis
11 plan prespecified a contingency for use of an
12 alternative methodology in case the data did not
13 meet the criterion for the preplanned primary
14 analysis.

15 On this slide, I will compare the results of
16 the key efficacy analyses that are actually quite
17 similar. The primary prespecified analysis for
18 Columbia was the Cochran-Mantel-Haenszel test
19 stratified by nine pooled study centers and risk
20 strata, shown here by the yellow boxes. The backup
21 test for the prespecified Cochran-Mantel-Haenszel
22 was an exact test, and both the exact CMH and the

1 Fisher's exact were performed and were supportive
2 of the primary result. Since the criterion of
3 Mantel-Fleiss was met, these exact tests were
4 conducted post hoc, and the post hoc tests will be
5 shown in green boxes.

6 The next prespecified efficacy analysis
7 performed by Columbia was the CMH test stratified
8 by 16 pooled study centers and risk strata. The
9 prespecified tests will be shown in blue. These
10 prespecified analyses were not reported by the FDA.

11 The CMH test stratified by two pooled study
12 centers, U.S. and non-U.S., and risk strata was
13 performed by Columbia, and the FDA performed this
14 test without the risk strata. And these results
15 nevertheless were very similar. A logistic
16 regression was also performed by both Columbia and
17 the FDA, and even with slightly different
18 covariates in the model, the results of treatment
19 were similar and supportive of previous analyses.

20 For the supportive secondary endpoint of
21 births less than 35 weeks, both Columbia and the
22 FDA found this to be supportive of efficacy.

1 Finally, the three race subgroups all favored
2 vaginal progesterone with the black and Caucasian
3 estimates exceeding the overall results. This
4 finding was exactly the same for the Columbia and
5 the FDA analysis.

6 Thus, despite what may have been an initial
7 impression of differences, there are many
8 similarities between the sponsor's analyses and
9 that of the FDA. Importantly, both show clear
10 evidence of efficacy in Study 302.

11 The logistic regression analysis needs some
12 further clarification. A logistic regression
13 analysis with seven prespecified covariables was
14 part of the prespecified analysis plan. Because 12
15 subjects did not have data on all seven covariates,
16 they were excluded from the analysis. Therefore,
17 the logistic regression is an analysis on a subset
18 of the ITT population. The result of this analysis
19 was supportive of the prespecified primary analysis
20 nevertheless.

21 The FDA's logistic regression did not follow
22 the prespecified analysis plan, and sponsor

1 statisticians were unable to reproduce the FDA
2 results exactly. Still, both the FDA analysis and
3 the prespecified effectively support the primary
4 analysis.

5 The FDA's statistical reviewer stated that
6 the use of the Cochran-Mantel-Haenszel to adjust
7 for pooled study site and risk strata does not
8 appear to be appropriate. Regarding the primary
9 analysis, there are situations where our
10 prespecified stratified CMH test would not be
11 appropriate such as when the Mantel-Fleiss
12 criterion is not met.

13 The prespecified analysis plan included
14 assessments to validate the use of the stratified
15 CMH test with nine pooled study centers. As
16 previously presented, the Mantel-Fleiss criterion
17 was met. In addition and also previously
18 presented, a preplanned alternative exact test was
19 performed, and it too demonstrated efficacy.

20 The FDA briefing package expressed concern
21 about the efficacy from pooled study center to
22 pooled study center. All preplanned tests support

1 that the variability is acceptable and consistent
2 with expected variation.

3 This slide shows the results for each of the
4 nine primary pooled study sites. Each pooled study
5 center is listed in the first column and included
6 between 49 and 56 patients. The second column
7 shows the number of individual centers in the pool.
8 The third and fourth columns show the number and
9 percent of preterm births less than 33 weeks, and
10 the final column provides the risk difference.

11 There was only one site, a site in India,
12 that had no births less than 33 weeks in the
13 placebo group. Seven of the nine primary pooled
14 sites had efficacy that favored vaginal
15 progesterone. Only two sites favored placebo, one
16 site in the U.S. and one site in India. Centers
17 with both the highest efficacy favoring
18 progesterone and the lowest efficacy favoring
19 placebo were outside the U.S. This type of
20 variability is common and expected in multicenter,
21 multinational randomized clinical trials.

22 According to the FDA, the most important

1 statistical analysis issue noted in this
2 application is the regional heterogeneity in
3 efficacy. The FDA did not ask us to power
4 Study 302 to show significant results in any
5 subgroups, and region is one of the many subgroups
6 assessed. As will be discussed in a moment by
7 Dr. Darney, the overall study result is the best
8 estimate of any subgroup result.

9 We are puzzled by analyses that exclude
10 trial data. In the prespecified analysis plan, we
11 did not propose sensitivity analyses where there
12 was post hoc exclusion of selected data because we
13 are not aware of statistical techniques of
14 excluding sites to support heterogeneity, and we do
15 not understand why the FDA performed this analysis.

16 Randomized clinical trials control for bias
17 by creating comparable patient characteristics
18 between treatment groups. This contributes to good
19 internal validity. What randomization cannot do is
20 eliminate variability in response across subgroups.
21 The source of variability in response in a
22 randomized clinical trial is often due to chance

1 variation attributable to known and unknown
2 factors.

3 Although the formal tests of the data
4 supported that there was no substantial reversal of
5 results in the strata, we explored the observed
6 variability by examining baseline characteristics.
7 Each of the demographic characteristics was
8 thoroughly evaluated, and while a number of them
9 were clearly correlated to outcome, and as such had
10 already been included in the logistic regression,
11 none could explain the variability in the data.

12 Several aspects of obstetrical care were
13 held constant across all centers. There were
14 regular clinic visits every two weeks, and the
15 study staff was available to the patients every
16 day.

17 We identified two post-baseline factors that
18 are known to create variability and appeared to
19 vary by geography, patient compliance and the
20 occurrence of chorioamnionitis. Compliance has
21 been well documented to be lower in U.S. than
22 non-U.S. centers, and this trial was no exception.

1 In addition in this trial, chorioamnionitis was
2 more frequent in the U.S.

3 This randomized clinical trial showed
4 acceptable variability in the data based on
5 analyses previously presented.

6 To help you with the question about
7 labeling, we have researched other approved drugs
8 which have addressed a concern about efficacy in
9 subgroups. Last year, there were two drugs
10 approved in which concerns about subgroup efficacy
11 were addressed in the label. Brilinta was approved
12 for acute coronary syndromes with a subgroup
13 finding in the U.S. population of p equals 009 that
14 favored placebo. Note the statement from the label
15 about the cautious interpretation of subgroups
16 because they could represent chance findings.

17 A second drug approved last year with
18 efficacy concerns in the subgroup was Benlysta.
19 This drug for the treatment of lupus had a subgroup
20 finding in black patients that was less than
21 placebo. Again, please note the statement from the
22 label that states that no definitive conclusions

1 can be drawn from subgroup analyses.

2 A third example is Toprol approved for
3 congestive heart failure, and even though the
4 response of U.S. patients was less than placebo for
5 total mortality, again, note the statement in the
6 label that states that subgroup analyses can be
7 difficult to interpret and may be chance effects.

8 These three examples of how subgroups that
9 favor placebo have been addressed in labeling may
10 provide some guidance in your consideration of
11 question number 2. Remember that both the U.S. and
12 non-U.S. subgroups in Study 302 favored
13 progesterone treatment.

14 In summary, the prespecified and agreed upon
15 analysis plan was shown to be appropriate for the
16 data, including the nine primary pooled study sites
17 strata. The prespecified analysis and the FDA
18 analysis both agree that progesterone decrease
19 preterm birth less than 33 weeks gestation.

20 Regional variability was expected and cannot be
21 explained by baseline characteristics. Chance
22 variation is supported by a number of tests of the

1 data.

2 The overall result of this study is that
3 progesterone decreased preterm birth less than
4 33 weeks by 44 percent, and this result is a more
5 reliable estimate of treatment effect than those
6 observed in any subgroup.

7 I would now like to introduce Dr. Philip
8 Darney. Dr. Darney is a distinguished professor of
9 obstetrics, gynecology and reproductive sciences at
10 the University of California San Francisco. He is
11 boarded in both obstetrics and gynecology and
12 preventative medicine and trained in epidemiology
13 and demographics at the Centers for Disease Control
14 and the London School of Hygiene and Tropical
15 Medicine. He has conducted and analyzed many
16 clinical trials. Dr. Darney was not an
17 investigator in this program.

18 Dr. Darney.

19 **Sponsor Presentation - Philip Darney**

20 DR. DARNEY: Thanks, Dr. Creasy.

21 I've been asked to discuss the
22 interpretation of subgroup findings in general and

1 specifically with regard to the Study 302 data in
2 which I was not an investigator and have no fiscal
3 interest in the sponsor. I am a paid consultant
4 for this meeting.

5 The point I hope to make is that data from
6 subgroups should be viewed with care because what
7 appears to be an obvious conclusion may actually be
8 misleading. In the subgroup analysis of 302 study,
9 the progesterone benefit may appear to be driven by
10 the non-U.S. centers with only a small effect seen
11 in the U.S. centers. This interpretation of the
12 results is misleading.

13 I'd like to share with you a compelling
14 example of the misinterpretation of subgroup
15 results from another aspect of preterm birth
16 research, and that is the prevention of respiratory
17 distress syndrome or RDS.

18 Mark Klebanoff, the NIH co-author of a 2003
19 New England Journal article on progesterone
20 prevention of preterm birth published a good review
21 of subgroup analysis in the American Journal of
22 Obstetrics and Gynecology in 2007. His review

1 concluded that most subgroup differences prove to
2 be spurious. Dr. Klebanoff cited as an example the
3 long delay in the wide acceptance of antenatal
4 steroids to prevent RDS.

5 This example of the misinterpretation of
6 subgroups comes from the 1981 publication of the
7 collaborative group on antenatal steroid therapy at
8 NIH. In their results, the overall treatment
9 effect was statistically significant for a
10 reduction in respiratory distress syndrome in
11 infants at a level of p equal to .05.

12 However, when the subgroup results were
13 examined, the analysis for the comparison of RDS
14 between the treatment groups controlling for gender
15 of the fetus showed a significant difference in
16 favor of the female fetus subgroup. In addition,
17 the analysis for the comparison of RDS between
18 treatment groups controlling for race showed a
19 significant difference in favor of African-American
20 mothers.

21 This subgroup analysis from 1981 suggesting
22 that only African-American women with a female

1 fetus could benefit from antenatal was incorrectly
2 interpreted, and it took 13 years to undo this
3 misinterpretation of these subgroups. It's now
4 accepted that antenatal steroids are a clear
5 benefit for all pregnancies at risk of imminent
6 preterm delivery.

7 Mark Klebanoff says that even when subgroups
8 are correctly defined and the test for interaction
9 of the subgroups is significant, most subgroup
10 differences prove to be spurious. I believe that
11 counsel is important for consideration today
12 because the delay in wide acceptance of antenatal
13 steroids due to subgroup misinterpretation turned
14 out to be costly.

15 From a statistical standpoint, the factors
16 to be considered when interpreting subgroups is the
17 overall pattern of results. The subgroup effects
18 are usually in the same direction as the overall
19 result of the study, and their individual
20 interpretation can be hazardous, as Klebanoff and
21 the RDS debacle emphasize.

22 When it comes to individual subgroup

1 results, reliability is low, and they should not
2 lead to conclusions. High false positive rates due
3 to multiple subgroup comparisons are dangerous. In
4 addition, high false negative rates are likely
5 because the small sample sizes of subgroups don't
6 provide adequate power for comparisons. Taken
7 together then, subgroup analysis presents the worst
8 of both worlds in terms of statistical error.

9 Another article addressing this issue was a
10 seminal one in JAMA 20 years ago, and that paper,
11 Yusuf and colleagues concluded that the overall
12 average result of a randomized clinical trial is
13 almost always a more reliable estimate of the true
14 treatment effect in subgroups than are the results
15 from the individual subgroups themselves.

16 I believe this is true today and in this
17 situation, and thank you for your attention, ladies
18 and gentlemen. I'll turn the podium back to
19 Dr. Creasy.

20 **Sponsor Presentation - George Creasy**

21 DR. CREASY: Thank you, Dr. Darney.

22 In the evaluation of an NDA with a single

1 key trial, the guidance allows for independent
2 substantiation from other trials attesting to the
3 safety and effectiveness of the drug in the
4 proposed indication. Independent substantiation
5 attesting to the safety and efficacy of
6 progesterone in the proposed indication is found in
7 the randomized placebo-controlled double-blind
8 trial of Fonseca and Nicolaides published in the
9 New England Journal of Medicine in 2007. Recall
10 that this trial, along with the findings of
11 Study 300, led us to design and conduct Study 302,
12 the key study in this NDA.

13 In their trial, Fonseca, et al., randomized
14 250 pregnant women, 125 of them to a vaginal oil
15 capsule with 200 milligrams of progesterone and 125
16 to a matching placebo. The subjects began
17 treatment at about 24 weeks gestation and ended
18 treatment at the end of week 34.

19 The results of their trial showed a
20 44 percent reduction in preterm birth less than 34
21 weeks gestation. The 95 percent confidence
22 interval over the relative risk does not cross

1 unity. Also, as you can see from the Kaplan-Meier
2 plot, vaginal progesterone is associated with a
3 delay in delivery relative to placebo between study
4 start and 34 weeks gestation. The results of the
5 Fonseca trial and the results of Study 302 are very
6 similar, both having a 44 percent reduction in
7 preterm birth at the 33- to 34-week interval.

8 A review of the world literature has been
9 conducted for randomized clinical trials of vaginal
10 progesterone and placebo where baseline cervical
11 length and pregnancy outcome were both known. The
12 criteria for this literature search included
13 studies with both singleton and twin pregnancies.
14 Dr. Romero and the collaborators of the identified
15 trials pooled their individual patient data for
16 analysis.

17 It is worth noting that the effect of
18 vaginal progesterone in women with a short cervix
19 across three different formulations shows a
20 42 percent reduction in preterm birth less than
21 33 weeks.

22 Now let me summarize the evidence presented

1 today for the efficacy of vaginal progesterone
2 gel 8%. Study 300 provided the hypothesis to be
3 tested in Study 302. As presented by Dr. Hassan,
4 Study 302 confirmed the findings in Study 300, that
5 women with a short cervical length in the
6 mid-trimester will respond to vaginal progesterone
7 gel 8% with a delay in delivery.

8 Study 302 demonstrated a statistically and
9 clinically significant 44 percent reduction in the
10 risk of preterm birth less than 33 weeks gestation
11 with the prespecified CMH test and confirmation by
12 multiple sensitivity analyses, including a
13 stratified analysis by U.S. and non-U.S. region as
14 well as evidence of improvement in infant outcomes.
15 The analysis of births less than 33 weeks gestation
16 by the FDA actually produced a similar result.

17 Finally, there is support from the
18 literature with the randomized control trials of
19 Fonseca published in 2007 as well as the individual
20 patient meta-analysis of Romero, et al. published
21 in 2011. Vaginal progesterone gel 8% effectively
22 reduces preterm birth in women with a short cervix.

1 I will continue now with the review of the
2 safety data for progesterone gel 8%.

3 In the review of the safety data for
4 progesterone gel 8%, I will first discuss the
5 pharmacokinetics and the overall extent of
6 exposure, then the maternal adverse events from the
7 clinical trial program. Following this, I will
8 review the neonatal and infant outcomes, including
9 the two-year infant safety follow-up. Finally, I
10 will move to the in-market safety experience from
11 spontaneous reporting.

12 Progesterone is sometimes referred to as the
13 pregnancy hormone. The reason for this is that
14 progesterone levels are higher during pregnancy
15 than at any other time. On this slide, the graph
16 shows the rise in maternal plasma progesterone
17 levels as pregnancy advances.

18 In order to evaluate the contribution of
19 progesterone to the maternal level from the gel
20 formulation, we conducted a study in 19 subjects.
21 Each subject was dosed daily beginning about
22 20 weeks gestation. At 28 weeks, we measured the

1 pre-dose and post-dose levels of progesterone. The
2 data on this slide includes the average number of
3 days of consecutive dosing, the average
4 progesterone level pre-dose, and the average
5 progesterone level post-dose. Minimum, median and
6 maximum values are also included.

7 There are two points to be made from this
8 slide. First, in the last column, the overall
9 change in progesterone serum level from pre-dose to
10 post-dose is about 16 nanograms per mL. This value
11 is reasonably consistent with a Cmax of
12 15 nanograms per mL in women without endogenous
13 progesterone dosed daily with the 8 percent vaginal
14 gel. The second point is that all values are well
15 within the normal range for this time in pregnancy.

16 Let's move now to the safety data from the
17 clinical program. This slide shows the number of
18 patients in the combined safety dataset of
19 Study 300 and Study 302. Study 300 was the larger
20 study with 637 subjects available for a safety
21 assessment. Study 302 had 459 subjects available
22 for a safety assessment.

1 The combined safety dataset includes 556
2 subjects who took at least one dose of progesterone
3 gel 8%. These 556 subjects who took at least one
4 dose of progesterone gel had an average duration of
5 treatment of over 14 weeks of once daily vaginal
6 administration. That translates into over 98 doses
7 on average per subject.

8 Shown here is a summary of the maternal
9 treatment emergent adverse events, abbreviated on
10 this slide as TEAEs, for the combined safety data
11 in this program. Note that the frequency of
12 reported events is the same between the
13 progesterone gel group and the placebo group for
14 each of the categories summarized on this slide.
15 There were no maternal deaths in this program.

16 Taking a closer look at the serious adverse
17 events, again, the frequency of reported serious
18 events is the same between the progesterone group
19 and the placebo group for each of the categories of
20 serious events summarized on this slide. The
21 complete list of adverse events which occurred in
22 5 percent or more of subjects is in your briefing

1 book. Not unexpectedly, the most frequent adverse
2 events in this high-risk pregnancy population are
3 premature labor, premature baby and uterine
4 contractions preterm. Most events occurred at
5 comparable frequencies between placebo and
6 progesterone.

7 On this slide, we have reduced the list of
8 all adverse events greater than or equal to
9 5 percent to just those events where the frequency
10 was greater for progesterone than for placebo. As
11 you can see, the difference is only between 1 and
12 4 percent for each event. The event with the
13 greatest imbalance between progesterone and placebo
14 is urinary tract infection. It may be worth noting
15 that this range of 5 to 9 percent is within an
16 expected range for pregnancy.

17 Turning now to the combined safety data for
18 the infants, we can note that among all infants
19 exposed to progesterone gel, the frequency of the
20 usual morbidities of prematurity never exceeds
21 placebo. The only exceptions to this finding are
22 the one case of hydrocephaly in the program which

1 occurred in the progesterone gel group, and there
2 were two additional cases of congenital
3 abnormalities at birth in the progesterone gel
4 group for a marginal increase in the percent of
5 congenital abnormalities diagnosed at birth.

6 An important design element of Study 300 was
7 the planned two-year safety follow-up of the
8 infants. The intervals of the safety follow-up
9 over the two years were six, 12 and 24 months. And
10 the parameters evaluated during each follow-up
11 visit included growth parameters, newly diagnosed
12 chronic morbid conditions, and newly diagnosed
13 congenital anomalies, as well as a screening for
14 overall mental and motor development with the
15 Denver II assessment tool.

16 The Denver II assessment tool was accepted
17 by the FDA as a method to screen for potential
18 safety concerns related to differential rates of
19 neurodevelopmental impairment. It should be noted
20 that the number of infants in the safety follow-up
21 program exceeded the minimum requested by the FDA
22 at the time.

1 There were no differences in length, weight
2 or head circumference between placebo and
3 progesterone exposed infants at the six, 12 and 24
4 month intervals. When we look at the data for
5 congenital abnormalities, chronic morbid conditions
6 and suspect Denver II growth in development
7 observed during the two-year safety follow-up,
8 again, we find a comparable frequency of occurrence
9 between progesterone gel exposed infants and
10 placebo infants.

11 There is now over 14 years of experience
12 with the use of progesterone gel 8% in the first
13 trimester of pregnancy with over 60 million doses
14 distributed during that time worldwide. As a
15 reminder, the progesterone in this formulation is a
16 natural form of progesterone that is bio identical
17 to that produced naturally by the placenta.

18 In the current use in the first trimester,
19 the administration is up to twice daily whereas the
20 proposed use in the second and third trimesters
21 where the endogenous progesterone levels are much
22 higher, the administration is just once daily.

1 Over 24 million doses have been prescribed
2 in the U.S. over the past 14 years, and in the two
3 years ending June 2011, 3.7 million doses have been
4 distributed in the U.S. with just 85 spontaneous
5 adverse events reported.

6 In summary, the recent clinical program with
7 progesterone gel 8% appears safe and well tolerated
8 when used once daily in the second and third
9 trimesters. Serum progesterone levels were in the
10 normal range for pregnancy. There was no signal
11 for fetal harm, and there was comparable infant
12 growth and neurodevelopment between the
13 progesterone group and the placebo group over the
14 two-year safety follow-up.

15 Finally, progesterone gel 8% has been a
16 well-tolerated treatment when used up to twice
17 daily in early pregnancy for more than 14 years,
18 and no safety signals have emerged from
19 post-marketing surveillance during that time.

20 Moving now to the risk and benefit, I would
21 like to introduce Professor Stuart Campbell.
22 Professor Campbell is a leader in the field of

1 ultrasound in obstetrics and gynecology. He
2 pioneered fetal biometry and the early diagnosis of
3 fetal abnormalities. Professor Campbell was
4 elected honorary fellow of both the American
5 College of Obstetricians and Gynecologists and the
6 American Institute of Ultrasound in Medicine. He
7 has actively participated in the challenges and in
8 the improvements ultrasound has made to the
9 practice of obstetrics.

10 Professor Campbell.

11 **Sponsor Presentation - Stuart Campbell**

12 DR. CAMPBELL: Madam Chairman, ladies and
13 gentlemen, I am a consultant with Columbia
14 Laboratories for today's meeting. I've not
15 accepted payment for my time, and my travel
16 expenses have been covered by the company.

17 About one year ago, I wrote an editorial
18 supporting the concept of universal cervical length
19 screening and vaginal progesterone treatment for
20 women with a cervical length between 10 and
21 20 millimeters in mid-gestation. On the basis of
22 the two largest multinational studies directed from

1 the Fetal Medicine Foundation in London and the NIH
2 in Wayne State University, Detroit, which we have
3 reviewed for you, I believe that the evidence was
4 so compelling that this therapeutic strategy would
5 save newborn lives and reduce the burden of infant
6 handicap that I stated, "Doing nothing is no longer
7 an option." Today my belief is even stronger, and
8 I wish to explain my reasons.

9 Today I'll be discussing the benefit-risk
10 ratio. This task should be theoretically easy as
11 the denominator, that is, the risk, by general
12 consensus for natural, micronized progesterone
13 administered vaginally appears to be vanishingly
14 small. However, I will begin with the numerator,
15 the benefit.

16 You've heard convincing evidence from the
17 presentation of Study 302 that vaginally,
18 progesterone has a significant effect in prolonging
19 gestation. I'd like to provide independent
20 substantiation of the results from the Study 302 by
21 presenting results of an individual patients'
22 meta-analysis. To do this, I will focus on the

1 five study individual patient data -- I will call
2 it IPD -- meta-analysis from Romero, et al., which
3 has been published online in the American Journal
4 of Obstetrics and Gynecology.

5 The advantages of an IPD meta-analysis are
6 outlined in this slide. It provides a systematic
7 review of the original data of each patient and is
8 the gold standard to summarize evidence across
9 clinical studies. It has considerable advantages
10 over conventional meta-analysis. Of particular
11 relevance to this meeting, it permits subgroup
12 analysis.

13 This study has leading figures from all
14 around the world as co-authors, but I should point
15 out that the bulk of the data comes from the two
16 leading fetal medicine centers in the world,
17 namely, the NIH center in Wayne State University in
18 Detroit led by Roberto Romero and the Fetal
19 Medicine Foundation at King's College Hospital in
20 London led by Kypros Nicolaides. The provenance of
21 this research is therefore impeccable.

22 The objective of this IPD meta-analysis is

1 stated in this slide. The objectives are highly
2 relevant to this meeting. There were five
3 randomized studies considered with 775 women
4 studied, 723 with singletons and 52 with twin
5 gestations. Eight hundred and twenty-seven future
6 infants were considered, 723 from singleton
7 gestations and 104 from twins.

8 The conclusions from the primary outcome
9 were that there was a significant 42 percent
10 reduction in the incidence of preterm birth before
11 33 weeks in the vaginal progesterone group.

12 Secondary outcomes showed reduced rate of preterm
13 birth before 28, 30, 32, 34 and 35 weeks gestation
14 of around 40 percent, and all these findings were
15 statistically significant.

16 Vaginal progesterone reduced the rate of
17 five neonatal outcomes: admissions to neonatal
18 intensive care unit, respiratory distress syndrome,
19 mechanical ventilation, composite neonatal
20 morbidity and mortality, birth weight less than
21 1500 grams. This shows that the combined relative
22 risk significantly favored progesterone. The only

1 study where the relative risk was greater than 1
2 was the study of Rode, which was carried out
3 exclusively on twin gestations.

4 As this application is concerned with
5 singleton pregnancies, we have performed a
6 prespecified analysis on singletons only. In
7 addition to the significant reduction of preterm
8 births at less than 33 weeks, there was a
9 significant reduction in preterm births before
10 35 weeks and before 28 weeks, and significant
11 reduction in the incidence of respiratory distress
12 syndrome.

13 To determine if there's confirmation of the
14 effectiveness of vaginal progesterone in the
15 reduction of preterm birth independent of
16 Trial 302, we have removed the Hassan study, and we
17 have already removed the Rode study in what is now
18 a three-study meta-analysis.

19 With the Hassan study removed, the primary
20 outcome of preterm birth before 33 weeks remains
21 significant as is preterm birth before 34 weeks.
22 Neonatal outcomes showed a major shift towards

1 improvement with admission rates to a neonatal
2 intensive care unit significantly reduced.

3 In summary, the efficacy of vaginal
4 progesterone gel has been independently confirmed
5 by this meta-analysis. I'm aware there is concern
6 in this meeting that subgroup analysis suggests
7 that there may be risk differences in the U.S. and
8 non-U.S. patients in Study 302. Dr. Creasy and
9 Dr. Darney have discussed the inadvisability of
10 subgroup analysis in this context. I would like to
11 address it from another perspective.

12 It is the release of pro-inflammatory
13 cytokines in the cervix and increase in the
14 reduction of matrix metalloproteinases which cause
15 degradation of extracellular matrix with softening,
16 effacement, and shortening of the cervix.
17 Progesterone modulates antibody production by
18 suppressing production of pro-inflammatory
19 cytokines.

20 It is inconceivable that the local effect of
21 vaginal progesterone in reducing cytokine
22 inflammation is likely to be different in women in

1 the United States. Do we really believe that
2 progesterone reduces preterm birth outside the U.S.
3 but not within the U.S.? To me, this is illogical
4 as there is no physiological basis to support such
5 a difference. Indeed, much of the original
6 research in this area has been pioneered in the
7 United States of America.

8 I would now like to look at the benefit-risk
9 ratio again and briefly discuss the denominator.
10 Progesterone gel 8% taken intravaginally daily has
11 been approved by the FDA for luteal support and ART
12 programs for 14 years and no significant adverse
13 signals have been reported. So the safety of
14 progesterone gel in the first trimester is well
15 established.

16 Studies in the second and third trimesters
17 show that progesterone vaginal gel does not cause a
18 significant increase in circulating progesterone
19 levels as its action is principally to increase
20 local levels of progesterone which reduce cytokine
21 inflammation in the cervix and choriodecidual
22 junction.

1 Vaginal progesterone is well tolerated by
2 mothers, and no signals of fetal harm have been
3 detected. Follow-up studies to 18 to 24 months of
4 age both in the U.S.A. and Europe revealed no
5 safety concerns. So we are on the fortunate
6 circumstance of having a treatment with minimal
7 risk.

8 Let us now reexamine the numerator, i.e.,
9 the potential benefit aspect of the risk-benefit
10 ratio.

11 In the key study, 302, there was a
12 significant reduction of preterm birth before
13 33 weeks in the study arm of 44 percent. Similar
14 reductions were also seen at gestations before
15 28 weeks and before 35 weeks gestation, and there
16 were noted improvements in infant outcomes.

17 The five-study IPD meta-analysis
18 demonstrated significant reduction in preterm
19 births at all gestations from 28 weeks through to
20 35 weeks and significant reductions in five
21 neonatal outcomes. So clearly, the benefits of
22 treatment with vaginal progesterone far outweigh

1 any risks.

2 In view of Study 302 and the IPD
3 meta-analysis, which I've described, I believe it
4 is probably unethical to conduct another randomized
5 study with the associated delay in implementing
6 therapy that can reduce mortality and handicap in
7 newborns. If progesterone gel 8% is not approved,
8 the only FDA approved product for prevention of
9 preterm birth in women would require pregnant women
10 to visit their healthcare provider for weekly
11 injections of a synthetic progestogen with its
12 associated higher systemic levels of progesterone
13 and as yet unproven in women with a short cervix,
14 which is the highest risk factor for preterm birth.

15 I want to quote from my editorial of 2011.

16 "Over the past 40 years, improvements in
17 neonatal care by pediatricians have contributed
18 greatly to the reduction in neonatal morbidity and
19 mortality, especially for low birth weight
20 newborns. Prenatal ultrasound has also made major
21 contributions to the reduction of infant
22 disability, not only through the detection of fetal

1 abnormalities and selective termination of
2 pregnancy but also through improved prediction and
3 monitoring of uterine growth restriction.

4 "Yet the elephant in the room has always
5 been spontaneous preterm birth for this is by far
6 the biggest cause of neonatal death, morbidity and
7 long-term, and irreversible damage to the child.
8 It is time to move the elephant by implementing
9 universal risk assessment for preterm birth with
10 cervical ultrasound and approving progesterone
11 gel 8% for the treatment of this high-risk
12 population.

13 "Despite the efforts of obstetricians, the
14 incidence of preterm birth has not changed in the
15 United States in over 20 years. This is not
16 peculiar to the United States. The graph of the
17 United Kingdom and other European countries is the
18 same. With this program, I believe we have a
19 unique opportunity to cause a significant reduction
20 of early preterm births in the United States and
21 throughout the world.

22 "Universal cervical length screening and

1 vaginal progesterone prevents early preterm births,
2 reduces neonatal morbidity, and is cost saving. I
3 believe doing nothing is no longer an option."

4 Thank you.

5 **Sponsor Presentation - George Creasy**

6 DR. CREASY: Thank you, Dr. Campbell.

7 Having completed our presentations, I would
8 like to return to the key agreement slide from the
9 introduction. We have shown a robust reduction in
10 preterm birth. There is no suggestion of an
11 increase in intrauterine fetal death or neonatal
12 morbidity. There was adequate postnatal follow-up
13 of the infants, and there is strong supportive data
14 attesting to the safety and effectiveness of
15 vaginal progesterone gel 8% for the proposed
16 indication.

17 Reduction of risk of preterm birth in women
18 with a singleton gestation and a short uterine
19 cervical length in the mid-trimester of pregnancy,
20 the key clinical study enrolled women with uterine
21 cervical length of 10 to 20 millimeters, is the
22 proposed indication before you today.

1 Joining me in answering questions today are
2 the experts shown here: Meena Khandelwal,
3 associate professor of obstetrics and gynecology
4 and maternal fetal medicine from Cooper Hospital;
5 Dr. P.Y. Liu, a statistician; Dr. Jim Phillips,
6 biostatistician; Dr. Larry Platt, professor of
7 OB/GYN at UCLA; Dr. Kathy Reape, vice president of
8 medical affairs at Watson; Dr. Jean Steichen,
9 professor of neonatology at the University of
10 Cincinnati; and Dr. Elena Yanushpolsky, director of
11 reproductive surgery and Brigham and Women's
12 Hospital.

13 That concludes the sponsor presentation.

14 **Clarifying Questions to the Sponsor**

15 DR. JOHNSON: I would like to thank the
16 sponsors for the information that's been provided.

17 Now we have a half an hour to allow the
18 committee to ask clarifying questions to our
19 sponsor. If you would please raise your hand as
20 you have questions that you would like to address
21 to the sponsor.

22 Dr. Sicalli.

1 DR. SICALLI: In 302, were the subjects who
2 were enrolled women who were screened routinely or
3 symptomatic women or some mixture?

4 DR. CREASY: By the inclusion and exclusion
5 criteria, the women in 302 were not to be
6 symptomatic. They were being screened for cervical
7 length as a routine part of mid-trimester
8 screening.

9 DR. SICALLI: All right. The way I read the
10 exclusion criteria, they were not in preterm labor.
11 I didn't read that they were not symptomatic, but
12 it might have been my misreading of the --

13 DR. CREASY: Well, they were definitely not
14 to have any symptoms. I don't remember the
15 specific exclusion criteria. But women who had
16 contractions or bleeding and so forth were not to
17 be considered for the trial.

18 DR. SICALLI: What about pelvic pressure?

19 DR. CREASY: Well, we probably didn't
20 address that directly. I don't think we addressed
21 that one directly in the inclusion and exclusion
22 criteria, pelvic pressure.

1 DR. SICALLI: Thank you.

2 DR. JOHNSON: Ms. Aronson.

3 MS. ARONSON: I have two questions, the
4 first relates to exclusion and compliance. Were
5 smoking and high caffeine intake excluded or
6 tracked at all? And as far as compliance, I
7 noticed this morning slide 22 mentioned at least
8 one dose. So the 20 percent compliance
9 means -- was smoking or high caffeine intake
10 included in that, or just can you explain
11 noncompliance?

12 DR. CREASY: Sure. I think the first
13 question I heard had to do with whether or not we
14 collected data about caffeine and smoking. And we
15 did not collect data on that, and it wasn't part of
16 the inclusion or exclusion criteria. So
17 presumably, the randomization would have put
18 patients equally with smoking and caffeine
19 consumption in both the placebo and the
20 progesterone groups.

21 With regard to compliance, I'm not sure I
22 understand the question about compliance.

1 MS. ARONSON: What made up the 20 percent of
2 noncompliance?

3 DR. CREASY: Oh, I see. So in some of our
4 assessments, we used a cutoff of 80 percent
5 compliance, and so if subjects were less than
6 80 percent compliant, they were considered to have
7 been noncompliant, although there was a range of
8 noncompliance, or a range of compliance, I guess I
9 should say.

10 Compliance was assessed by the return of
11 applicators. So if an applicator was returned
12 unused, then we knew it wasn't used, and we
13 calculated that as a noncompliant dosing.

14 MS. ARONSON: And so it didn't make any
15 difference whether it was the one dosing or the
16 multiple dosing?

17 DR. CREASY: I'm not sure I understand.

18 MS. ARONSON: As far as compliance. In
19 other words, what was prescribed?

20 DR. CREASY: Well, the compliance was
21 calculated -- so if a woman returned two
22 applicators for a week, then she would have been

1 considered to have used five applicators and two
2 were returned. So her compliance for that week
3 would have been five out of seven and so on for
4 patients who returned one, two, three or four
5 applicators.

6 Does that answer your question?

7 MS. ARONSON: Thank you.

8 My second question, I noticed on page 66 of
9 the briefing document that they were two cases of
10 hypospadias, and there's been a link to a higher
11 rate of hypospadias to women using progesterone in
12 ART cycles.

13 Do you have any available information about
14 the baseline characteristics of these two subjects
15 and how much dosing they took?

16 DR. CREASY: How much dosing the two
17 patients with the two cases of hypospadias took?

18 MS. ARONSON: Also, the baseline
19 characteristics.

20 DR. CREASY: I don't know if I have those
21 two cases at my immediate disposal, so I can't
22 answer your question immediately about that.

1 MS. ARONSON: Thank you.

2 DR. JOHNSON: Dr. Montgomery Rice.

3 DR. MONTGOMERY RICE: Good morning. I have
4 two questions, but I can just do one if you only
5 want me to.

6 I would like to know who performed the
7 ultrasounds, and how did you certify the competency
8 of the individuals performing the ultrasounds, and
9 what was your intravariability between sites and at
10 individual sites.

11 DR. CREASY: Okay. So I have three
12 questions: Who performed the ultrasounds, what was
13 their level of expertise or certification --

14 DR. MONTGOMERY RICE: How did you confirm
15 the competency of those individuals?

16 DR. CREASY: Okay, and then some question
17 about the variability.

18 The ultrasounds were performed either by
19 technicians or physicians who were already
20 experienced in ultrasound technique. In this
21 trial, we had a quality program that had two stages
22 in it.

1 Slide up, please. The first stage was a
2 pre-randomization. Sonographers or physicians who
3 were to participate in that aspect of the trial,
4 that is, measuring the cervical length by
5 transvaginal ultrasound, were to submit images to
6 our expert reviewer for assessment of the presence
7 of landmarks and so forth to qualify or certify
8 individuals as readers or scanners for the trial.

9 Then after folks were certified into the
10 trial, whether they were technicians or physicians,
11 all of the images of the randomized patients were
12 reviewed for quality, but there was no central
13 assessment or whether or not the measurement was
14 correct. The measurement always was taken by
15 whatever the physician at the site determined the
16 measurement to be, and the quality assurance
17 physician then just helped us make sure that the
18 image capture systems were producing images that
19 had good landmarks and could be assumed to have
20 been the correct measurement.

21 DR. MONTGOMERY RICE: So that was limited,
22 though, to each site. So there was no third party

1 who looked at the variability from different sites,
2 so that individual PI or whomever certified it at
3 that site?

4 DR. CREASY: Our expert sonographer
5 certified patients into the trial but did
6 not -- was not a funnel in the randomization of
7 patients, were not part of the assessment --

8 DR. MONTGOMERY RICE: Let me make sure I
9 clarify my question.

10 DR. CREASY: Okay.

11 DR. MONTGOMERY RICE: So at each site,
12 someone was deemed as the person who confirmed the
13 clarity. And does clarity mean I can see a clear
14 picture, or does clarity mean that 18 means 18?
15 What does clarity mean?

16 DR. CREASY: I'm not sure I -- maybe I
17 misspoke. There were one or more either
18 technicians or physicians at each site who through
19 this stage 1 procedure were certified to
20 participate in the trial to do ultrasound
21 measurements. We had a website where materials
22 existed for the review of the procedure, the

1 technique and so forth. Then the images were
2 submitted to our expert reviewer just to confirm
3 that their procedures were producing images that
4 were of adequate quality. Then once certified,
5 they could begin randomizing patients into the
6 trial.

7 Since the measurement of cervical length
8 wasn't the endpoint of the trial -- the endpoint of
9 the trial was when did that patient deliver -- we
10 did not use a centralized reader for the inclusion
11 of the patient.

12 DR. MONTGOMERY RICE: The measurement,
13 though, was part of the inclusion, was that not?
14 Did I misunderstand you?

15 DR. CREASY: No, the measurement was part of
16 the inclusion criteria. That's correct.

17 DR. MONTGOMERY RICE: So my question to you
18 is, at an individual site, someone confirmed that
19 this person met this measurement so they could be
20 included.

21 DR. CREASY: Correct.

22 DR. MONTGOMERY RICE: And what I'm asking

1 you is that the confirmation that that was accurate
2 over and over and over again was by that individual
3 who was deemed competent at that site?

4 DR. CREASY: Correct.

5 DR. MONTGOMERY RICE: And then my second
6 question is, was there any external review that
7 looked at that confirmation across sites, that
8 randomly I'm going to pull five at this site, I'm
9 going to pull five at this site --

10 DR. CREASY: No.

11 DR. MONTGOMERY RICE: -- and I'm going to
12 compare some variability or anything? That's all
13 I'm asking.

14 DR. CREASY: I understand. No, we didn't do
15 that aspect across sites the way you're describing
16 it. We did not do that.

17 DR. MONTGOMERY RICE: I think the doctor
18 who's the lead PI is dying to say something.

19 [Laughter.]

20 DR. HASSAN: I just wanted to clarify that I
21 think the answer that you wanted was, is at the
22 individual sites, the investigator was responsible

1 for that measurement. So when that is submitted
2 for randomization, they took responsibility for
3 that measurement.

4 DR. MONTGOMERY RICE: That's right. And
5 then I just wanted to confirm that there was not
6 some third party that looked at it and confirmed it
7 based on the pictures that were sent in across
8 different sites.

9 DR. HASSAN: The third party did receive the
10 images after randomization, looking again for the
11 quality of the image obtained. They did not
12 reexamine at length because that was deemed the
13 responsibility of the investigator.

14 DR. MONTGOMERY RICE: Okay. And I'll wait
15 till I come back around for my next question.

16 DR. CREASY: It may be helpful -- I mean,
17 part of the reason we didn't do this variability is
18 I think the variability has been described in the
19 literature already, and if I could ask Dr. Platt to
20 come and comment on that. This is the reason we
21 didn't take this step is because it's pretty well
22 known already.

1 DR. PLATT: I'm Dr. Lawrence Platt,
2 professor of OB/GYN, UCLA, David Geffen School of
3 Medicine at UCLA. I am here today as a consultant
4 to Watson and Columbia. I am unpaid for my time.
5 They did pay my travel, and I have no financial
6 benefit of the outcome of this meeting.

7 Could I just have that previous slide? This
8 one up, please.

9 It is well recognized that the
10 intra-observer variability of transcervical
11 ultrasound is less than 10 percent. It is perhaps
12 one of the easiest measurements to make that we
13 teach our residents, that we teach clinicians, and
14 that when we do quality review.

15 I think, as pointed out, there was an expert
16 consultant who certified, trained, and did quality
17 assurance, as we do, for example, in nuchal
18 translucency today, where we look so
19 much -- epidemiologically monitor the images. So
20 he did look at images through the course of this
21 study but not on an ongoing basis where you had a
22 central reader read every single one; so that there

1 was definitely an oversight of quality assurance in
2 this study.

3 DR. ORZA: Can I ask just really quickly
4 right on this point what is the standard error of
5 cervical length measurements, if that's acceptable?

6 DR. PLATT: Slide up again, please. Again,
7 less 10 percent variability, and a standard error
8 will be less than that in the majority of cases. I
9 think today with the increased frequency of the
10 transducers that are available compared to even
11 studies a decade ago that are far superior. And
12 when we talk about the range of 10 to 20, I would
13 submit to you that I believe that there will be no
14 measurement greater almost than 21 millimeters that
15 would have been, quote, read as 20.

16 DR. ORZA: I meant in millimeters, what's
17 the standard error.

18 DR. PLATT: Oh, it's going to be less than a
19 millimeter.

20 DR. JOHNSON: Dr. Greene.

21 DR. GREENE: I had a question about in the
22 sponsor's document that they provided, page 33 and

1 37 speaks to the sample size calculations. And I
2 noticed that the efficacy of the treatment was
3 anticipated to be 50 or 55 percent in the two
4 trials respectively.

5 Can you just explain where those numbers
6 came from?

7 DR. CREASY: Sure. Dr. Phillips?

8 DR. PHILLIPS: My name is Jim Phillips. I'm
9 a biostatistical consultant for Columbia
10 Laboratories, and I'm a paid consultant. I do not
11 have any financial interest in the outcome of this
12 meeting.

13 As you will recall from the presentation,
14 the study was planned with a power of 93 percent
15 based on a 22 percent placebo response rate and a
16 55 percent reduction. The establishment of the
17 22 percent placebo response rate was based on
18 previous data from the literature as well as data
19 that we had collected from the Study 300. And we
20 anticipated this to be a conservative estimate.

21 The 55 percent reduction was more of a
22 clinical decision to find a meaningful reduction,

1 figuring over half of a reduction in that response
2 rate would be meaningful clinically. So that
3 mainly was the premise.

4 Also, because of the sample size being
5 reasonable in the beginning, the 93 percent power
6 was consistent with giving us a clinically
7 meaningful difference with a reasonable sample size
8 and a large power.

9 DR. GREENE: Can I just follow up on that
10 question? So the reason I ask in part is that
11 seems rather optimistic given the prior studies.
12 Certainly, the big Mease NICHD trial didn't show
13 that degree of effect size, nor did the de Fonseca
14 vaginal progesterone. So I was just -- it seemed
15 rather optimistic, and I was wondering if there was
16 some other reason for it.

17 DR. CREASY: I can comment further that at
18 the time that we started the trial, we had data
19 from Fonseca's short cervix trial and data from our
20 subgroup analysis in 300. We looked at -- since we
21 were planning a 1 to 2 centimeter trial, we looked
22 at the 1 to 1 and a half centimeter data in the

1 Fonseca trial. The reduction in that subgroup
2 actually was about 75 percent, and in our subgroup
3 analysis -- well, we found 100 percent reduction,
4 which we were never going to power it at 100
5 percent.

6 So we had 100, we had 75, and so we were
7 bringing it down towards 44. We thought that
8 probably, possibly could even do a little better
9 than what was found with the women with the history
10 of preterm birth. So it was a little more
11 optimistic, but it was still well below the other
12 data that was available to us to examine and try
13 and determine what that effect size might be.

14 DR. JOHNSON: Dr. Orza, did you have another
15 question?

16 DR. ORZA: I did. I've just got another one
17 related to this.

18 I thought I read in the FDA document that
19 FDA had asked for a significance level of .01 since
20 it was to be the only study, and so I was wondering
21 why it was powered for .05. That was the question
22 that just popped up now, but I had a different one.

1 Can I -- I'll make it that one.

2 DR. JOHNSON: Because we're limited -- that
3 one, that it is.

4 DR. CREASY: So the question is why it was
5 powered at .05, or I'm not -- yes?

6 DR. ORZA: Yes, when I thought the FDA had
7 asked for .01.

8 DR. CREASY: Sure. Well, we had just
9 completed our 300 study, and we had some evidence
10 from our subgroup analysis in the 300 study that
11 vaginal progesterone was working in the short
12 cervix patients. And we at the time felt that that
13 was a bit of a supportive trial for us as we were
14 moving forward in the program.

15 So that's part of the answer, but let me ask
16 Dr. Phillips to bring in the rest of it.

17 DR. PHILLIPS: Well, as previously stated,
18 we did power the study at the .05 level with
19 93 percent power, with the assumptions previously
20 stated. In fact, those same assumptions also
21 provide 80 percent power.

22 Slide up, please. So here is the initial

1 assumptions in the top of this slide and the power
2 calculations in the middle of this slide. And by
3 the way, these were based on Fisher's exact test.
4 And in the bottom of the slide, it shows you with
5 these same assumptions, we actually had 80 percent
6 power at the 1 percent level of statistical
7 significance a priori.

8 DR. JOHNSON: Dr. Gillen.

9 DR. GILLEN: I wonder if we can bring up
10 slide CR-16. So this is the meta-analysis that
11 excludes the 302 subjects as well as the twin
12 study, and so I just wanted a little bit of
13 clarification.

14 So in thinking about this as a
15 meta-analysis, we have 125 of the total 146
16 subjects that are coming from the Fonseca study, so
17 approximately 85 percent there. And I just wanted
18 clarification. The Fonseca study did not include
19 subjects from the United States; is that correct?

20 DR. CREASY: That's correct.

21 DR. GILLEN: So that's one. Second question
22 is just more of a clarification question on the

1 potential discrepancy in the distribution between
2 cervical length by region. I know that the means
3 have been reported to be the same, but I'm a little
4 worried about the tells of the distribution.

5 Do we have any comparison in the 302 study
6 of cervical length among patients by, say, quintile
7 breakdown across regions?

8 DR. CREASY: For the 302 study?

9 DR. GILLEN: Correct, for the 302 study.

10 DR. CREASY: I don't think I have that
11 readily available, that is, a quintile breakdown.
12 The median was around 1.7, but I don't think we did
13 a further breakdown than the median.

14 DR. GILLEN: Is there a way that we can
15 obtain that?

16 DR. CREASY: Yes, we can get that. And you
17 want it by -- just to clarify, you would like a
18 tertile or quartile breakdown by region?

19 DR. GILLEN: Correct.

20 DR. CREASY: And this would be U.S. versus
21 non-U.S.?

22 DR. GILLEN: That would be the primary one

1 that I'd be interested in, yes.

2 DR. CREASY: Okay. Very good.

3 DR. JOHNSON: Dr. Schwarz.

4 DR. SCHWARZ: Along the same lines, I was
5 thinking about things that were different between
6 the regions. Can you clarify where the four people
7 who were lost to follow-up were located?

8 DR. CREASY: I will have to look that up. I
9 don't know off the top of my head where those four
10 individuals were. I think they were spread across
11 centers. I'm quite certain they were -- there
12 weren't even two of them at the same center, but
13 I'll have to check. That's an easy to look up.

14 DR. JOHNSON: Dr. Emerson.

15 DR. EMERSON: I have several questions that
16 relate to subgroups. First, I'd like to commend
17 Dr. Darney for very nicely stating all the problems
18 with subgroups. But it would therefore be
19 interesting to have the comments on how we're
20 supposed to take the subgroup analysis from
21 Study 300 as being supportive in any way, and given
22 that you're finding a very negligible result

1 overall, and the quote from the Yusuf paper would
2 say that's really what we should be using instead
3 of the subgroup analysis -- but if we were to take
4 that subgroup analysis, wouldn't this also be
5 saying that the treatment is quite harmful in the
6 patients without the short cervix and shouldn't we
7 have a contraindication for that?

8 If the 1 percent difference in the overall
9 group and something like a 10 percent difference in
10 the subgroup -- although I never saw that number
11 actually presented; I'm just reading off the
12 Kaplan-Meier plot -- wouldn't that argue that in
13 the other group that it has to be quite harmful?

14 DR. CREASY: So the question is whether or
15 not the treatment is harmful with women with a
16 longer cervical length. Did I get that?

17 DR. EMERSON: Well, there are two parts.
18 One is, given that we spoke to the fact that
19 subgroups shouldn't be trusted at all, how is the
20 Study 300 at all to be viewed supportive? But if
21 we were to take it as being supportive, then what's
22 going on in the other group, the non-short cervix

1 group?

2 DR. CREASY: I understand. I'd like to
3 address the second question about any potential for
4 harm.

5 Slide up, please. These are not projecting
6 well -- but these are three survival curves coming
7 from the 300 study data. The curve at the top, the
8 reason it projects not so well is because the two
9 survival curves are one on top of the other. So in
10 the overall trial results of Study 300, there
11 wasn't an effect detected.

12 As we look at the first quartile of cervical
13 length, the lower left Kaplan-Meier curve, you can
14 see the curves are beginning to separate. The
15 remaining patients are shown in the Kaplan-Meier
16 curve beside it at the lower right, and those
17 curves are also on top of each other.

18 So when we pull out the short cervix
19 patients or in this case, the patients with a
20 cervical length in the first quartile, had a
21 cervical length of less than 3.2 centimeters, less
22 than 32 millimeters. So those who were less than

1 32 millimeters are on the left. Those with 32 or
2 more millimeters of cervical length are on the
3 right.

4 We have a separation in favor of
5 progesterone on the left in the lower quartile, and
6 really no impact of progesterone, no harmful
7 effect, if you will, I think can be detected from
8 the survival curve on the right. I hope this
9 answers your second question.

10 DR. EMERSON: It does partially, although I
11 would like to note that it's very difficult as we
12 keep changing the summary measures that we're using
13 for a particular distribution. And in this case,
14 we're changing also the subgroups that we're
15 looking at, that this has 172 subjects rather than
16 116 that are quoted in many other results.

17 DR. CREASY: That's true. The 116 then
18 becomes -- what we evaluated then was we saw that
19 the curves were beginning to separate at
20 32 millimeters, and that's not a generally
21 recognized short cervix, if you will, I think. So
22 we looked lower at 3 centimeters, 2.8. That was

1 more or less the limit of this data was
2 2.8 centimeters. But below 3.2, the separations
3 favor progesterone, and above 3.2, there really is
4 no effect, no evidence of a detrimental effect.

5 DR. EMERSON: So we're fishing through all
6 of these subgroups quite a bit?

7 DR. CREASY: In 302, we did look through at
8 the data to try to understand what was going on.

9 DR. EMERSON: So how should we judge this as
10 being supportive, given that you're dismissing any
11 other subgroup analyses?

12 DR. CREASY: I understand. We are trying to
13 position it as the hypothesis-generating study.

14 DR. EMERSON: Okay. So you're not regarding
15 that it's supportive of it. It's just the
16 hypothesis generation?

17 DR. CREASY: That's the way we're --

18 DR. EMERSON: So -- really combine --

19 DR. CREASY: That's hypothesis generating,
20 and we confirmed that hypothesis then with
21 Study 302.

22 DR. EMERSON: So there is another role of

1 subgroups here, and this plays a lot to the single
2 pivotal study. And that is to find some evidence
3 of mechanism of action, to be looking for dose
4 response or looking in the higher risk group or
5 being able to think through there.

6 Which of these subgroups provide support
7 there? So a priori, for instance, we might expect
8 that subjects who in some sense got higher dose,
9 either through the compliance or through length of
10 treatment, the earlier preventive strategy, did we
11 also not look at a presumed mechanism of action to
12 look at those subgroups that we felt were at higher
13 risk for what it was that we thought we were
14 treating?

15 Which of those subgroups do you think are
16 supportive in that sense, of looking more towards
17 the mechanism of action that we'd like to see in a
18 pivotal study?

19 DR. CREASY: Well, we did conduct, though we
20 didn't present -- shall I continue?

21 DR. JOHNSON: Yes, please.

22 DR. CREASY: We did conduct, although we

1 didn't present, what we called a modified-intent-
2 to-treat analysis, where we looked at the group of
3 the more compliant subjects, those who took at
4 least 80 percent of their drug. And there was
5 marginal increase in the efficacy in that group
6 compared to the group overall as we and everyone
7 might have expected.

8 So with regard to other sort of high-risk
9 factors, this is probably the most powerful
10 predictor of preterm birth. There weren't other
11 risk factors in the trial short of the 16 percent
12 of the patients that had a history of preterm
13 birth, other risk factors that would make patients
14 much more of a risk.

15 DR. EMERSON: So how would you have thought
16 that the earlier treatment would be -- that the
17 subgroup of women who you managed to get earlier in
18 their pregnancy and start administering the
19 treatment, and also what the clinical relevance is
20 of two women who might have the same degree of
21 cervical shortening but at different gestational
22 ages, what might we expect if the treatment works

1 as you'd anticipate it to work?

2 DR. CREASY: In terms of different -- I just
3 want to make sure I get the question straight.
4 Different cervical lengths at different gestational
5 ages and starting the treatment earlier or later,
6 it's -- I think it's difficult for us to tease that
7 out of our data, quite honestly. We enrolled over
8 a relatively narrow range, which was between 20 and
9 the end of the 23rd week, and we had also a very
10 narrow range of cervical length, 10 to
11 20 millimeters. So the variance in there wasn't
12 great, and the period over which we enrolled
13 gestational-age-wise was also not very great.

14 We had conducted -- I think we looked at
15 above and below the median for cervical length, and
16 the treatment effect appeared to be about the same
17 in those subgroups.

18 DR. EMERSON: I believe actually it showed
19 that the treatment effect was less in the women who
20 enrolled at a higher gestational age.

21 DR. CREASY: At a higher gestational
22 level -- we'll put --

1 DR. EMERSON: I'm sorry.

2 DR. JOHNSON: Dr. Emerson, if you would move
3 towards the mic.

4 DR. EMERSON: I'm sorry. I believe that
5 the -- you had actually a paradoxical effect. I
6 said it exactly wrong there, that I guess I,
7 a priori, if this treatment worked, would have
8 thought it would have done better the earlier you
9 had administered the treatment, and we did not see
10 that.

11 DR. CREASY: Well, I think that speaks to
12 the variability of subgroups. It wouldn't be -- I
13 mean it wouldn't seem to be plausible that someone
14 taking more drug would have less effect than
15 someone who took less drug, potentially. And so we
16 attributed that just to the variability of
17 subgroups.

18 DR. JOHNSON: Now, we are at our time for a
19 break. I would ask the committee's allowance to go
20 five more minutes. There are three more members
21 who have not yet had an opportunity to ask a
22 question.

1 Is that acceptable? Great.

2 Dr. Weinstein.

3 DR. WEINSTEIN: You said that most of the
4 centers were university centers or high-risk
5 perinatal centers. Having been at that my whole
6 career, the level of ultrasound is so different
7 than what occurs in the community.

8 How can you really be comfortable that the
9 community doctor who has a technician who
10 doesn't -- who's not trained to do this high level
11 of ultrasound can actually do your cervical
12 lengths? And what makes you think that if it's
13 20 millimeters -- or 21 millimeters, they say,
14 well, let's just go ahead and treat her since it's
15 only 1 millimeter difference, how comfortable are
16 you that the 10 to 20 will really be held when it
17 gets out into the community level?

18 DR. CREASY: First, I would like to say that
19 there wouldn't be any harm if there was a mistake
20 by a millimeter or 2 in the treatment. There
21 wouldn't be any harm. But I'd like to ask
22 Dr. Platt to address the question that you asked

1 about the community physicians.

2 DR. PLATT: Again, Larry Platt from UCLA.
3 The use of the transvaginal ultrasound is, number
4 one, easy to learn. We talked earlier about the
5 variability in the measurements, and there is no
6 evidence that we could prove today that the single
7 measurement of transvaginal ultrasound assessment
8 of length has significant variability between a
9 well-trained sonographer in the community versus a
10 trained sonographer at an academic ivory tower.

11 I would submit as the person in charge of
12 the quality assurance program -- co-person in
13 charge of the quality assurance program of the NIH
14 fetal growth study, which is basically academic
15 centers -- that there's variability amongst
16 academic centers as well. And I think the quality
17 assurance that was done in this study, the
18 oversight by, I believe it's Dr. George Bega, who
19 is well known in ultrasound, that there was no
20 significant difference between centers.

21 Furthermore, if you look across regions, in
22 the European part of the world, most of these are

1 physicians doing it who are well trained in
2 ultrasound. It's not as if we're looking for a
3 minor malformation that the old RADIUS trial and
4 others have shown a significant difference between
5 community and academic centers. I think that this
6 is a measurement that is universally accepted. And
7 I think that the -- can I have this slide up? I'll
8 just say it; that I think that the universal
9 transvaginal screening certainly meets all the
10 criteria for routine screening, and I think it has
11 applicability across all centers, academic and
12 community.

13 DR. JOHNSON: Dr. Harris.

14 DR. HARRIS: Thank you.

15 I'd like to go back to --

16 DR. CREASY: Professor Campbell would like
17 to comment on this, also.

18 May I have Professor Campbell come?

19 DR. CAMPBELL: Well, I would just like to
20 confirm what Dr. Platt says. Cervical length
21 measurement is one of the easiest ultrasound
22 techniques to acquire. It's very easy to train

1 junior doctors, sonographers to do this.

2 I think, in fact, over-diagnosing is not the
3 issue. I think a short cervix is very easy to
4 diagnose. I think the under-diagnosis is the
5 problem because sometimes the cervix can appear to
6 be long but is in fact an incompetent internal os.
7 And if you press on the fundus of the uterus,
8 suddenly you find that amniotic fluid is bulging
9 through the internal os, and, in fact, it's a short
10 cervix.

11 So you won't over-diagnose this condition,
12 and part of the training is to actually get people
13 to recognize a short cervix when it might not be
14 initially apparent from the scanner.

15 DR. JOHNSON: Dr. Harris, you will be our
16 last questioner at this time.

17 DR. HARRIS: Thank you.

18 I'd like to go back to the issue of the FDA
19 request for compelling and robust reduction in
20 preterm births. I think your biostatistician
21 indicated that you had powered the study at
22 80 percent for 0.01, but your data is at 0.02 plus.

1 So how should we interpret that difference between
2 what the FDA required and what you actually came up
3 with?

4 DR. CREASY: Well, the study was actually
5 powered at .05. I mean the power curve -- on the
6 power curve, we could see that we also had some
7 power at a .01 level. But the trial was actually
8 powered at a .05 level. So what we observed a .02,
9 we believe that with all of the other analyses that
10 were done to support this -- slide up.

11 DR. HARRIS: But I'm asking a different
12 question. I understand you powered it at .05. I'm
13 not understanding -- and maybe it's a question for
14 the FDA, who said that if it's a single trial
15 rather than multiple trials, the compelling and
16 robust met a finding of difference in significance
17 at 0.01.

18 So that's not where you are, so how should
19 we interpret that, or should the FDA answer that
20 question?

21 DR. CREASY: It is true that we did not
22 achieve a .01 level. But I think in the totality

1 of the results, given that there's such a great
2 need, given that short cervical length is such a
3 powerful predictor of preterm birth, that these
4 results are very compelling. It's not just the
5 result at the 33-week level. There's also a
6 comparable reduction at 28 weeks where the risk to
7 the babies is even greater, and it extends on the
8 other side to less than 35, a comparable reduction.

9 So there is also some evidence of
10 improvement in infant outcome, and this result is
11 consistent with other studies. So indeed, we
12 didn't hit the .01 level, but I think the evidence
13 is very compelling that this is a proper treatment
14 for women with a short cervix.

15 DR. JOHNSON: Thank you.

16 We'll take a 10-minute break. We will
17 restart at 10:31, and there will be time for
18 Dr. Henderson, Dr. Montgomery Rice, and Dr. Orza to
19 again bring their questions forward after the FDA
20 presentation.

21 (Whereupon, a recess was taken.)

22 DR. JOHNSON: Okay. We will now proceed

1 with our presentations from the FDA. I'd like to
2 remind public observers at this meeting that there
3 will be a meeting for open public discussion.
4 Public attendees may not participate unless
5 specific request to the panel.

6 So now allow us to begin with our discussion
7 from the FDA. First, we will have Dr. Wesley.

8 **FDA Presentation - Barbara Wesley**

9 DR. WESLEY: Good morning. I am Barbara
10 Wesley, and I am the primary clinical reviewer for
11 this new drug application or NDA.

12 The major question before you is, does
13 progesterone gel reduce the risk of preterm birth
14 in women with a singleton gestation and a short
15 cervix at mid-trimester of pregnancy? The specific
16 role of progesterone with respect to preventing or
17 initiating labor and delivery has not been fully
18 characterized in humans.

19 In the FDA presentation, we plan to briefly
20 review the clinical program of this NDA, provide
21 you with the FDA analyses of the data submitted,
22 present the issues that could have impacted

1 efficacy results, summarize the efficacy issues for
2 you to consider, and then summarize the safety
3 review.

4 In February of 2004, the division met with
5 the applicant to discuss requirements for
6 conducting a single study to support approval. We
7 advised that one large phase 3 trial might be
8 adequate if it showed a robust statistically
9 significant reduction in preterm births at less
10 than or equal to 32 weeks gestation with no
11 suggestion of an increase in intrauterine deaths or
12 neonatal morbidity or mortality, and it included
13 adequate infant follow-up.

14 In April of 2004, we clarified what we meant
15 by robust findings in the context of this study. A
16 p-value of 0.01 -- I repeat, a p-value of 0.01
17 include endpoints to assess clinical benefit,
18 specifically a reduction in the incidence of
19 significant neonatal morbidity and no fetal or
20 maternal safety concerns.

21 This application included data from two
22 phase 3 clinical trials conducted by the Columbia

1 Laboratories and the National Institute of Child
2 Health and Development. The principal efficacy and
3 safety trial, Study 302, was conducted in women
4 with a sonographic short cervix. In addition,
5 limited supportive data was provided by a post hoc
6 subgroup analysis of an earlier phase 3 trial,
7 Study 300, that had been conducted primarily in
8 women who had a previous singleton preterm birth.

9 The applicant requested guidance on
10 submitting the subgroup analysis of short cervix
11 subjects in the initial Study 300. The division
12 informed the applicant that it considered this
13 post hoc analysis to be hypothesis generating only
14 and that an additional study to test this
15 hypothesis would be needed if the applicant wished
16 to pursue an indication for treatment of a
17 population in which short cervix was the risk
18 factor for preterm birth.

19 The applicant intended to provide supportive
20 data of efficacy in a sonographic short cervix
21 population from Study 300, but only 10 subjects
22 from Study 300 matched the entry criteria of Study

1 302 which was cervical length between 1 and
2 2 centimeters. Therefore, our review focused on
3 Study 302.

4 There were 23 sites participating in the
5 U.S. and 21 participating outside of the U.S. It
6 was randomized in a one-to-one ratio by study site
7 and risk strata defined as the presence of absence
8 of a previous preterm birth. It was powered to
9 detect a 55 percent reduction in preterm birth,
10 anticipating a 22 percent rate of preterm birth in
11 the placebo arm and a 10 percent rate of preterm
12 birth in the progesterone arm.

13 As you can see, 45 percent of the subjects
14 were from the United States.

15 The efficacy endpoints were as follows: The
16 primary endpoint was preterm birth less than
17 33 weeks gestation. The key secondary endpoint was
18 the composite index of perinatal mortality and
19 neonatal morbidity on a zero to four scale. Other
20 secondary endpoints were preterm birth less than
21 28 weeks, less than 35 weeks, and less than 37
22 weeks gestation.

1 The scoring of morbid events and mortality
2 is shown on this slide, ranging from a score of
3 zero for no events to a score of 4 for a perinatal
4 death, that is, death from 28 weeks gestation to
5 28 days of life. The morbid events included
6 respiratory distress syndrome, bronchopulmonary
7 dysplasia, intraventricular hemorrhage,
8 periventricular leukomalacia, proven sepsis, and
9 necrotizing enterocolitis.

10 In the next group of slides, I will present
11 the major results of Study 302. More detailed
12 results of Study 302 and 300 will be presented
13 subsequently by Dr. Kate Dwyer.

14 As stated previously, the primary efficacy
15 endpoint was the percent of preterm births less
16 than 33 weeks gestation. The primary efficacy
17 analysis was based on the intent-to-treat or ITT
18 population, defined as all subjects who receive
19 study medication and was adjusted for region,
20 maternal age and cervical length.

21 There was a treatment difference of negative
22 6.3 percent, indicating a trend toward efficacy in

1 the progesterone gel arm. The confidence interval
2 included one or unity, indicating that these
3 results were not statistically significant. It is
4 also noteworthy that the placebo rate was
5 15.2 percent, which was somewhat lower than the
6 anticipated 22 percent.

7 The results of the neonatal morbidity and
8 mortality score were as follows. The majority had
9 none of the morbid events and no mortality.
10 Therefore, they scored zero. In the other
11 categories, the numbers were relatively small. The
12 p-value was 0.455, indicating that the difference
13 between the placebo and progesterone gel groups was
14 not statistically significant.

15 Results of gestational age secondary
16 endpoints are listed on this slide. While there
17 was a trend toward efficacy in the progesterone gel
18 arm, the results for reduction of preterm birth at
19 less than 28 and less than 37 weeks were not
20 statistically significant. The reduction in
21 preterm birth at less than 35 weeks gestation was
22 very marginally significant.

1 We can all agree that in addition to
2 reduction of mortality, the reduction of both
3 short- and long-term morbidity is the goal of
4 therapy to reduce the risk of preterm birth. The
5 applicant submitted an analysis of individual
6 morbidity and mortality, which were components of
7 the zero to four morbidity/mortality index
8 presented previously.

9 There are several noteworthy observations.
10 There were fewer deaths in the progesterone gel
11 arm. In the progesterone gel arm, there were also
12 fewer cases of respiratory distress syndrome and
13 bronchopulmonary dysplasia. However, there were
14 more cases of proven sepsis and necrotizing
15 enterocolitis.

16 The applicant has indicated that the fewer
17 cases of respiratory distress syndrome in the
18 progesterone arm was statistically significant. In
19 the next slide, I will present the FDA analysis of
20 respiratory distress syndrome.

21 I remind you that neither analysis has been
22 adjusted for multiplicity. Different adjustments

1 were made by the applicant and the FDA which will
2 further be explained by Dr. Dwyer. Nevertheless,
3 the FDA analysis reveal a p-value of .054, and the
4 confidence interval included 1 or unity, indicating
5 that these results were not statistically
6 significant.

7 Now I will ask Dr. Dwyer to come to the
8 podium and present the FDA efficacy analysis.

9 **FDA Presentation - Kate Dwyer**

10 DR. DWYER: Good morning. My name is Kate
11 Dwyer, the statistical reviewer for this
12 application.

13 This morning, you have already heard the
14 details of the study conduct, brief efficacy
15 summary, and the concerns we have about this
16 application. I will focus on some of the
17 challenges that were noted in this multinational
18 trial during our review of the efficacy data.

19 In general, we look for consistent efficacy
20 result across countries or regions. For a
21 multinational study, the efficacy should also be
22 demonstrated in U.S. subjects for which the drug is

1 intended. We will also look to see whether a few
2 sites or countries are influential in driving the
3 overall result. In addition, we look for
4 consistent efficacy results with the important
5 clinical subgroups. For this application, they are
6 age and race. Analysis by age and race are also
7 part of our routine evaluation as a regulatory
8 agency.

9 Two analysis populations were predefined in
10 the protocol. The intend-to-treat population is
11 considered the primary analysis population while
12 the modified intend-to-treat population is
13 considered as supportive analysis population. The
14 definitions of those populations are presented in
15 this slide. The MITT population is limited to
16 subjects who had 80 percent or greater compliance
17 during the treatment period.

18 This slide shows the similarities and
19 differences in population characteristics by
20 treatment and region. Overall, the demographics
21 are similar across treatment groups but different
22 across regions for maternal age, race, BMI and

1 cervical length. Patient compliance is also
2 significantly different between U.S. and non-U.S.
3 region, 22.8 percent in U.S. versus 2.4 percent in
4 non-U.S. We will address this later in our
5 analysis.

6 Before I present our efficacy results, I
7 will point out the differences between the
8 applicant and our analysis. In the overall
9 population, the applicant adjusted for pooled site,
10 so 44 sites grouped into nine sites and risk
11 strata, which is the presence or absence of prior
12 preterm birth.

13 However, we have the following comments:
14 First, only 15 percent of subjects had a history of
15 preterm births. So this leads to a small number of
16 subjects in each stratum by pooled site and risk
17 strata. There are also large variations in
18 treatment effect, thus inconsistent across pooled
19 site. Last, model adjusting for region and other
20 covariates show that the history of preterm births
21 is not a statistically significant risk factor in
22 preterm births for this study.

1 In order to test the robustness of the
2 applicant's results from this single study, we
3 conducted exploratory analysis adjusting for
4 different factors. A by-region analysis is
5 routinely done for multinational trials. This
6 resulted in us using two regions versus the
7 applicant's nine pooled regions. The covariates
8 are chosen based on their significance in a
9 logistic regression model. These are maternal age
10 and cervical length.

11 Now we present the overall efficacy result.
12 Here are the overall efficacy result for the
13 primary endpoint based on the applicant's
14 prespecified analysis and our exploratory analysis.
15 Our analysis adjusting for region, maternal age,
16 and cervical length shows that progesterone gel is
17 not associated with a significant reduction in
18 preterm birth.

19 The confidence interval for the relative
20 risk includes 1. Recall that our advice to the
21 applicant for demonstrating efficacy using a single
22 study is a p-value less than .01. Both analyses

1 showed here has a p-value greater than .01.

2 Next are the results for the secondary
3 gestational age endpoint. Both applicant's and our
4 analysis are similar. Although the result for
5 gestation age less than 35 weeks are statistically
6 significant, they are not adjusted for
7 multiplicity.

8 Now we move on to the by-region efficacy
9 analysis. Recall that for multinational studies,
10 we investigate if efficacy is demonstrated in the
11 U.S. for which the drug is intended. Here are the
12 percent of preterm births at less than 33 weeks
13 gestation by country. Second and third columns are
14 the percentage for each treatment arm, and the
15 fourth columns are the treatment differences.

16 Note that the treatment differences range
17 from minus 2.4 percent to 50 percent. For the U.S.
18 countries, South Africa and Belarus has no preterm
19 births in the progesterone gel arm and yet have the
20 highest preterm birth rate in the placebo arm. In
21 contrast, the preterm birth rate in India and the
22 Ukraine are low in both treatment arms.

1 Compared to the U.S., the rate in the
2 non-U.S. regions are lower in both treatment
3 groups. Those findings indicate that the efficacy
4 is not consistent across countries and the region.

5 As noted before, we want to see if efficacy
6 is consistently demonstrated across regions. In
7 the U.S., the relative risk is .89, and it's not
8 significant in reducing the preterm in less than
9 33 weeks gestation. In the non-U.S. region, the
10 relative risk is .2, and it's significant in
11 reducing preterm at less than 33 weeks gestation.

12 In addition, the treatment effect in the
13 non-U.S. region is four times higher than that in
14 the U.S. This difference is also confirmed by the
15 significant region by treatment interaction.

16 The treatment differences for the secondary
17 endpoints are shown here. In the U.S., there's no
18 significant treatment differences. In the non-U.S.
19 region, there is significant treatment difference
20 only at less than 35 weeks gestation. Again, those
21 analyses are not adjusted for multiplicity.

22 Here, the Kaplan-Meier curve for gestational

1 age at birth for the U.S. treatment occurs from
2 week 20 to week 37 or delivery. The blue line with
3 circles represents the progesterone gel arm, and
4 the black line with asterisks represents the
5 placebo arm. The curves show that there's no
6 separation between the two treatment arms at all
7 gestational ages for U.S. women.

8 Here are the Kaplan-Meier curves for
9 gestational age at birth for the non-U.S. region.
10 In contrast to the U.S., the curves are separated
11 between week 28 and 37 weeks gestation. The
12 differences are greatest at week 33 and 35.

13 Note that no preterm births occurred in the
14 progesterone gel arm between weeks 27 and 34. This
15 is a different pattern from that observed in the
16 U.S. While both treatment arms had preterm births
17 occurring throughout the treatment period, this
18 separation for overall population showed by the
19 applicant is due to non-U.S. region.

20 In summary, those regional efficacy analyses
21 do not demonstrate efficacy of progesterone gel in
22 the U.S.

1 Now we move on to our sensitivity analysis.
2 To investigate if a few sites or countries are
3 influential in driving the overall result, we also
4 address the applicant's point that the high
5 noncompliance in the U.S. may influence efficacy.

6 Recall that two countries may have
7 contributed to the overall treatment effect. Here
8 are the efficacy results for the primary endpoint
9 after excluding those two countries. When those
10 two countries are excluded from our analysis, the
11 treatment difference decreased from minus
12 6.3 percent to minus 3.5 percent overall and
13 decrease from minus 9.7 percent to minus
14 4.8 percent in the non-U.S. region. The treatment
15 overall and in the non-U.S. regions are no longer
16 significant. In addition, a similar result is seen
17 for all secondary gestational age time point.

18 Here, we address issues of noncompliance in
19 the U.S. Recall that the noncompliance rate was
20 22.8 percent in the U.S. and 2.8 percent in
21 non-U.S. region. We used the MITT population
22 because noncompliant subjects were excluded.

1 The result based on the compliant subjects
2 showed that the treatment effect increased in all
3 three analyses as expected. However, the treatment
4 effect in the U.S. remains not significant at all
5 gestational age time points.

6 In summary, those sensitivity analyses show
7 that results are sensitive with respect to the two
8 outlier countries and noncompliance in this study.

9 Now we move on to our subgroup analysis by
10 age and by race. We also present analysis based on
11 cervical length for supportive Study 300 only.

12 This analysis is by maternal age quartiles
13 with the two middle age group combined because the
14 treatment effects are similar. Note that in women
15 younger than 22 years of age, the rate of preterm
16 birth was higher in the progesterone gel arm. For
17 women 22 aged or older, progesterone gel has a
18 favorable treatment effect.

19 This analysis is by race. Those three race
20 groups are equally distributed in the overall
21 population. The preterm birth in placebo-treated
22 group vary widely by race. This may be due to

1 different regional distributions in the U.S. and
2 non-U.S. regions. Overall, efficacy is minimal in
3 Asian subjects.

4 This table shows 33 subjects with a cervical
5 length of 1 to 2.5 centimeters for supportive
6 Study 300 that will be used in our subgroup
7 analysis. This subgroup was chosen also because it
8 includes the 9 subjects in the the original short
9 cervix only subgroup of Study 300 with cervical
10 lengths 2.5 centimeters or less.

11 In those women with cervical lengths between
12 1.0 and 2.5 centimeters, the treatment differences
13 vary among the four gestational age time points.
14 No conclusion can be drawn from those 33 women.

15 In addition, I want to point out Study 300
16 failed to show any treatment effect for the entire
17 ITT population of the women who had a history of
18 preterm birth.

19 In summary, our analysis was performed to
20 investigate the robustness of the applicant's
21 results. The results of both applicant's and our
22 exploratory analysis of this single study did not

1 show robust efficacy. Efficacy was also not
2 consistent across regions. In the U.S., there was
3 no treatment effect in either the ITT or MITT
4 populations at all gestational age time points.
5 Although the sample size from the two non-U.S.
6 countries are small, they appear to influence the
7 overall study result.

8 In addition, the efficacy was not consistent
9 by age and race. Study 300 did not provide
10 additional supportive data.

11 So next, I will turn the podium to Dr. LaRee
12 Tracy.

13 **FDA Presentation - LaRee Tracy**

14 DR. TRACY: Good morning. I'm your surprise
15 guest speaker today. These slides that I'm going
16 to present are not among those that were provided
17 to you in advance. They can be provided to you
18 afterwards.

19 My name is LaRee Tracy. I'm a statistical
20 team leader in the Office of Biostatistics, and I
21 was asked to perform an independent review of the
22 manuscript by Romero, et al., which was earlier

1 described by the sponsor. I was not part of the
2 review team for this NDA.

3 I will also note that the manuscript by
4 Romero, et al. is not current published. It is
5 considered as an accepted manuscript, and so I
6 found it available at the AJOG website.

7 So as described already by the sponsor, the
8 meta-analysis by Romero, et al. included data from
9 five randomized double-blind placebo-controlled
10 trials. It was a patient level meta-analysis, and
11 that in itself is a strong parameter of the study
12 design.

13 The population of interest in this
14 meta-analysis included women with a cervix of less
15 than or equal to 2.5 centimeters. However, not all
16 the trials included among that meta-analysis
17 included women who met that criterion. And it's
18 important to note that data from three of the five
19 trials, that is, the Cetingoz, the Rode and the
20 O'Brien trial, actually consisted of data from a
21 subset of these trials, and therefore represents a
22 non-random subset. So in a sense, this really is

1 not a meta-analysis of randomized clinical trials
2 but rather a meta-analysis of two randomized
3 clinical trials plus additional data from three
4 subgroups.

5 This slide provides the features of the five
6 trials included in the meta-analysis. The first
7 trial, the Fonseca, et al. trial published in 2007,
8 which has been described already in brief by the
9 sponsor, was among the five trials. It's important
10 to mention that this trial evaluated a
11 200 milligram per day dose, not the 90 milligram
12 per day dose that's being sought by the sponsor,
13 and that was studied in the other trial that is the
14 Hassan trial. So in a sense, this trial evaluated
15 a dose two times that which is being sought.

16 In addition, this study included women with
17 a cervix of less than 1.5 centimeters, and the
18 primary endpoint was a preterm birth less than
19 34 weeks.

20 The O'Brien trial evaluated the 90 milligram
21 dose. However, as already noted, data from this
22 trial consisted of a subset of women with a cervix

1 of less than 2.5 and did have the requirement of
2 prior preterm birth.

3 The Centingoz trial published in 2007
4 evaluated a 100 milligram dose. Inclusion required
5 that women had had a prior preterm birth. This
6 study also evaluated twin pregnancy and women with
7 a uterine malformation. As noted a moment ago,
8 data from this trial were of a subset and do not
9 represent the ITT or a random subset. And as
10 already described in detail, the Hassan trial
11 evaluated the 90 milligram dose and included women
12 with a cervix between 1 to 2 centimeters.

13 And finally, the Rode trial of 2011 also
14 evaluated the dose of 200 milligrams per day. It
15 looked at women with twin pregnancies, and
16 represents a post hoc subset of data based upon
17 women with a cervix of less than or equal to
18 2.5 centimeters.

19 So some other notable findings with respect
20 to this manuscript is that the Fonseca trial
21 contributed 45 percent of the data; however, no
22 data are available on this trial on cervical length

1 between 1.6 and 2.5 centimeters.

2 Similarly, the Hassan trial contributed
3 44 percent of the overall pooled effect size, and
4 no data on cervical length between 2.1 and 2.5
5 centimeters are available from this trial. And
6 finally, the data from the remaining three trials,
7 the Centingoz, the Rode and the O'Brien, only
8 contributed 2.9 percent, 4 percent and 3.7 percent
9 respectively.

10 The systematic review as described in the
11 manuscript identified 1,875 nonduplicate records of
12 which 1,865 were excluded. However, the authors of
13 this manuscript do not provide a summary for the
14 reasons or purposes of excluding those 1,865
15 abstracts or documents that were identified in the
16 systematic review. And just to note, during my
17 review of this manuscript, I identified at least
18 one other published trial, which has I think been
19 referred to already today, the Fonseca 2003 paper,
20 which is also published in AJOG, which appears to
21 have similar study designs to that of the five
22 selected for the meta-analysis in the Romero study.

1 So I have general concerns with respect to the
2 final selections of trials included in the Romero
3 meta-analysis.

4 In addition, the authors in the Romero
5 meta-analysis state the following in their comments
6 section: "The findings of this IPT, or individual
7 patient meta-analysis, favor the use of a daily
8 vaginal administration of 90 milligrams of
9 progesterone because it is the lowest dose that
10 reduced the risk of preterm birth less than
11 35 weeks, 33 weeks, and neonatal morbidity and
12 mortality."

13 I would contend that this is a false
14 statement, given that among the five trials used in
15 the meta-analysis only two, the O'Brien and the
16 Hassan, studied that 90 milligram dose and the
17 other trials studied doses of 100 or 200 milligrams
18 per day. Efficacy for the 90 milligram dose cannot
19 be extrapolated from these data based on higher
20 doses. Furthermore, the 90 milligram per day was
21 given in a gel formulation, whereas the
22 100 milligram and 200 milligram day doses were

1 given as suppositories.

2 The authors argue that there is a loss of
3 product over the course of daily treatment with a
4 suppository, and therefore suggesting that the
5 90 milligrams per day and the 100 and 200
6 milligrams per day dosages are equivalent. This is
7 a weak argument.

8 The focus of the Romero, et al.
9 meta-analysis is in women with a short cervix
10 defined as less than or equal to 25 millimeters.
11 However, the two studies that contributed the most,
12 that is, over 85 percent, to this meta-analysis,
13 that is, the Fonseca and the Hassan study, enrolled
14 women with shorter cervical lengths; that is, less
15 than 15 millimeters -- that's the Fonseca -- and 10
16 to 20 millimeters; that is the Hassan study.

17 Among the remaining three trials, only one
18 randomized a subset of women with cervical length
19 of less than or equal to 25 millimeters, and that
20 was the O'Brien trial. However, results from this
21 subset were not published due to small numbers.
22 And the other two publications do not account for

1 cervical length in the randomization, and
2 therefore, the subsets chosen by the authors in the
3 Romero paper are likely nonrandom via subsets.

4 Finally, I want to end with a couple of
5 comments with respect to the interpretation or the
6 presentation of the results in the meta-analysis at
7 manuscript. The authors present a pooled estimate
8 based on a relative risk of .58 and a 95 percent
9 confidence interval of .42 to .80. The authors'
10 principal finding is that there is a 42 percent
11 significant reduction in rate of preterm births at
12 33 weeks.

13 This is a misleading conclusion as it
14 suggests a reduction based on absolute risk, and,
15 in fact, this is based upon a relative risk. So in
16 truth, it should be interpreted as 42 percent less
17 likely to have had preterm birth compared to women
18 exposed to placebo.

19 An FDA pooled analyses of these data, as
20 presented in the manuscript, achieved a risk
21 difference of negative .09 with a 95 percent
22 confidence interval going from negative 14 to

1 negative .04. And the results of this should be
2 interpreted as suggesting an absolute risk
3 reduction which ranges from 14 percent to
4 4 percent, given all the caveats that I've already
5 stated with respect to the variation across studies
6 in dosages as well as cervical lengths. And
7 finally I will note, I was able to replicate the
8 relative risks as presented in the meta-analysis.

9 Thank you for your attention, and I'll now
10 turn this back over to Dr. Wesley.

11 **FDA Presentation - Barbara Wesley**

12 DR. WESLEY: Now I would like to summarize
13 the FDA efficacy findings and provide you with our
14 conclusions.

15 Both the FDA and the applicant have concerns
16 about issues that may have impacted the efficacy
17 results. The FDA is concerned that there are
18 several findings that suggest the multinational
19 data cannot be generalized to the U.S. The
20 applicant is concerned that the rate of higher
21 noncompliance in the U.S. and a possible higher
22 prevalence of chorioamnionitis in the U.S. may have

1 skewed the results.

2 How well does the overall international
3 population generalize to women in the United
4 States? We demonstrated that there were wide
5 differences in the placebo preterm birth rates by
6 country; wide differences in the progesterone gel
7 preterm rates by country; a complete lack of
8 preterm births in some countries in either the
9 placebo or progesterone gel arms despite having a
10 cervical length between 1 and 2 centimeters; and
11 wide differences in treatment effect by country.

12 In the next few slides, I will review the
13 wide variation seen in the placebo preterm birth
14 rates, the progesterone gel preterm birth rates,
15 and the treatment differences between countries.
16 Because some countries had extremely small sample
17 sizes, I am also going to show you rates by primary
18 pooled sites. This grouping avoids some of the
19 instability in rates that would result from
20 including countries that only enrolled one or two
21 subjects. Even with using the primary pooled site
22 groupings, the rates of preterm birth in both the

1 placebo and progesterone gel arms remains highly
2 variable.

3 A background rate, which is an estimate of
4 the anticipated placebo rate, was, as previously
5 stated, assumed to be a 22 percent rate of preterm
6 birth. The placebo rate in the U.S. averaged
7 19 percent with a pooled site range from 15 to
8 23 percent, which was close to the anticipated
9 rate. However, the placebo rate in the non-U.S.
10 region averaged 12 percent with a pooled site range
11 from zero to 35 percent. These data suggest that
12 at-risk populations outside of the United States
13 are not the same populations as at-risk U.S. women.

14 The response to treatment was also quite
15 variable. As stated previously, the anticipated
16 preterm birth rate in the progesterone gel arm was
17 10 percent. Study results showed the preterm birth
18 rate to be higher than anticipated in the U.S., a
19 rate of 17 percent of preterm birth with a pooled
20 site range of 11 to 22 percent.

21 In addition, the preterm birth rate was
22 lower than anticipated in the non-U.S., a rate of

1 only 2 percent with a pooled site range of zero to
2 6 percent. There were actually six non-U.S.
3 countries with no preterm births in the
4 progesterone gel arm. Again, these data suggest
5 that the non-U.S. populations are not the same
6 population of at-risk women.

7 This slide illustrates the differences in
8 the treatment effect between the U.S. and non-U.S.
9 regions. The overall treatment effect was minus
10 2.4 percent in the U.S. pooled sites, ranging from
11 a minus 12 percent reduction to a plus 7 percent
12 increase in preterm birth. In the non-U.S. pooled
13 sites, the treatment effect was minus 9.7 percent,
14 ranging from a minus 31 percent reduction to a plus
15 9 percent increase in preterm birth.

16 The applicant proposed two explanations for
17 the lack of efficacy in the United States. First,
18 there was an increased rate of poor compliance in
19 the U.S. subjects. And to quote from the
20 applicant's submission, "Regional differences in
21 chorioamnionitis may have contributed to the
22 observed differences between the U.S. and non-U.S.

1 regions."

2 This slide reminds you of the marked
3 difference in noncompliance between the U.S. and
4 non-U.S. populations. In addition, in the U.S.,
5 there was a greater noncompliance in the treatment
6 arm, whereas in the non-U.S., there was a greater
7 noncompliance in the placebo arm.

8 As stated previously, we did an analysis of
9 the MITT population in the U.S. which removed
10 noncompliant subjects from the U.S. database.
11 However, despite this, there still was no
12 significant reduction in preterm birth in the
13 United States.

14 The applicant reported 17 cases of clinical
15 chorioamnionitis in the U.S. versus only three
16 cases in the non-U.S. region. There is no
17 internationally accepted diagnostic criteria for
18 chorioamnionitis. Therefore, it is not clear
19 whether this is a true difference or represents a
20 difference in diagnostic criteria. Also, there is
21 no accepted screening test to identify most cases
22 of chorioamnionitis at the time when progesterone

1 gel begins. Therefore, even if chorioamnionitis
2 impacted efficacy, we could not address this in
3 labeling.

4 Nonetheless, when all cases of
5 chorioamnionitis were removed from the database, as
6 you can see from the applicant's analysis, the
7 confidence interval included zero, indicating that
8 the treatment effect in the U.S. was still not
9 statistically significant.

10 In summary, overall in the FDA analysis, the
11 treatment effect of progesterone gel compared to
12 placebo was not statistically significant for
13 either preterm birth less than 33 weeks or for the
14 neonatal morbidity/mortality index. In both the
15 FDA and applicant's analyses, progesterone gel did
16 not significantly reduce the rate of preterm birth
17 at any evaluated gestational age or improve the
18 neonatal morbidity/mortality index in the U.S.
19 subjects, which was 45 percent of the total
20 population.

21 The FDA analysis showed large variations in
22 the treatment effect of progesterone across

1 countries. The sensitivity analysis that excluded
2 subjects from the two countries with the greatest
3 treatment effects, only 7 percent of the total
4 subjects, resulted in lack of statistical
5 significance at all gestational ages evaluated,
6 both for the overall population and the non-U.S.
7 population.

8 Pooling of data from Study 300 and Study 302
9 is not appropriate due to different at-risk
10 populations. Results of Study 300 do not support
11 approval of progesterone gel for this indication.

12 In the next couple of slides, I will provide
13 a brief summary of the safety findings.

14 The phase 3 clinical safety database
15 consisted of a total of 1,119 subjects with 568
16 subjects who were exposed to progesterone gel for a
17 mean duration of 13 weeks. There were no maternal
18 deaths, and the rates of fetal, neonatal, and
19 infant deaths were similar in both treatment arms.
20 The rates of adverse events and serious adverse
21 events were also similar across treatment arms.

22 Infant follow-up data from Study 300 was

1 done between 6 and 24 months of age. The primary
2 objective of this study was to determine if there
3 were differences in achievement of developmental
4 milestones between children whose mothers receive
5 progesterone gel and those whose mothers received
6 placebo. The data was comparable in each arm,
7 suggesting there was neither a positive nor
8 negative effect of progesterone gel in the
9 offspring of these mothers.

10 So I end with the question I posed to you in
11 the beginning, does progesterone gel reduce the
12 risk of preterm birth in women with a singleton
13 gestation and a short cervix at mid-trimester of
14 pregnancy? Thank you.

15 **Clarifying Questions to the FDA**

16 DR. JOHNSON: Now the advisory committee can
17 move to clarifying questions for the FDA. I want
18 to remind our committee that we did have three
19 people who did not have the opportunity to ask
20 questions of the sponsor. They will get the
21 opportunity perhaps at the end of this session or,
22 if not, they will certainly get that opportunity,

1 the first opportunity in the afternoon when we have
2 time for questions again.

3 Let's go ahead and proceed directly to
4 questions for the FDA. Those who have questions,
5 if you could kindly raise your hands.

6 Dr. Orza.

7 DR. ORZA: Is there any reason to be
8 interested in looking at the babies beyond two
9 years?

10 DR. WESLEY: In a previous application, we
11 did a follow-up of infants, and we had a consult
12 from a developmentalist. And we were informed that
13 two years of age is a very good predictor of even
14 later outcome and is a reasonable point in time in
15 which you can collect, and enough patients will be
16 around to get the data.

17 So it's basically a weighing of
18 when -- obviously, it would be ideal to get all
19 patients throughout childhood and adolescence and
20 adulthood, but it's reasonable to expect that you
21 can get a good number by 24 months, and it's still
22 very predictive of the later morbidities.

1 DR. JOHNSON: Dr. Henderson.

2 DR. ORZA: Sorry. It might not be a good
3 analogy, but I was wondering with something like
4 DES, how far out it was that we were discovering
5 things that we wouldn't have known within two
6 years?

7 DR. WESLEY: The FDA monitors all drugs
8 throughout any period through the voluntary
9 submission of adverse events to the FDA. And if we
10 see any patterns, then we will further require
11 further studies. Anything that comes up, we can
12 always require a safety study to be done.

13 Generally, in the clinical trial data, the
14 populations are not large enough to pick up some of
15 these, and unfortunately you do have to wait till a
16 drug is approved to get the hundreds of thousands
17 of patients to pick up some of these. In addition,
18 we are much better now than we used to be at the
19 time that DES came through the FDA in terms of
20 doing safety surveillance, preapproval. We have a
21 lot more emphasis on that than we used to, and I
22 would not anticipate any untoward effects that

1 would be such a surprise as DES was.

2 DR. SOULE: I also just want to add to that
3 that this product has been used widely in early
4 pregnancy, actually more in the period of
5 organogenesis. And so we have a great deal of
6 safety data over a number of years on this product
7 already.

8 DR. JOHNSON: Dr. Henderson.

9 DR. HENDERSON: I have a question about the
10 22 percent background preterm delivery rate. Is
11 that to 37 weeks, or for all the populations that
12 we studied, were you looking at their rates of
13 preterm delivery up to 33 weeks? So is it
14 22 percent will deliver by 33 weeks or the
15 completed 37?

16 DR. SOULE: That figure was just drawn from
17 the applicant's power calculations. That was the
18 expected placebo preterm delivery rate that they
19 used. That's where we got that.

20 DR. HENDERSON: Twenty-two percent would
21 deliver by 33 weeks as a background rate?

22 DR. SOULE: We were using the placebo rate

1 as a surrogate for a background rate, and I think
2 perhaps the sponsor could address how they came up
3 with that number. My belief is it was based on
4 what they expected at less than 33 weeks.

5 DR. HENDERSON: The only reason I'm curious
6 about it is because one of the problems with the 17
7 hydroxy study, the placebo rate had a huge preterm
8 delivery rate, and it was explained that only folks
9 who had a bad outcome would be willing to enroll.
10 And if they had a bad outcome, it was very likely
11 that they had a very early preterm delivery. So
12 that justified it.

13 So as we're going forward, I just wanted to
14 know if we could get a better idea of the
15 background rates for all the populations that we
16 study.

17 DR. JOHNSON: Did you have a comment you
18 wished to make?

19 DR. CREASY: I maybe can provide some
20 clarification about the 22 percent placebo rate.
21 It was targeted at less than 33 weeks gestation,
22 and it was derived from the two previous trials

1 primarily that were conducted, the one by Fonseca
2 where the placebo rate was in the 35 to 36 percent
3 range at 34 weeks. And we observed at 32 weeks,
4 less or equal to 32, in the subgroup from the 300
5 study, a 29.8, or something like that, placebo
6 rate.

7 So both of those placebo rates that we
8 observed from previous randomized clinical trials
9 were a bit higher, so we were trying to pick a more
10 conservative rate for our 33-week primary endpoint.

11 DR. JOHNSON: Yes, I wanted to ask, can you
12 give me your assessment of why there is a
13 difference in looking at the incidence of preterm
14 birth, the ITT population in the FDA analysis
15 compared to the sponsor's analysis? Certainly at
16 less than 33 weeks, we see a significance with the
17 analysis by the applicant but no significance from
18 the FDA.

19 If you could clarify that.

20 DR. DWYER: We addressed a different factor
21 based on our model. So the applicant used the
22 pooled sites, so we changed it. Since there are

1 large variations, we changed it to two regions.
2 The major difference is region. Then we also
3 address two factors, which is maternal age and
4 cervical length. That's why it's different.

5 DR. JOHNSON: So the difference is due to
6 the fact that you adjusted for region and maternal
7 age?

8 DR. DWYER: And the cervical length. We
9 actually have a backup slide showing those
10 differences.

11 DR. JOHNSON: Thank you.

12 Dr. Sicalli.

13 DR. SICALLI: My question is similar. I
14 know that maternal age and cervix length are
15 associated with preterm delivery risk, but neither
16 was a factor that distinguished the placebo group
17 from the progesterone group. In other words, they
18 were evenly distributed in both treatment groups.

19 So are you concerned that by adjusting for
20 cervical length and maternal age, you're
21 over-controlling?

22 DR. DWYER: As we said, our purpose is to

1 check the robustness of the sponsor's results. So
2 this is our exploratory analysis based on our
3 model. So we only adjust for three factors. Since
4 region is -- ours is only two versus the sponsor's
5 nine, so it's actually -- our certification is not
6 that more.

7 DR. SICALLI: My question wasn't about
8 region, though, but cervical length and maternal
9 age. It seems to me that effectively, you're doing
10 stratified analyses and therefore decreasing the
11 ability of the study to show a statistically
12 significant result by using a stratification that
13 wasn't planned prior to or at the time of the study
14 design.

15 DR. SOBHAN: Maybe I can add something.
16 This was not a stratification variable. The
17 stratification variable was previous preterm birth
18 or not, but maternal age was not. So that was
19 considered a risk factor in this trial, so we
20 tested for it, if it is really a significant factor
21 or not. And we found out that there were, so we
22 adjusted for it.

1 But to answer your question whether we are
2 overdoing it, I don't think we can answer that. It
3 was significant. That's why we had to adjust for
4 it.

5 DR. JOHNSON: Dr. Montgomery Rice.

6 DR. MONTGOMERY RICE: Are we only directing
7 our questions -- which part are we on, FDA or
8 sponsor or which --

9 DR. JOHNSON: We're actually on FDA. Can we
10 return to you if you have a sponsor question?

11 DR. MONTGOMERY RICE: Well, I have one for
12 the FDA.

13 DR. JOHNSON: Very good then. Proceed.

14 DR. MONTGOMERY RICE: But it will be
15 continued with the sponsor.

16 I guess my question is, when you allow the
17 trial to go through and -- sort of two points.
18 You-all defined robust with one trial at .01. And
19 then they came back to you in discussions, and they
20 powered it for .05. What was the discussion then?
21 Because you were still only saying to them they
22 would have a single trial. So I mean at some point

1 did you say, well, you are going to be challenged
2 because we have defined robustness at .01 but yet
3 you only powered the study at .05?

4 I'm confused about why did they proceed
5 under those circumstances.

6 DR. WESLEY: When the applicant comes to the
7 FDA for guidance and we provide our best available
8 guidance, it doesn't mean that we're necessarily
9 correct. The applicant has the right to make some
10 changes, knowing that it could be a review issue.
11 They have a right to do that. Had they come in and
12 it was robust at 33 weeks, then that would have
13 been a review issue.

14 So it doesn't necessarily dictate -- we
15 don't necessarily dictate. We tell them our
16 advice. It's guidance. It's not rules or
17 regulations. It's just guidance. And it's at
18 their risk if they want to change it, but they have
19 every right to do that.

20 DR. SOULE: I guess the other thing I'll add
21 is we're obviously working within the limits of our
22 resources. We have a process called special

1 protocol assessment where sponsors can come to us
2 with a phase 3 protocol and ask us very specific
3 targeted questions about things they would like to
4 do in the protocol, and we do answer those in great
5 detail.

6 That was not used in this application. The
7 sponsor did not request that type of a review from
8 us, and therefore, we do review phase 3 protocols
9 but we don't obviously address every single factor,
10 particularly where the sponsor has not asked us for
11 particular guidance.

12 DR. MONTGOMERY RICE: And then the other
13 part to you-all is, was there any consideration
14 based on what had been published in the literature
15 and knowing that some of the data was -- some of
16 the hypothesis of the success of progesterone, that
17 it had been done with vaginal suppositories,
18 micronized progesterone.

19 Was there ever any consideration that there
20 should be a three-arm study comparing the vaginal
21 micronized versus this product, or did you think
22 that there was something -- or did the sponsors say

1 to you-all that there was something so unique about
2 this vaginal gel that two arms was enough?

3 DR. SOULE: Again, I think that's not really
4 within FDA's purview. We're not the ones who
5 design the trials. The sponsor had a particular
6 product they wanted to bring to market. We felt at
7 that time that it was ethical to have a placebo
8 control arm, and they did not propose testing any
9 other formulations or other products.

10 DR. MONTGOMERY RICE: And I would just
11 comment that based on some of the differences that
12 we've seen with hormone replacement, some of the
13 challenges we have seen with some of the different
14 products, I think all of us would say that if we
15 had to do it back over again, we might have done
16 some different things.

17 DR. JOHNSON: Ms. Aronson.

18 MS. ARONSON: Forgive my potential patient
19 perspective naivete, but I'm going to focus back on
20 the smoking and high caffeine intake as risk
21 factors. Was this ever discussed as including
22 these factors? And it was suggested that these two

1 factors would have been randomized earlier.

2 Is that so? And, of course, I'm concerned
3 if there were more, for instance, smokers or high
4 caffeine intake subjects in the placebo arm that
5 might have weighted it in some way.

6 DR. WESLEY: Preterm birth has been
7 characterized very eloquently by Dr. Romero in the
8 audience as a syndrome. It's got multiple causes,
9 multiple associated factors, and there's no way you
10 can control for just those without looking at the
11 other 10, 20, 30 factors that go into preterm
12 birth.

13 So randomization should have taken care of
14 the smoking and the caffeine intake. There was no
15 further delineation of those two factors.

16 DR. JOHNSON: Dr. Clarke.

17 DR. CLARKE: Just, again, some clarification
18 of the original discussions that were held before
19 the study design was approved. For the robustness
20 of the study, it was a multicenter, was the
21 requirement, multicenter study. It turned out it
22 was multinational, as you might expect. But then

1 is there ever -- I presume the understanding there,
2 even if it's not in writing, is that if the results
3 are different in the U.S. compared to other sites,
4 that that is an issue. Even though it's not stated
5 that and even though in the overall analysis of the
6 overall study, we do see apparently close to a
7 significant result.

8 So is that part of the discussion, and it's
9 understanding that it has to show benefit in the
10 U.S. to get approval in the U.S., or is it that the
11 overall study is considered adequate?

12 DR. SOULE: I think, as you note, obviously,
13 we are always going to look at U.S. efficacy.
14 Whether we would hold sponsors to an absolute
15 p-value, not necessarily, but I think the bigger
16 context of this is also the issue of this being a
17 single trial, that even on an overall global level,
18 really didn't meet the standards that we set for
19 it.

20 DR. BIETZ: I would just also like to
21 comment that if there are differences across
22 regions as perhaps seen in this case, that an

1 explanation of the reasons for those differences
2 would be very helpful to us.

3 DR. JOHNSON: Dr. Rosen.

4 DR. ROSEN: Can you put back up the slide on
5 the modified intention to treat? I think it's
6 slide 35. And I just want to ask a little more
7 carefully about that modification because the
8 sponsor is concerned that compliance was a major
9 issue.

10 So can we go over that again? Because you
11 also made some comments, which weren't in the
12 written notes, about the difference between the
13 placebo group and the treatment group in terms of
14 compliance for each of the different geographic
15 locations. If I'm not mistaken, one was the
16 placebo was higher for the U.S. group in terms of
17 noncompliance, and in the non-U.S. group, it was
18 the treated group.

19 Is that correct? Other way around? Can you
20 clarify that for us because it's not clear?

21 DR. WESLEY: What is correct is in the U.S.
22 there was a greater noncompliance in the treatment

1 arm.

2 DR. ROSEN: In the treatment arm. Okay.

3 DR. SOULE: If we could put up slide --

4 DR. WESLEY: And that was slide --

5 DR. SOULE: Slide 51, please.

6 DR. ROSEN: Okay. My question is that it
7 was mentioned by the sponsor that they did a
8 modified intention to treat analysis.

9 Is that identical to what the FDA provided,
10 or is it different?

11 DR. WESLEY: As far as I know, it's the same
12 one.

13 DR. ROSEN: Was it corrected for -- I mean
14 confounded by age and location?

15 DR. SOULE: The FDA analysis, which is
16 presented on the next slide if you want to go to
17 slide 52, that was similar to all of our other
18 analyses in that we adjusted for region, maternal
19 age, and cervical length. And the sponsor did
20 theirs with their different adjustment factors.

21 DR. ROSEN: With different adjustment.

22 DR. SOULE: Yes.

1 DR. ROSEN: And they didn't present that
2 data; is that correct?

3 DR. CREASY: No. No, we didn't in the core
4 presentation earlier this morning.

5 DR. JOHNSON: Dr. Harris.

6 DR. HARRIS: Thank you.

7 Back to the issue of U.S. versus non-U.S.
8 sites and your conclusion that this did not have
9 generalizability, what would it take to have
10 generalizability if you have multinational sites,
11 multiple ethnic and racial groups as part of the
12 analysis? That's one thing.

13 The second thing is your subgroup analyses
14 and your sensitivity analyses are post hoc. And
15 did those have adequate power to draw the
16 conclusions that you did, or were they diluted out
17 because the sample sizes were too small?

18 And lastly, since the rates of preterm birth
19 were lower in the placebo groups non-U.S., wouldn't
20 that drive the bias towards placebo rather than
21 towards the treatment arm?

22 DR. SOULE: I'll tackle some of those, and

1 then I'll turn to my colleagues.

2 I think as far as your last comment about
3 the rates of preterm birth -- placebo preterm birth
4 being lower, the overall average was lower, but as
5 we showed you, there was great variability. Ad in
6 certain centers, particularly Belarus and South
7 Africa, the placebo rates were as high as 36 to 50
8 percent. So it was just an incredibly diverse
9 experience in the placebo arms.

10 DR. HARRIS: But isn't that the whole point
11 of randomness and allocation, to see that, and then
12 assume because you've done the randomization that
13 that's a chance event and not some bias in the
14 design of the study or bias on the part of the
15 investigators?

16 DR. SOULE: Well, I think the
17 overall -- when you ask what it would take to
18 establish generalizability, I think there were just
19 enough variations. And I think particularly when
20 you go back and look at the Kaplan-Meier curve for
21 the U.S. overall, you really can see that there
22 just is basically no treatment effect in the U.S.

1 And I think that concerned us, and the more we
2 looked into it, we began to see pretty large
3 discrepancies between the U.S. and non-U.S.
4 populations.

5 DR. DWYER: Could you show slide 31? So
6 from here, you see although the study is now
7 powered to show the efficacy in both regions, but
8 from this curve here you can see there is no
9 separation because this is -- we don't even take
10 into account the power. You can see there's no
11 separation.

12 Also, by analysis, we did a region by
13 treatment, so we find out the interaction is
14 significant. So if the interaction is significant,
15 by analysis, you need to do the separate study by
16 region.

17 DR. JOHNSON: Dr. Emerson.

18 DR. EMERSON: So could we look at slide 25,
19 which is looking at the differences in the adjusted
20 analyses that were undertaken. And there's
21 possibilities for several things that could be
22 going on here, and I was just wondering if you

1 could provide any insight.

2 You're seeing that both your point estimate
3 is closer to the null, which could well be just
4 this factor of it was more important to provide
5 more -- a finer gradation among the sites than just
6 the non-U.S. and U.S., if that was a really
7 important variable.

8 There's also possibility that there is some
9 effect modification that the Mantel-Haenszel
10 statistic as it provides its weight is giving a
11 whole lot more emphasis to certain ones of the
12 strata, according to what those baseline rates.

13 Do you have a feel for the relative
14 contributions of these two things, these
15 differences we're getting?

16 DR. SOBHAN: I think with respect to
17 Cochran-Mantel-Haenszel, I think if you have very
18 thin data, you have a lot of stratum, then results
19 sometimes could be little difficult to -- although
20 CMH is very robust in terms of that, but
21 because -- we didn't disagree with the sponsor's
22 CMH test all. We just said we want to look at it

1 differently. All estimates are based on model-
2 based estimation because we had to adjust for other
3 things. And the biggest difference, as you
4 noticed, is how we pooled the sites.

5 DR. EMERSON: So in your pooling, were there
6 substantial imbalances created among the -- across
7 the treatment arms -- and for that that would be
8 explaining this. But, basically, the two different
9 analyses are in effect removing some amount of sort
10 of conditional confounding. But there's also the
11 possibility -- again, if this were just an issue of
12 adjusting for the sites and there was a common odds
13 ratio, we might expect the point estimates to
14 change, but we wouldn't expect the p-value to
15 change --

16 DR. SOBHAN: Right.

17 DR. EMERSON: -- unless it was a really huge
18 baseline effect. What I'm wondering about in this
19 is it also looked like across the sites were
20 relatively balanced at each site, that the
21 randomization paid off. So now my question is, is
22 more towards the amount that any variation,

1 heterogeneity of effect across sites, is being
2 weighted quite differently in the Mantel-Haenszel
3 statistics and leading to this concept.

4 But do you have any observations that you
5 could look at?

6 DR. SOBHAN: It could have. As you saw, the
7 treatment effect in both directions, so we thought
8 there is a quantitative as well as qualitative
9 interaction, but we did not go deep into
10 qualitative part. We just wanted to address the
11 quantitative interaction. So that could have
12 potentially contributed to this wider confidence
13 interval. We have not examined that part.

14 DR. JOHNSON: Dr. Henderson.

15 Now we'll return to the sponsors, great.

16 Dr. Gut.

17 DR. GUT: I do h a question to FDA.

18 If I understood correctly the statistical
19 presentation, FDA excluded patients with very high
20 efficacy, from analyzation. Of course as a
21 consequence, the overall efficacy was not
22 statistically significant.

1 I wonder, did FDA conduct an audit in this
2 two regions or two sides and found any particular
3 reason to exclude those sides and analyses.

4 DR. SOULE: We did conduct some site
5 inspections. Those two particular countries were
6 not among the sites inspected. We primarily based
7 our selection -- and we do that very, very early in
8 the NDA submission cycle, especially with foreign
9 inspections, it takes a great deal of time to get
10 those set up. We primarily chose them based on the
11 number of subjects enrolled in the sites. So we
12 inspected several sites in India. But as you can
13 see, those particular sites were actually fairly
14 small contributors in terms of subjects.

15 DR. GUT: But you are usually very good in
16 picking the sites, so I will guess that you will
17 pick these sites to check that everything was fine.
18 Thank you very much.

19 DR. SOULE: Yes, in retrospect, we might
20 have made different selections. But as I say, we
21 used -- we actually have a algorithm that we use to
22 select sites, and these were not the ones that fell

1 out at that point.

2 DR. GUT: Thank you very much.

3 DR. JOHNSON: Dr. Hoeger.

4 DR. HOEGER: I also had a question relative
5 to the FDA's inclusion of non-U.S. sites, and when
6 the Makena went through its trials, did you include
7 non-U.S. sites in the approval of that drug? And
8 if so, did you see this variation in preterm
9 delivery rates of such a dramatic nature as was
10 shown here?

11 DR. WESLEY: The Makena trial was done by
12 the maternal fetal medicine units of the National
13 Institute of Health, and it did not include foreign
14 sites. That particular trial did not.

15 DR. JOHNSON: Dr. Orza.

16 DR. ORZA: I wanted to follow up on your
17 earlier comment at the 14 years' worth of
18 experience with this drug, albeit at a different
19 point in the pregnancy. Do we have a number of
20 14-year-olds on which we have information? I mean
21 the children that were born to these mothers. And
22 are there in that set some girls who on whom we

1 have information about menarche? I mean I assume
2 we don't have any information on women of
3 childbearing age, but do we at least have something
4 on menarche?

5 DR. SOULE: The data I was referring to was
6 spontaneous post-marketing reports. I would ask
7 the company. Perhaps they may have more specific
8 data, but what FDA relies on in this particular
9 situation is just the post-marketing spontaneous
10 reports.

11 DR. JOHNSON: Now we will return to
12 questions for the sponsors. Dr. Henderson.

13 DR. HENDERSON: Thank you.

14 I was struck by all the material that was
15 presented by the differences in BMI. And I
16 wondered in groups that didn't have an effect, say,
17 for example, the less than -- that did have -- that
18 did not. I'm sorry. The women less than 22 years
19 of age versus those who were older, was there a
20 difference in their BMI that was akin to the
21 difference in the BMI from the U.S. and the
22 non-U.S. population? First question.

1 Second question, in the U.S. population, we
2 have a few women who are not -- have a BMI of 29.
3 I know we're not looking at subgroups and that's a
4 dirty word, but in the U.S. subgroup population of
5 women who have a BMI of, say, 24, did they have an
6 effect, was an effect seen with progesterone gel?
7 And then vice versa of the non-U.S. populations,
8 occasionally they must have somebody who has a BMI
9 of 29 in their subgroup who have a larger BMI. Did
10 you not see an effect in that non-U.S. population?

11 DR. CREASY: Excuse me while I try and get
12 the right slide here.

13 DR. HENDERSON: Sure, that's fine. I'm not
14 going anywhere.

15 DR. CREASY: We have a forest plot split
16 out -- we showed you the forest plot in the core
17 presentation of all of the data. We have forest
18 plots for the U.S. and the non-U.S. region, and
19 we'll find it shortly. So if we could come back to
20 this question, please.

21 DR. JOHNSON: Dr. Montgomery Rice.

22 DR. MONTGOMERY RICE: I will make a comment

1 before I ask the question to say that I am not a
2 proponent of off-label use of products.

3 Particularly, I would not promote that at this
4 meeting, but I have to talk about realism.

5 Now, Dr. Hassan who alluded in her
6 presentation -- I think she said that -- she gave a
7 number of the potential use of progesterone in
8 prevention of preterm birth and that it had become
9 standard use in your practice. Someone made a
10 comment. I can't remember which one. Dr. Hassan,
11 I'm sorry, made a comment that it had become
12 standard use in their practice. And so I'm just
13 being realistic.

14 I guess my question is, if we were to do a
15 head-to-head trial and we were to use micronized
16 progesterone vaginally as compared to vaginal
17 progesterone gel, do you believe that there would
18 be any difference in the outcome? Let's say that
19 we've both seen data that supports that in the
20 different trials, that they're both effective in
21 decreasing preterm birth.

22 So do you believe that there's something so

1 unique about this product that says that it will
2 produce a different -- I'll let you answer that
3 first.

4 DR. CREASY: Sure.

5 DR. MONTGOMERY RICE: And I really want one
6 of the clinicians to answer it.

7 DR. CREASY: And I'm going to get to that.

8 DR. MONTGOMERY RICE: Okay. And I'm not
9 saying you're not a clinician but one of the ones
10 who practice.

11 DR. CREASY: I just want to make sure I
12 understand the question. The question has to do
13 with formulation effects in vaginal dosing, as I
14 understand it, looking at head-to-head comparisons;
15 is 200 really equivalent to 90 given the difference
16 in the formulations?

17 We have a lot of experience with vaginal
18 dosing at Columbia Laboratories. We've had this
19 bioadhesive gel on the market for 14 years, and
20 there have been many, many studies in the
21 infertility space that help us understand what's
22 going on in this intravaginal topical application.

1 We know a lot more about the difference in doses
2 when it comes to dosing in infertility.

3 So if I may begin there, I'd like to ask
4 Dr. Yanushpolsky to talk about the difference in
5 the infertility space with regard to micronized
6 progesterone dosing and formulation differences.

7 DR. YANUSHPOLSKY: Thank you. I'm Elena
8 Yanushpolsky. I'm a reproductive endocrinologist
9 at the Brigham Women's Hospital in Boston, and I
10 have no interest in the product or the company, but
11 I'm a paid consultant for today. And the fertility
12 field has been using vaginal gel for quite many
13 years, and I personally have been involved with
14 multiple studies using this product for over a
15 decade.

16 So the pharmacokinetics have been known for
17 quite some time showing that the local effect and
18 levels of progesterone in the uterus are much
19 higher with vaginal administration compared to
20 intramuscular administration even though the
21 reverse is true for the serum levels. So that is
22 one thing, so this very elegant study with

1 hysterectomy specimens just demonstrated clearly.

2 We have looked at the comparison
3 between -- in our field, there have been
4 comparisons made between intramuscular
5 progesterone, intravaginal progesterone in the form
6 of suppositories and in the form of -- and by
7 Crinone, based on histological advancement of the
8 endometrium. And the vaginal suppositories, at the
9 dose of 200 milligrams three times a day, was
10 comparable to the intramuscular progesterone
11 advancement of the endometrium histologically. To
12 then transport this into the Crinone vaginal
13 preparation, similar histological results were
14 observed as well.

15 However, we are well aware in the fertility
16 field of the pharmacokinetic issues. But most
17 important results are the ones that are of clinical
18 outcomes to us. So with respect to dosing, the
19 doses that were looked at with respect to vaginal
20 gel is once a day preparation, which is presented
21 in the study, as well as twice a day preparation
22 granted in a different application. This is

1 fertility. However, this is a side-by-side
2 comparison from an Italian study using a once-a-day
3 and twice-a-day vaginal preparation. It showed no
4 difference in clinical outcomes for us, that is,
5 pregnancy rates. And I personally have been
6 involved with a larger study of once-a-day vaginal
7 gel use which demonstrated and published the same
8 results as a previously published study with twice-
9 a-day administration.

10 So the higher doses of vaginal preparations
11 don't seem to improve the efficacy, and once-a-day
12 doses are adequate and comparable with intravaginal
13 suppositories that have been used previously.

14 DR. CREASY: So I know you --

15 DR. MONTGOMERY RICE: Thank you for the
16 data, but that was not the answer to my question.
17 My question was, compared to vaginal micronized
18 progesterone suppositories that are inexpensive,
19 that we have compounded at multiple pharmacies that
20 we've used for years, compared to your gel that you
21 have, is there something unique. And from a
22 clinical outcome perspective, would we expect that

1 there would be a difference in those? Because
2 there are studies that looked at the micronized
3 progesterone. I don't remember the author, but it
4 was definitely a couple of papers that looked at
5 that, and they showed a comparable reduction in
6 preterm births.

7 So I'm trying to understand what makes this
8 one unique. And when we're talking about approving
9 this, if we know, as was stated by one of the
10 clinicians, that people are already doing this,
11 what is going -- what's the uniqueness?

12 DR. CREASY: I understand. I'm sorry that
13 this is taking so long to get to this.

14 if I may have this slide up.

15 I'm going to ask Dr. Hassan to speak in a
16 moment about the use in short cervix across the
17 trials. We don't have a head-on-head comparison in
18 short cervix. We do have head-on-head comparisons
19 in the field of infertility that Dr. Yanushpolsky
20 was just talking about, comparing the different
21 formulations.

22 So these are two studies that highlight the

1 differences in the infertility space between dosing
2 with a bioadhesive gel and dosing with some other
3 non-bioadhesive formulation. So in tablets, it
4 takes up to 300 milligrams a day to achieve similar
5 pregnancy rates. On the right here, the percent
6 there is the percent of the pregnancy rate in these
7 infertility studies. So the DUTY study showed
8 300 milligrams is equivalent to 90 more or less on
9 a clinical outcome.

10 With regard to the capsules, the study below
11 by Geber was a study of the same capsules that were
12 used -- I don't -- actually, that was a study in
13 Brazil. Whether it was Utrogestan or Prometrium,
14 I'm not sure. Very similar oil capsule, though,
15 with 200 milligrams of micronized progesterone. It
16 takes three of those a day or 600 milligrams in the
17 infertility space to get a comparable pregnancy
18 rate.

19 I'll ask Dr. Hassan to speak about --

20 DR. MONTGOMERY RICE: So what you're saying
21 is the benefit is that it's one-time dosing versus
22 three-times-a-day dosing. Now, before you -- let

1 me just clarify. I've done ART for 15 years, so
2 I'm very familiar with this. But I just want to
3 make sure that we're clarifying that you're saying
4 that your benefit that you're showing is it's just
5 a dosing, that's it's one-day dosing, once-a-day
6 dosing versus using a pill that's three times a
7 day.

8 DR. CREASY: Well, it's that, and in
9 addition, in the Geber study, that was three times
10 200 milligrams. So we're talking about, yes, once
11 a day and also a reduced dose. The bioadhesive
12 nature of our delivery system provides for a very
13 effective use of 90 milligrams that can only be
14 matched with other formulations by 300 or
15 600 milligrams. With oil capsules in particular,
16 it's 600 milligrams.

17 Whether this holds true in short cervix, we
18 don't know, but I think what we can say from our
19 own experience is that we deliver a very potent
20 dose of micronized progesterone in this
21 intravaginal topical delivery. And that potent
22 dose works very well in the infertility space where

1 we're trying to affect the endometrium. And it was
2 our prediction that in the prevention of preterm
3 births, that this would also be a very potent dose.
4 And across studies, it appears to be as potent as
5 at least a single dose of 200 milligrams in an oil
6 capsule.

7 But I can ask Dr. Hassan to comment, if you
8 like.

9 DR. MONTGOMERY RICE: Just on your clinical
10 experience, do you believe that whether a patient
11 uses this one 90-milligram potent dose compared to
12 twice-a-day dosing or three-a-day dosing with a
13 micronized progesterone compounded capsule or pill,
14 do you think there would be a different clinical
15 outcome?

16 DR. HASSAN: Well, we -- again speaking, we
17 believe that the -- as I said to you, we have
18 changed our practice in which we do universal
19 screening of cervical length, and we do administer
20 progesterone gel to women because of the findings
21 of the study; again, because of the efficacy
22 findings. And they use that every day, as you

1 said. A daily dose certainly would be more
2 accepted by the patient than multiple dosing.

3 In addition, that gel, they've found it to
4 be bioadhesive, and there's some preference to that
5 as well. And so those are some of the reasons
6 we've found that this is important for them.

7 DR. MONTGOMERY RICE: But you believe it's
8 based on patients' preference and not necessarily
9 on some mechanism of action that is ensuing with
10 the gel versus with the micronized progesterone
11 leading to the outcome?

12 DR. HASSAN: I do believe there is -- and
13 this is not based on evidence of mine, but in terms
14 of the efficacy that was shown in our trial was
15 moving towards the -- showing difference in
16 neonatal outcome, and this was the progesterone gel
17 that was tested as opposed to the Fonseca trial,
18 which was using other sort of micronized
19 progesterone, which did not demonstrate that.

20 So I do think because of the bioadhesive
21 gel, there could be that difference, although I
22 don't have a study to quote you on that.

1 DR. JOHNSON: Well, thank you.

2 We are going to return after lunch for our
3 public speakers. We will then have the opportunity
4 for Dr. Hoeger, Dr. Henderson, Dr. Orza, Dr.
5 Gillen, and Dr. Weinstein to ask their questions
6 and any others to the sponsor.

7 We will reconvene in this room at 1:00 p.m.
8 Do take your personal belongings with you at this
9 time. The ballroom is secured by FDA staff during
10 the lunch break. Panel members, do remember that
11 you should not discuss the meeting during lunch
12 amongst yourselves or with any members of the
13 audience. Thank you, and we'll see you back at
14 1:00.

15 (Whereupon, at 12:03 p.m., a luncheon recess
16 was taken.)
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18
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22

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

(12:03 p.m.)

Open Public Hearing

DR. JOHNSON: If we could get going, now we're at the beginning of our open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at an open public hearing session of the advisory committee meeting, the FDA believes it's important to understand the context of each individual's presentation. For this reason, the FDA strongly encourages you, the open public hearing speaker, at the beginning of your written or oral presentation to advise the committee of any financial relationship you may have with the sponsor, its product and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

1 Likewise, FDA encourages you at the
2 beginning of your statement to advise the committee
3 if you do not have any financial relationship. If
4 you choose not to address this issue of financial
5 relationship at the beginning of the statement, it
6 will not preclude you from speaking.

7 The FDA and this committee place great
8 importance on the open public hearing process. The
9 insights and comments provided can help the agency
10 and this committee in their consideration of the
11 issues before them. That said, in many instances
12 and for many topics, there are a variety of
13 opinions. One of our goals today is for this open
14 public hearing to be conducted in a fair and open
15 way, where every participant is listened to
16 carefully and treated with dignity, courtesy and
17 respect. Therefore, speak only when recognized by
18 the chair, and we do thank you for your
19 collaboration and cooperation.

20 So open public hearing speaker number 1, you
21 can step up to the microphone.

22 DR. GOLDSTEIN: Good afternoon. My name is

1 Mitchell Goldstein. I am a physician, a practicing
2 neonatologist, and associate professor of
3 pediatrics at Loma Linda University Children's
4 Hospital. I am also the immediate past president
5 of the National Perinatal Association and PAC/LAC.

6 I want to acknowledge that Watson
7 Pharmaceutical has paid for my travel here today to
8 this meeting. However, I have no financial
9 arrangements with them, nor do I have a financial
10 interest in the outcome of this presentation today.

11 As I mentioned, I'm an associate professor
12 at Loma Linda. I am a practicing neonatologist.
13 As such, I come from things from a very different
14 end of the spectrum, and that is that I take care
15 of the babies who are born prematurely, and a
16 certain numbers of these babies as well, who have
17 ongoing morbidities and mortalities as a result of
18 being born too early. It is for this reason that
19 this is a very important and very concerning topic
20 for me.

21 In listening to the presentations today, I
22 was struck by a concern for the adjustment of the

1 p-value and how the individual strata were adjusted
2 and how this information was obtained by FDA
3 statisticians. I am not certain as to how these
4 differences in strata and in particular how the
5 p-values might have altered from those that were
6 originally presented in the presentation.

7 There were some other concerns that I had
8 with respect to the presentations today insofar as
9 well, the fact that yes, the rate of prematurity
10 was lower in the placebo group than otherwise might
11 have been anticipated, but also in the fact that
12 there was a fairly large noncompliance number in
13 the actual treatment group; and how this relatively
14 large number, which was in the mid-20s may have
15 resulted in an adjustment that might have given
16 enhanced statistical significance if we had assumed
17 perhaps that there was 100 percent compliance
18 between the groups.

19 One of the concerns I have, again, as I had
20 mentioned previously, was the fact that as a
21 neonatologist, I take care of premature babies.
22 And it is the prevention of prematurity in

1 particular that is something that for me is a very,
2 very important topic.

3 I do have to acknowledge that if not for a
4 very avant-garde approach by my mother's
5 obstetrician 48 years ago -- he gave my mother
6 progesterone -- I might not be here today in the
7 sense that at that time, that therapy was new, but
8 it was understood that progesterone could possibly
9 help mothers who had had frequent losses or who
10 were unable to get pregnant to carry to term. And
11 I am perhaps the poster child for that particular
12 therapy.

13 My sense is that the role of vaginal
14 progesterone is very important in the prevention of
15 preterm delivery in moms who do have short
16 cervixes. Although there may be a question in
17 terms of whether one modality or another; or for
18 that matter, the vehicle is important. It is
19 important to take into consideration this issue of
20 noncompliance, and the issue of three doses per
21 day, or for that matter, one dose a day, or the
22 fact that perhaps a bioadhesive may in some ways

1 cause the progesterone to be more effective if one
2 dose perhaps is missed; so in essence, an every-
3 other-day treatment in a noncompliant woman.

4 Then finally, I would like to close with
5 just looking at it from the big picture. And we
6 talk here about morbidities, and we talk here about
7 mortality in babies who are born prematurely.
8 Let's talk about not only the primary outcomes but
9 also the secondary outcomes because prematurity of
10 any sort is not good for the development of a baby.
11 And we know this, and we have a national initiative
12 to prevent prematurity.

13 We need to acknowledge that a term baby has
14 much fewer complications than a preterm baby. And
15 whether this in terms of bronchopulmonary
16 dysplasia, retinopathy of prematurity, or other
17 morbidities, or the fact that in life, this child
18 succeeds, has a better job, is a better teacher, is
19 a better physician, is a better lawyer, is a more
20 important contributor to society, these things are
21 what are important.

22 Again, I would urge the FDA to consider this

1 issue for its full potential. Thank you.

2 DR. JOHNSON: Thank you.

3 Our open public hearing speaker number 3,
4 please.

5 MS. ROBINSON: Hello, I'm Maiysha Robinson.
6 I'm here to speak to you about my experience with
7 the progesterone gel versus my experience without
8 it. Watson provided my transportation here.

9 In 2008, I was pregnant with my first child
10 when I learned my cervix was shortening rapidly.
11 The doctors discussed my options with me, and I was
12 enrolled in a 2008-2009 short cervix trial. Not
13 knowing if I was receiving a progesterone or the
14 placebo, I used the gel every night like I was
15 told. My pregnancy went 38 weeks, which is full
16 term medically, and I delivered a 6 pound, 4 ounce
17 healthy baby girl named Maonie (ph).

18 Two years later, I was pregnant with my
19 second child, and again, my cervix was shortening
20 rapidly. The doctors discussed my options, which
21 were few. I asked Dr. Kindawell (ph) about my
22 results from the trial. Did I receive the

1 progesterone gel or the placebo? She told me I
2 received the progesterone gel. However, they were
3 no longer running that trial, so they couldn't just
4 give me the gel.

5 They contacted my insurance company to try
6 to get me the progesterone gel, but my insurance
7 company wouldn't pay for it. There is no way I can
8 afford for pay for it. Dr. Kindawell and her
9 assistants tried everything possible to get me that
10 gel. Even though it worked for me but because it
11 wasn't FDA approved, my insurance company would not
12 pay for it.

13 My only option was to get the cervical
14 cerclage, what lasted for two weeks and caused in
15 infection in my body as well as my baby's. So at
16 25 weeks, I gave birth to a 1 pound, 13 ounce baby
17 girl. I named my baby Myasia (ph). Maiysha was 13
18 inches long, had grade 3 bleeds on her brain, had
19 trouble breathing and had to stay in the incubator
20 for two and a half months. I had to stay in the
21 hospital for two weeks due to a serious infection
22 caused by the cerclage.

1 After two and a half months, Myasia finally
2 came home from the hospital. The breathing tube in
3 her throat compromised her airways and caused
4 tracheomalacia. She has to take nebulizer
5 treatments with Albuterol and Pulmicort daily.
6 Just a cold makes it really hard for her to
7 breathe.

8 Myasia is developing slower than her sister.
9 She has physical therapy once a month to help with
10 her motor skills. She is growing stronger every
11 day. By the graces of God and the doctors and
12 nurses at Cooper Hospital, she survived, and right
13 now she's a small but healthy 10-month-old. Though
14 she is classified as special needs, I'm doing
15 everything possible to promote her physical and
16 mental development so by the time she starts
17 school, she can be placed in normal classes.

18 I ask that the FDA please approve the
19 progesterone gel because it can help other mothers
20 that have a short cervix and may be at risk for
21 preterm birth. It helped during my first
22 pregnancy, and I wish I had it during my second

1 pregnancy to prevent everything we went through.

2 So again, I ask that you take what I'm
3 saying into consideration because the next mother
4 may not be as lucky as I was. All mothers should
5 have the choice to use the progesterone gel and
6 have healthy babies. Thank you.

7 DR. JOHNSON: Thank you very much.

8 And now public speaker number 4.

9 MR. SIEGEL: Good afternoon. I would like
10 to just acknowledge that Watson did provide my
11 transportation here today for this meeting, but
12 that I'm not being compensated in any further way
13 for my opinion today.

14 I am here to speak about the pandemic of
15 premature birth as it relates to my personal
16 experience and the frightening statistic that
17 12 percent of all live births are preterm, one in
18 eight babies in this country every year.

19 The perinatal stats show only nominal
20 improvement in the most recent year, largely
21 attributed to an increased awareness of specific
22 healthy pregnancy initiatives such as smoking

1 cessation programs and managing gestational
2 diabetes.

3 My experience with prematurity began six
4 years ago. My daughter was born at 27 weeks
5 gestation, weighing less than 2 pounds. She was
6 immediately treated for respiratory distress
7 syndrome. During her nearly two-month stay in the
8 hospital neonatal intensive care unit, she was
9 treated for multiple medical issues, including
10 cardiac, pulmonary and ophthalmologic. Subsequent
11 to hospital discharge, she was treated in
12 outpatient programs for persistent respiratory and
13 orthopedic complications.

14 The costs of my daughter's medical care
15 during her first year exceeded \$1.15 million.
16 Today at six years of age, she is still treated in
17 a comprehensive physical therapy program, a cost I
18 share with my municipality's school district. The
19 very high costs for treating children born too soon
20 is a burden to our healthcare system, including
21 insurers and employers as well as society at large.

22 During the past six years, my daughter has

1 spent countless hours with doctors, nurses and
2 therapists in a variety of specialties. My wife
3 and I have attended every appointment for treatment
4 and evaluation. It is difficult to determine the
5 costs of my time away from work, not to mention
6 that time which my daughter has lost from school or
7 beneficial play with friends.

8 I came here today from New Jersey to ask the
9 FDA and this committee to do what is necessary to
10 address this pandemic of premature birth. If your
11 most difficult day of life was your first, you'd
12 beg for attention to a problem which affects more
13 than a half million babies and families every year
14 in the United States. I'm speaking for those
15 smallest citizens who have no voice.

16 If you've ever looked upon a low birth
17 weight child in distress, you'd undoubtedly feel
18 compelled to take action. I watched my own flesh
19 and blood struggle for every breath. This
20 experience has changed me permanently, and I hope
21 that by speaking of my family's experience, there
22 can be positive change for the millions of babies

1 yet to be born. Any treatment option that would
2 spare other families the issues that we had is
3 vital and would be welcome.

4 My story has a happy outcome. This is due
5 to many years of research, medicine, technology and
6 resources of thousands. I thank you for the
7 opportunity to speak today and for your thoughtful
8 consideration of treatment options for preterm
9 birth.

10 DR. JOHNSON: Thank you.

11 Open public speaker number 5.

12 MS. MEEHAN: Good afternoon. My name is
13 Judith Meehan. I'm the CEO of the National Healthy
14 Mothers Healthy Babies Coalition. And thank you
15 for the opportunity to speak on the topic that is
16 of crucial relevance to the families that we serve.

17 I'd like to disclose that in 2011, our
18 charitable and nonprofit organization received an
19 unrestricted educational grant from Watson
20 Pharmaceuticals. Consistent with our mission, this
21 support was for the purpose of conducting
22 educational activities to inform our constituents

1 about emerging science and preterm birth
2 prevention.

3 Our coalition was started after the Surgeon
4 General's conference in 1981 focused on infant
5 mortality, recognizing a need for communication
6 across the disciplines about the many issues that
7 contribute to a child's chances at a healthy start.

8 Three decades later, infant mortality is, of
9 course, still a critical problem. Prematurity has
10 emerged as a crisis within a crisis. Of course,
11 prematurity is integral to the devastating reality.
12 Many children born here in the United States do not
13 make it to their first birthday.

14 For those that do survive and even for those
15 born very late preterm, prematurity comes with
16 lifelong challenges for affected babies and their
17 families. Being born too small and too soon puts
18 an individual at risk for a host of health issues.
19 It has made life with disability a reality for
20 millions of Americans, and with approximately half
21 a million babies being born prematurely each year,
22 it makes the need for solutions to the problem

1 immediate and drastic.

2 For the professionals we serve, the National
3 Healthy Mothers Healthy Babies Coalition offers a
4 form to share science and start a dialogue when
5 information critical to the health of mothers,
6 babies and families becomes available. Over the
7 decades, we have seen exciting, incredible
8 advancements. We've mobilized our partners to
9 educate about new vaccines, vaccines that prevent
10 disease and save lives. When experts have
11 translated data into guidelines, we've had real
12 resources to keep kids safer in cars.

13 In the case of these issues, the science has
14 offered tools, strategies and solutions. Up until
15 now, we've not had this kind of powerful ammunition
16 to fight the prematurity crisis. How hard it is to
17 know just how harsh the reality might be, yet not
18 have solid footing around prevention, real
19 explanations and innovations that a mom can use to
20 increase her chances for the best possible birth
21 outcomes.

22 We hope that the science in front of you

1 offers that, answers, promises and potential, a
2 start at solving the prematurity crisis. We know
3 these studies and the volume of knowledge the
4 research represents may have very broad impact and
5 thus require even more careful consideration.

6 National Healthy Mothers Healthy Babies
7 Coalition thanks you for your thorough review of
8 the science. We thank you for looking to the
9 experts whose careers in obstetrics offer context,
10 more about weighing risk, including the risk of
11 inaction any longer.

12 Every woman deserves to have the
13 information, diagnosis, and treatment available to
14 give her child the best possible start in life.
15 This research and its review stands to affect
16 millions of women contemplating or planning a
17 pregnancy someday as well as those who are today
18 awaiting the arrival of a child, possibly at great
19 risk. Thank you.

20 DR. JOHNSON: Thank you very much.

21 Open public hearing speaker number 6.

22 MS. RYAN: Hello, my name is Kate Ryan. I'm

1 with the National Women's Health Network. It's a
2 nonprofit advocacy organization that works to
3 improve the health of all women. We bring the
4 voices of women consumers to the policy and
5 regulatory decision-making bodies. We are
6 supported by our members and don't take financial
7 contributions from drug companies, medical device
8 manufacturers, insurance companies, or any entity
9 with a financial stake in women's health
10 decision making.

11 As acknowledged by everyone here today,
12 preterm birth is a terrible problem for women and
13 babies and is the most frequent cause of infant
14 death. And, of course, the children who do survive
15 are at increased risk of serious long-term health
16 problems. We also understand that one in eight
17 births are premature and that this number has been
18 steadily increasing over the last 30 years.

19 Of course, women who face this problem want
20 safe and effective preventive treatment options.
21 And as the problem has grown, drug developers have
22 been increasingly interested in finding products to

1 meet this need. Unfortunately, however, there's
2 been negligible success.

3 Many companies have tried and failed to
4 develop safe and effective preventive treatment for
5 preterm labor, and many of the preventive
6 treatments recommended to women today have been
7 shown not to work. There is only one FDA-approved
8 product to prevent preterm labor in women with a
9 history of preterm birth, and it's only moderately
10 effective.

11 As the FDA noted in the background document
12 for this meeting, several drugs are prescribed off
13 label to prevent preterm birth, and there is no
14 evidence that these treatments actually work to
15 prevent early births. Furthermore, some of the
16 drugs that have been used off-label for this
17 purpose have serious risks, and women have died as
18 a result of using them in an effort to sustain
19 their pregnancies long enough to give birth to a
20 healthy child.

21 Women deserve safe and effective treatments
22 for preventing premature birth, not a potential

1 pipe dream and not a product that would threaten
2 their health or the health of their future
3 children.

4 The progesterone gel that the advisory
5 committee is evaluating today is also one of the
6 failed products I just mentioned. As was discussed
7 this morning, the company did a trial testing this
8 exact gel for preventing preterm birth in women
9 with a history of preterm and failed to show it was
10 more effective than the placebo. But thinking
11 there might be something more promising hidden in
12 those results, the company did this second trial,
13 looking at a more narrowly defined group of women,
14 those with a short cervix. And they've tried to
15 show that this progesterone gel was effective in
16 the subset.

17 But the results we see today show that,
18 unfortunately, the sponsor was unable to provide
19 evidence that this treatment works, even in the
20 smaller group. Instead, the company is essentially
21 putting forward a theory that it might work in some
22 women.

1 When unmet health need is so great, we
2 understand that many concerned people, women,
3 clinicians and drug developers, may be willing to
4 accept a moderately or even minimally effective
5 product as long as it's safe. But we're concerned
6 that this gel may not, in fact, be minimally
7 effective or even effective in a narrow group of
8 women, but rather that it isn't effective at all
9 for anyone.

10 We went through the data, and we agree with
11 the FDA's assessment that the progesterone gel did
12 not reduce preterm labor more than the placebo for
13 women at the U.S. trial sites at any gestational
14 age. And although analysis showed a reduction in
15 preterm labor in the non-U.S. population at
16 specific gestational ages, other FDA analyses
17 failed to show the gel was more effective than the
18 placebo. And it's possible, even likely, that the
19 effectiveness finding is simply a coincidence.

20 Additionally, the explanations proposed by
21 the sponsor to explain the discrepancy between the
22 U.S. and non-U.S. efficacy results don't stand up

1 to rigorous analysis. First, the sponsor suggested
2 a lower compliance among U.S. women was to blame
3 for the lack of effectiveness; yet the FDA analysis
4 excluding women who were less than 80 percent
5 compliant, I believe, showed that there was no
6 difference between the treatment and the placebo.
7 And the sponsor also suggested that the lack of
8 effectiveness in the U.S. could be explained by
9 higher rates of chorioamnionitis, but when these
10 cases were excluded from the analysis, the results
11 still remained nonsignificant for U.S. women.

12 In short, the data doesn't support this
13 explanation. We understand the temptation to grasp
14 at straws when trying to find something to help
15 create these very wanted families, but giving women
16 false hope or unproven treatments is not the
17 answer. Women deserve better.

18 We recognize and appreciate that the sponsor
19 collected strong data to support the safety of its
20 product for women and their children, and we are
21 encouraged that the two-year infant follow-up study
22 suggests no long-term impact of maternal treatment

1 with progesterone gel.

2 Unfortunately, however, drugs taken during
3 pregnancy to prevent preterm birth have had a
4 tragic history in this country. As one of the
5 committee members noted this morning, millions of
6 women were exposed to DES, and their daughters and
7 granddaughters are still suffering negative health
8 outcomes as a result.

9 Consequently, even if we felt this product
10 were effective and were recommending approval, we'd
11 still urge the FDA to require long-term post-market
12 safety studies following those exposed to this
13 product and would probably recommend the
14 establishment of registries to better facilitate
15 follow-up.

16 But in conclusion, we need to have more than
17 theories before recommending that women take this
18 drug to prevent preterm labor. We need evidence.
19 And as the FDA warned in its report, if a drug is
20 to be approved based on a single trial, there must
21 be robust statistical evidence that the product is
22 safe and effective, and that's just simply not the

1 case here. Thank you.

2 DR. JOHNSON: Thank you very much.

3 Now if speaker number 7 would come up for
4 the open public hearing.

5 MS. PAUL: Thank you and good afternoon. My
6 name is Kai Paul, and I participated in the
7 progesterone gel clinical trial. Watson has
8 provided my trial here today, but I am not being
9 paid or my participation nor my opinion.

10 It is my pleasure to have this wonderful
11 opportunity to stand here today to represent the
12 outstanding and tremendous results of this medical
13 breakthrough. In November of 2010, I was
14 expecting. I was about five months pregnant when I
15 was diagnosed having a short cervix, which put me
16 in a category of having a very, very high-risk
17 pregnancy, and I was sent to the hospital
18 immediately that day.

19 I didn't fully understand exactly what they
20 had diagnosed me with at the time, but the doctors
21 at the hospital told me that there was a
22 possibility that my unborn child could

1 spontaneously abort or I could deliver him
2 prematurely. I was terrified. It seemed as if my
3 world just came crashing down, and there was no
4 solution to this besides bed rest alone with only
5 bathroom use.

6 I had been in nursing school. I was forced
7 to drop out. I had no other choice. In one day,
8 my life completely changed. It wasn't until a few
9 days after being in the hospital and had a regular
10 scheduled appointment where I went to the clinic
11 and I was approached by two nurses who were
12 involved in the recruitment process for the
13 clinical trial study, where they explained to me
14 that there was some exciting news that could
15 possibly, just possibly give me a chance to have a
16 full-term pregnancy and to have a healthy baby. I
17 immediately jumped up on the opportunity.

18 What they explained to me about the clinical
19 trial really was -- it was no hassle to me at all.
20 Even being on strict bed rest, it was no hassle at
21 all. It just involved a simple application at the
22 same time every night, and that was it, a

1 gel-filled applicator, and that was it.

2 I have always been a believer in medical
3 research. And to know that there was a
4 possibility, that there was just something out
5 there that could just give me a chance to have my
6 son full-term, I was all for it. And again, today,
7 I am still for it.

8 I continued using the progesterone gel
9 roughly until around 37 weeks pregnant. About that
10 time, my cervix had stabilized. Everything was
11 fine. And again, on February 27th of 2011, I had a
12 wonderful bouncing baby boy, and his name is Chase.

13 Again, me and Chase just ask that you just
14 give this opportunity to mothers that are like me,
15 future moms, you want to be a mom, you imagine or
16 dream of being a mom, just give them an opportunity
17 to have the same opportunity of the progesterone
18 gel that I did. And thank you.

19 DR. JOHNSON: Thank you very much.

20 Now for open public hearing speaker
21 number 8.

22 DR. DATTEL: Good afternoon. Bonnie Dattel,

1 I'm a maternal fetal medicine specialist, professor
2 and assistant dean in Eastern Virginia Medical
3 School in Norfolk, Virginia. My travel today was
4 paid by Watson, and I was an investigator in both
5 the 300 and 302 trials. However, I am not here to
6 speak as an investigator but rather as a
7 practitioner of maternal fetal medicine in a very
8 high-risk area for preterm delivery. I have spent
9 the great bulk of my career treating women for
10 preterm labor and preterm delivery. And, in fact,
11 the last 24 hours in the hospital, I was doing that
12 in Norfolk just last night.

13 It is a problem that we have not had a dent
14 in despite decades of research and multiple
15 different therapeutic modalities that we have
16 attempted to try to arrest preterm labor and effect
17 longer gestational ages in women who present with
18 signs and symptoms or with short cervix.

19 In today's world with the newer technologies
20 that we have, the use of ultrasound for the ability
21 to detect short cervix, we have a new avenue in
22 which to perhaps prevent preterm delivery for

1 women. The use of vaginal progesterone appears to
2 be a very exciting avenue for this. I think the
3 data supports very much that it's efficacious both
4 in international trials and in the trials that were
5 performed in the United States.

6 The ability to have women receive this
7 progesterone trial and achieve a term delivery is
8 extremely important. The population of women that
9 I deal with in Norfolk, Virginia is an extremely
10 high-risk urban population, and we found that the
11 use of vaginal progesterone was one that was
12 appealing and one in which patients would have a
13 relatively high compliance versus some of the other
14 modalities for the treatment of preterm labor, many
15 of which do not have as much efficacy.

16 Despite some of the misgivings of the data,
17 I think that the safety profile of this particular
18 product as well as the efficacy margin of it
19 supports its use, and I urge the FDA to give
20 approval so that we have something more in our
21 armamentarium to prevent preterm birth,
22 particularly in women with a presence of a short

1 cervix. Thank you.

2 **Clarifying Questions (continued)**

3 DR. JOHNSON: Thank you very much. I would
4 like to thank all the public speakers for the
5 opportunity to provide their information. We have
6 now concluded our open public hearing portion of
7 our meeting, and we no longer can take comments
8 from the audience.

9 Now we have time to move to clarifying
10 questions to the presenters, either the sponsors or
11 the FDA. And I would like to start off with
12 Dr. Hoeger.

13 DR. HOEGER: Thank you.

14 My question was to the pharmaceutical
15 company. We talked a little bit about this before
16 the break, and I wanted to just follow up with a
17 formulation question regarding the use of the
18 progesterone gel versus the data that were provided
19 in the meta-analysis with the progesterone
20 compounded. And I would just comment that the data
21 that you provided for fertility really wouldn't be
22 particularly relevant since we're looking at a

1 different endpoint. And as well, endometrial
2 levels would not be something that would be
3 particularly relevant in the preterm labor
4 discussion.

5 So is it your -- do you have a hypothesis
6 about the effects on the cervix itself with respect
7 to the formulation of progesterone or just
8 progesterone in contact with the cervix?

9 DR. CREASY: So if I understand your
10 question, it's about the effects of the bioadhesive
11 gel and the progesterone in it against the cervix
12 since the data that we showed earlier was more of
13 in the infertility space?

14 DR. HOEGER: Yes, that was endometrial
15 levels, I think.

16 DR. CREASY: Yes, okay. I realize that was
17 a very long explanation, and we didn't really
18 finish it very well. But the point is that the
19 mechanisms that were discussed earlier in our
20 presentation this morning by Dr. Murtha are all
21 very local cellular mechanisms, metalloproteinases,
22 inflammation, and so forth and that the vaginal

1 local application of progesterone works very well
2 in the endometrium and will also work very well
3 against the cervix. And it's for that reason that
4 it's being applied locally, having a good impact
5 locally. That's why we saw the delay in cervical
6 shortening in the 300 study, that pharmacodynamic
7 effect to slow the shortening between 20 and 28
8 weeks, and that's why we were seeing an effect
9 overall in Study 302 to delay birth at 33 weeks, a
10 44 percent reduction.

11 DR. HOEGER: But do you hypothesize there's
12 a difference between the gel and the micronized
13 progesterone?

14 DR. CREASY: Well, the gel contains
15 micronized progesterone, and there is -- we have no
16 head-to-head study.

17 Let me ask Dr. Murtha to address this.

18 DR. MURTHA: Amy Murtha, just for
19 reintroduction. I am actually glad to have the
20 opportunity to address this question.

21 So we don't have a head-to-head comparison,
22 obviously, of the 200 milligrams of micronized

1 progesterone compared to the Crinone. Obviously,
2 we don't have that data.

3 I think just as a sort of general point in
4 pregnancy, as a clinician, I always like to use the
5 lowest possible dose for any medication that I use
6 in pregnancy. And so if it's possible to get away
7 with 90 milligrams and it's effective, then that's
8 what I would prefer as an obstetrician. And I
9 think anytime we can expose at a lower dose, it's
10 better.

11 I think from a practical perspective, in our
12 practice at Duke what we have been doing since I've
13 been there, which is nearly 20 years, is we've been
14 screening cervical length using transabdominal
15 ultrasound and then following up with an
16 intravaginal ultrasound if the cervix is short.
17 And now since the Hassan trial has come out, we've
18 actually been offering vaginal progesterone.

19 From a very practical perspective in that
20 setting, it's very difficult for us to get that
21 product for most of our patients where the
22 insurance companies won't pay for it. If we try to

1 get Crinone, which we have been able to do with
2 some insurance companies, it takes a little bit of
3 time to be able to do that. And as an alternative,
4 we'll certainly use the micronized 200-milligram
5 compounded vaginal suppository.

6 I think some have concerns about what you're
7 actually getting when you get a compounded drug and
8 whether or not there's variability in the amount of
9 drug that's in that product. And we don't really
10 have a way of knowing that. So from an access
11 perspective, it would be a whole lot easier to have
12 an FDA-approved product.

13 Does that answer your questions? I hope
14 that it actually answers a couple people's
15 questions.

16 DR. JOHNSON: Dr. Henderson.

17 DR. HENDERSON: To the sponsor, Dr. Hassan,
18 you said when you're screening the cervix for
19 cervical length, when are you doing this? This is
20 when you do your routine anatomy scan, or you
21 schedule a separate cervical screening session?

22 DR. HASSAN: We have moved to try to make it

1 that all patients get their anatomy scan for
2 convenience of the patient and obviously, the
3 system.

4 DR. HENDERSON: What gestational ages would
5 you do this?

6 DR. HASSAN: We would recommend it between
7 19 and 23 and six-sevenths weeks.

8 DR. HENDERSON: One more question. One of
9 the public speakers said that they were on bed rest
10 after they started getting -- were enrolled in the
11 study. Was that part of the protocol, that they
12 were maintained on bed rest?

13 DR. HASSAN: No, it was not part of the
14 protocol. There was no standard with regards to
15 the issue of bed rest because I know that there is
16 no efficacy that has been demonstrated for that.

17 DR. HENDERSON: Thank you.

18 DR. JOHNSON: I had just a comment from
19 Dr. Montgomery Rice.

20 DR. MONTGOMERY RICE: We keep talking about
21 the micronized progesterone, but correct me if I'm
22 wrong, in the Forson (ph) study -- was that --

1 Fonseca study was 100 milligrams?

2 DR. HARRIS: Two hundred.

3 DR. MONTGOMERY RICE: 200 milligrams.

4 DR. HARRIS: QHS.

5 DR. MONTGOMERY RICE: QHS.

6 DR. HARRIS: Once-a-day dosing.

7 DR. MONTGOMERY RICE: But it was a once-a-
8 day dosing.

9 DR. JOHNSON: Now, at the request, we're
10 going to take a short break from our questions.
11 The FDA has requested that we allow an individual
12 to make comments in regards to the meta-analysis.
13 I would like to ask Dr. Romero to come up to the
14 microphone, Dr. Romero.

15 DR. ROMERO: Good afternoon, and I would
16 like to thank the officials for the FDA for the
17 opportunity to speak. I'd like to identify myself.
18 I'm Roberto Romero. I'm chief of the perinatology
19 research branch of NICHD. I am here in sponsored
20 travel for those know what that technicality is,
21 and I have spoken to my director who has authorized
22 for me to speak today.

1 During the presentations this afternoon,
2 there were some references to an individual patient
3 meta-analysis in which I am the presenting author.
4 And there were four statements that were made that
5 I think that need to be corrected because there
6 were incorrect statements.

7 The first was about the purpose of the
8 meta-analysis was to identify studies in which
9 women with a short cervix were randomized to
10 progesterone or placebo. One of the statements
11 that was made is an individual considered in that
12 one study was not included. That was the study of
13 Fonseca conducted in Brazil.

14 Fonseca is one of the authors of our paper.
15 The reason why that paper was not included in the
16 meta-analysis is because he did not measure the
17 cervix. So if he did not measure the cervix, it
18 cannot be included in our meta-analysis.

19 The second statement was made, I believe, I
20 want to interpret that is not a question of a
21 statement being in the false in the paper, but our
22 interpretation would be considered by an individual

1 to be false. And the statement was we recommended,
2 based on the conclusions of our meta-analysis, that
3 90 milligrams was reduce the rate of preterm birth
4 and the rate of complications. And we recommended
5 the 90 milligrams is an adequate dose because it's
6 the lowest dose of progesterone. We compare 90 and
7 100 versus 200. We did a p for interaction, and
8 there was no difference between the doses. When
9 there is no interaction, then the effectiveness is
10 the same with all the caveats of our analysis.

11 The third point that was made is one of our
12 arguments was characterized as weak. We were
13 commenting on the differences between the gel and
14 the suppositories. A practicing clinician will
15 know that when we place a suppository in the
16 vagina, because of the temperature, it will melt.
17 With a gel, that doesn't happen because the
18 bioadhesive gel is applied to the wall of the
19 vagina. So frequently, when we place a suppository
20 of a tablet, patients expel part of the dose from
21 the vagina. So those are the four statements.

22 The last point that was made is that we

1 infer effectiveness as a function of cervical
2 length, and that is not correct.

3 Let me say that I don't have any conflict of
4 interest. I'm entirely funded by NIH, and I came
5 as a member of the public. And I thank you very
6 much for the opportunity to clarify these points.

7 DR. JOHNSON: Thank you, Dr. Romero.

8 Now, Dr. Orza.

9 DR. ORZA: I wanted to follow up on two
10 points from the public comment session. One, you
11 already alluded to about the bed rest. Is there
12 any way to tell, if it wasn't part of the protocol,
13 how many women or which women were on bed rest
14 and/or some other intervention in addition to the
15 study drug? That's the first one.

16 DR. CREASY: We didn't capture information
17 about the local medical care, bed rest and so forth
18 in the trial. We assumed that the randomization
19 process would take care of that, and that at each
20 center, whatever the local trend or tendency was
21 with regard to bed rest or not, that that would
22 tend to sort out between the two treatment groups.

1 So we didn't capture that.

2 DR. ORZA: Is it a possible explanation for
3 the kind of dramatic differences between centers?

4 DR. CREASY: I'm going to let Dr. Hassan
5 answer that question.

6 DR. HASSAN: So with regards to the bed
7 rest, there has been no evidence that bed rest
8 makes a difference in outcome, so we would not
9 expect that bed rest would have an effect on the
10 outcome of preterm birth.

11 DR. ORZA: And then the second was related
12 to my question from this morning about whether we
13 have any data from the 14 years of experience with
14 this drug on children further out, and specifically
15 whether there are any reproductive effects in girls
16 that are -- do we have any way of even looking for
17 that?

18 DR. CREASY: In the data that has been
19 collected over the 14 years, we don't really have
20 data that would go out that far. As a sponsor of a
21 drug, of course, we participate actively in the
22 collection of spontaneous reporting. The field

1 people are always on the lookout for anything they
2 hear about an adverse event, so they can encourage
3 physicians to report it. All we have are the
4 spontaneous reports, and within that database,
5 there's no evidence of any problem. But there have
6 been no prospective studies.

7 DR. ORZA: But something like a change in
8 the age of menarche, for example, is not something
9 that would show up in spontaneous adverse event
10 reporting.

11 DR. CREASY: Well, possibly not because
12 there's such a variation in the range of the start
13 of menarche that it may not be noticed, small
14 changes in that. I would have to agree with you
15 there.

16 DR. HENDERSON: Dr. Gillen.

17 DR. GILLEN: Thank you.

18 I wonder if we can bring up the sponsor's
19 slide CE-49? I just wanted to add really a comment
20 and clarification on it. I think it's worth
21 noting.

22 So the reason I wanted to bring this up is I

1 think that we're talking a little bit about apples
2 and oranges on this particular slide, and I wanted
3 to make it clear, at least my understanding of
4 what's happening here.

5 There's a comment that's being made as to
6 whether we should be pooling by study site and
7 looking at an adjusted overall summary measure
8 across study site strata and risk strata, which is
9 the CMH test that was done originally. And arguing
10 against that is this idea if you have small sample
11 sizes in these strata, it's difficult to tell if
12 you have large heterogeneity. And if you have
13 large heterogeneity, perhaps a summary measure
14 across all is not the best thing to be doing. And
15 that's kind of what our purview is here, is to
16 think about heterogeneity and consistency across
17 the key subgroups.

18 I bring it up just because the response is
19 that, well, the Mantel-Fleiss statistic says it's
20 okay. Well, that's not actually what that's
21 testing. That's not what that's saying. That's
22 actually an asymptotic approximation to the test,

1 okay? It doesn't tell us scientifically what we
2 should be focusing on.

3 In my reading of this, I think while one
4 message can be construed as saying is this an
5 appropriate test, it is if you're willing to take
6 the overall summary measure, then the Mantel-Fleiss
7 is saying that the statistic can be applied. But
8 again, I think that there is two questions here.
9 One is do we really want to summarize things as one
10 particular summary measure or relative risk between
11 the two treatments groups, and then the other is if
12 we've decided to do that, is this test appropriate.

13 So that's really just a comment because I
14 don't think it came through necessarily, and I'm
15 happy for rebuttal.

16 DR. PHILLIPS: Yes, this is Jim Phillips
17 again. Yes, perhaps it was not stated clearly, but
18 the purpose of that Mantel-Fleiss statistic, which
19 as you mentioned, just for the approximation of the
20 chi-square, we did do a Breslow-Day test, which was
21 also prespecified at the protocol, and we obtained
22 a result for that test. And we got a p-value of

1 .184.

2 Subsequently, in a post hoc analysis, we
3 applied a Zelen's test, which is an exact
4 counterpart to that. And we got something a little
5 bit higher, .254. So we're somewhat encouraged by
6 that, but that doesn't really answer the question
7 because that test is low powered, and even if we
8 gather evidence against heterogeneity, it doesn't
9 say that they're homogenous.

10 So when we look at the distribution of the
11 18 strata -- slide up, please -- so this
12 represents -- actually, there's 15 strata because
13 when you multiply the nine study sites by the two
14 risk strata, there are three of these strata that
15 don't have any observations in the preterm birth
16 strata.

17 Now, this slide is a forest plot of the risk
18 difference, but it would be similar by looking at
19 the odds ratios or the relative risks in terms of
20 the dots on the left and the dots on the right.
21 And so these aren't in a rank order presentation;
22 they're just sort of arbitrarily according to the

1 nine and the two risk strata.

2 But the key thing is that 10 out of 15 of
3 these sites were in the favor of progesterone, and
4 five of them were in favor of placebo with -- if
5 you recall, the nine primary sites that were
6 presented earlier, sites 3 and 7 were the ones
7 favoring placebo, the one in the U.S. and the one
8 in the non-U.S. And so those two sites are also
9 represented. Both of those strata were also on the
10 wrong side with one additional strata.

11 But we think that -- or I think what this
12 data shows us is that what's important for the
13 Cochran-Mantel-Haenszel test in terms of its
14 interpretation of summing across the strata is that
15 the vast majority of the treatment effect is in the
16 same direction, not necessarily whether the odds
17 ratio is actually equal to one across the entire
18 thing. I don't know that that's a reasonable
19 expectation for any stratification factor, but that
20 the magnitude of the order goes in the same
21 direction.

22 Then furthermore, just to -- as the previous

1 slide that you were pointing out had, was that we
2 also -- to further confirm the issue of small
3 sample size and distributional assumptions and
4 directionality was the exact test, and that also
5 was conducted to further allay concerns about
6 issues with the sorts of distributional assumptions
7 going on.

8 DR. GILLEN: I agree, and I thank you for
9 the additional information on the within strata
10 point estimates. I mean again, there are two
11 different issues, and going back to the last one,
12 the exact test is saying after you've gone ahead
13 and chosen to summarize these across all strata,
14 should we be looking at the small sample versus
15 large sample?

16 DR. JOHNSON: Dr. Weinstein.

17 DR. WEINSTEIN: I appreciate Dr. Hassan's
18 enthusiasm for the progesterone gel, but what I'm
19 concerned about and don't understand is your center
20 had exactly the same results on placebo versus gel,
21 20.8 versus 20, according to the data that we were
22 shown. And yet you seem to have established a

1 standard of care because you said it's done in all
2 patients.

3 I'm curious with your enthusiasm, how do you
4 give informed consent in an unbiased manner, and
5 who is paying for this since it's something that
6 has not been accepted at many other centers yet?

7 DR. HASSAN: So our site was probably the
8 largest site in the trial, and we had a study that
9 was powered for 450 subjects. I would not expect
10 to see a difference in 49 patients at our site. We
11 have significant confidence in the results of the
12 trial as it relates to the 44 percent reduction in
13 the risk of preterm birth less than 33 weeks, based
14 on all the prespecified sensitivity, the primary
15 endpoint analysis, as well as the sensitivity
16 analyses.

17 So based on that result, we are going
18 forward with that treatment plan. And we're not
19 the only center. I think others amongst us here
20 today and others around the country have moved
21 towards universal screening and the use of
22 progesterone to these women with a short cervix

1 because the evidence is compelling.

2 DR. WEINSTEIN: But how do you give unbiased
3 informed consent because you've already made a
4 decision, and you've stood here and almost implied
5 it is the standard of care, which I don't think a
6 lot of us would necessarily agree that Wayne State
7 sets the standard of care.

8 But how do you give unbiased informed
9 consent? I'm curious how you do that.

10 DR. HASSAN: So I wouldn't want to -- yes, I
11 did not give the impression that Wayne State is
12 setting the standard of care for the country, but
13 myself as well as others around the nation, other
14 centers -- we're not the only one -- have also
15 moved to this universal screening.

16 We consent the patients by saying to them
17 these are the results of the study of Fonseca as
18 well as the study that we have just presented today
19 with great confidence in the results. And again, I
20 will have my colleague come up as well and speak
21 from a person that wasn't an investigator in the
22 trial.

1 So we give them that information, and we are
2 confident that we are giving them informed consent.
3 We additionally add the point that there is minimal
4 risk to this medication, and that is something that
5 they appreciate as well, and that the use of it is
6 also very fairly easy for them to do on a daily
7 basis.

8 So when we see the ability to decrease
9 preterm birth, as you know and others know as well,
10 then we use this treatment that we think is very
11 promising that has been shown in 2007 by Fonseca as
12 well by us to try to decrease the rate of preterm
13 birth.

14 But I will let Dr. Murtha speak as well
15 since she was also not an investigator in the
16 trial.

17 DR. MURTHA: So I think as I said before,
18 we've been looking at the cervix transabdominally
19 for years and not knowing what to do with it. And
20 very often, we look at it transabdominally and
21 intravaginally if the cervix is short. And if we
22 have somebody who has a short cervix, we've

1 really -- it's been quite a frustrating experience
2 because the only thing we've had to offer that
3 patient population was a cerclage and telling them
4 to go on bed rest, both of which are not really the
5 best therapeutic interventions.

6 For me, when the Fonseca trial came out, it
7 makes perfect sense that if there's cervical
8 remodeling happening and you apply progesterone,
9 which we know can inhibit cervical modeling,
10 extracellular matrix degradation and so forth, it
11 makes sense that it might be effective. So it has
12 really good biologic plausibility.

13 We talked about implementing a strategy when
14 that first trial came out and decided to not do
15 that, wait for another trial. From a clinical
16 practice perspective, now that we have the second
17 trial, we're doing that. We're offering it to
18 patients in a similar fashion as Dr. Hassan
19 described.

20 We tell them about the studies, and we give
21 them the choice. And we talk about cerclage still.
22 We talk about vaginal progesterone. We talk about

1 their other options as well if they've had a prior
2 preterm birth. And we lay it all out, and then we
3 decide what is the best intervention for that
4 particular patient.

5 DR. JOHNSON: Dr. Rosen.

6 DR. ROSEN: So I want to ask the sponsor
7 about power calculations because I think we're all
8 sort of struggling a bit with this.

9 So can you put up slide 14 in the sponsor,
10 and that is the post hoc analysis that you did to
11 hypothesis generation as suggested by the FDA.

12 Can you go over that with us again? It's 14
13 on your sponsor.

14 DR. CREASY: CE?

15 DR. ROSEN: CE-14, yes. So I guess the
16 fundamental question -- that might not be it. It's
17 the Kaplan-Meier curve for reduction in preterm
18 birth of women with a cervical length less than 30.

19 DR. CREASY: Was this for Study 300 or --

20 DR. ROSEN: Yes, Study 300, that's what I
21 want to -- that's it. Okay.

22 DR. CREASY: That's 300.

1 DR. ROSEN: So in the FDA briefing, you
2 represent 58 subjects with the gel and 58 placebo,
3 but that is all individuals less than
4 25 millimeters, correct?

5 DR. CREASY: This is less than or equal to
6 30.

7 DR. ROSEN: Less than 30. Did you do that
8 same analysis for those between 10 and 20? Because
9 in the briefing, it says there were only nine
10 subjects that had that size. And if you did, did
11 you look at the analysis to determine whether there
12 were enough differences so that you could calculate
13 some power?

14 DR. CREASY: In the 300 study, we had 116
15 less than or equal to 30, and I believe it was 46
16 less than or equal to 28. And then it was 9, so
17 less than 20. So they're really weren't enough
18 patients to look at, at the less than 20.

19 DR. ROSEN: Right. So your power
20 calculations were really based on a difference at
21 the 30 or 28 range rather than the size that you're
22 going to look at for your 302 study, correct?

1 DR. CREASY: Oh, yes. Well, we based it on
2 the available data, and we used the information
3 that we had here for less than or equal 30 and less
4 than 28, and we used the Fonseca range, which was
5 10 to 20.

6 DR. ROSEN: Okay. And then did you --

7 DR. CREASY: Or 10 to 15, excuse me.

8 DR. ROSEN: Did you look at the -- I know
9 300 is multinational, but the majority were U.S.

10 DR. CREASY: Two-thirds.

11 DR. ROSEN: Yes. Did you look at the
12 one-third that wasn't to see if there was any
13 efficacy in the one-third that was non-U.S.?

14 DR. CREASY: Well, actually, in the 300
15 study, if we do a forest plot of all patients U.S.
16 and non-U.S., the U.S. showed a risk difference
17 that favored progesterone whereas the non-U.S.
18 actually a big favored placebo in that trial. And
19 this is just variability of subgroups from trial to
20 trial, but overall, the trial didn't work. As you
21 can see, the overall result crosses zero.

22 DR. JOHNSON: Yes, Dr. Emerson had a

1 comment.

2 DR. EMERSON: Just that was done on the
3 entire sample size rather than just the ones who
4 were less than --

5 DR. CREASY: Oh, yes. Slide up. It's a
6 similar pattern for those less than or equal to 30
7 millimeters. Actually, for the less than or equal
8 to 30 millimeters, the U.S. population was
9 significant and the non-U.S. actually favored
10 placebo. But this is -- again, it's the
11 variability of the subgroups from trial to trial.

12 DR. JOHNSON: Yes, I had a question, if you
13 could pull up CE-42. Listening to the open public
14 hearing speakers, clearly, what some of the
15 individuals who have a history of preterm labor and
16 preterm delivery want to see is something that's
17 going to lower the risk to their infants. And if
18 you look at this data, the only thing you've been
19 able to show -- correct me if I'm wrong -- is a
20 decrease in respiratory distress syndrome. But the
21 usual markers would be neonatal intensive care
22 admission and number of days in the NICU.

1 You were not able to show that. Can you
2 tell me why you think you were not able to show
3 that benefit although you did see a decrease per
4 your data in preterm delivery?

5 DR. CREASY: I don't know for sure why the
6 NICU days didn't become statistically significant.
7 There was just a marginal difference overall in
8 NICU days. Most of the NICU days, it turned out,
9 were from the U.S. There were a lot fewer NICU
10 days outside the U.S. all in all. So I don't -- we
11 don't know the answer about why the NICU days were
12 not significant.

13 DR. JOHNSON: Dr. Montgomery Rice.

14 DR. MONTGOMERY RICE: You just challenged me
15 again with looking at that data. I guess my
16 question goes back to -- and I am concerned about
17 what would happen if approval occurs, and are we
18 going to be faced with the fiasco that occurred, I
19 believe, after the Makena was approved. And
20 patients who we believe would benefit from that
21 medication were then hit with significant -- we saw
22 a significant increase in cost associated with

1 that. And I think all of us who do this work every
2 day were appalled -- would be the appropriate word
3 that I would use -- how the cost went up,
4 particularly to that vulnerable population, in
5 women who really needed it the most. And you can
6 hear from the public hearing that the patient who
7 was struggling with getting Crinone, when I would
8 have hoped that perhaps she would have been offered
9 oral -- I mean, excuse me, vaginal, at least
10 vaginal micronized progesterone because I'm still
11 not convinced that there's that significance of a
12 difference based on the information that I've seen.

13 So I guess my question to you is, do you
14 have any idea that if it were approved, are we
15 going to see comparable costs? I was back over
16 here trying to -- I haven't prescribed Crinone in a
17 while, but I remember when it came out. I mean it
18 comes in 15-dose applications or something like
19 that, and you can get it from 170 to \$200,
20 depending on where you get it from. We're talking
21 about somebody using it for 25, starting week 25,
22 every day. So I guess that would end up being

1 about 1,000 or \$1200.

2 Are we looking at comparable costs, or are
3 we going to see something that goes up to \$1,000
4 for 15 applications?

5 DR. CREASY: I'm going to ask Dr. Reape, our
6 representative from Watson, to answer that.

7 DR. REAPE: Good afternoon. I'm Kathleen
8 Reape. I am vice president of medical affairs and
9 women's health clinical research for Watson
10 Pharmaceuticals, and I am a full-time employee of
11 Watson.

12 So I understand your concern, and I can say,
13 speaking on behalf of Watson, that we are acutely
14 aware of the issues related to the pricing of the
15 17 hydroxy progesterone caproate product. And I
16 can assure that that approach will not be repeated.
17 And I will also state that, as you mentioned, this
18 is sort of a different situation than the other
19 product in that this is an already approved product
20 for ART that is available, and we anticipate that
21 the pricing would be the same as the currently
22 available Crinone product, which is actually in the

1 range of what you stated.

2 DR. JOHNSON: Dr. Sicalli.

3 DR. SICALLI: I have a question for the
4 sponsor. We saw how FDA made the p-value go down
5 by adjusting for different variables than you did,
6 and I posed a question about whether adjusting for
7 cervical length and age was appropriate. And I
8 wonder what your response is to the difference in
9 the use of adjustments in the two analyses.

10 DR. CREASY: Well, I'll just begin by saying
11 that we conducted the prespecified analysis, and
12 then I'll let Dr. Phillips finish.

13 DR. PHILLIPS: Yes, I think just to
14 emphasize that we prespecified everything in our
15 analysis plan, and we followed that analysis plan
16 as it was written before we knew any of the results
17 of the trial. I think it's been presented today
18 that there were some post hoc things done, and I
19 think that our position is that in a post hoc
20 manner, it would be relatively easy to manipulate
21 the p-value up and down, if you will, by picking
22 certain variables in certain manners.

1 In fact, we don't have data, but we actually
2 excluded the two worst performing sites; and by
3 doing that, we can make the p-value go less than
4 .01. So it works in both directions.

5 DR. SICALLI: Let me make my question more
6 pointed then. If prior to the study, it had been
7 suggested to you that you include maternal age and
8 cervical length as prespecified adjustments, what
9 would your response have been?

10 DR. PHILLIPS: Well, as you may recall, we
11 had planned a preplanned logistic regression
12 analysis, including maternal age and cervical
13 length along with some other variables that we felt
14 were related to the risk of preterm birth. And so
15 we did that on purpose a priori so that we could
16 have an adjustment accounting for these variables
17 that we already knew were related to the risk of
18 preterm birth. And when we did that analysis, we
19 still saw the treatment effect hold up, although
20 the p-value was .044. But nevertheless, it was
21 intended to be a supportive analysis to just give
22 us an idea of what the treatment effect was after

1 adjusting for these preknown, prespecified
2 variables. And so I believe that if we had done a
3 logistic regression and then selected variables
4 that were significant predictors, that that might
5 have not been, a priori, an appropriate approach
6 from a preplanned statistical analysis planned
7 perspective.

8 DR. JOHNSON: Dr. Orza.

9 DR. ORZA: I need a little help
10 understanding two things, one, the difference in
11 the weeks. Thirty-two weeks come up in the
12 epidemiologic kind of background information when
13 we're talking about the problem of prematurity
14 generally. And then I think in the FDA materials,
15 there's a discussion about 32 versus 33 and where
16 the sponsor is going set that. And then in the
17 sponsor's materials and in the other studies and in
18 the meta-analysis, 33 comes up and 35 comes up.

19 I just need a little help understanding the
20 significance of the various cutoffs and how much
21 difference it really makes whether we're talking
22 about 32 versus 33 or 33 versus 35 and how that

1 might play into our understanding of the findings.
2 Anybody.

3 DR. MURTHA: So I think I'll give that one a
4 shot and see if I can answer your question, but I
5 think probably again for the practicing
6 obstetrician, neonatologist, a baby born
7 preterm -- and generally if we get below 35 weeks,
8 those are the babies that spend some time in the
9 intensive care nursery.

10 So the way I usually think about it is
11 they've got to go to the ICN, it's not a good
12 thing. So if that's where they end up, that's what
13 I would like to try to prevent. So whether it's
14 35, 34, 33, if it's me having that baby or if I'm
15 the woman having that preterm baby, it doesn't make
16 really that much difference.

17 How we got at those gestational age cutoffs,
18 that I would probably leave to them to answer. But
19 from my perspective, a week in utero is one less
20 week they spend in the intensive care nursery with
21 all the associated risks and complications that
22 come with that.

1 DR. CREASY: In the design of the trial
2 itself, we had designed this Trial 300 with less
3 than or equal to 32 weeks in discussion with the
4 division. That was kind of the preferred
5 gestational age cut point for them.

6 One of the last times this advisory
7 committee met -- actually, some time ago, 2006, the
8 recommendation was for less than or 35 weeks,
9 something less than 35 weeks. So this 302 trial
10 became a collaboration between the NIH and Columbia
11 and the FDA sort of. So we negotiated this less
12 than 33 weeks. It was actually six days more than
13 we had in our previous trial, but that was to
14 accommodate some of the interests of the NIH with
15 whom we had a clinical trials agreement.

16 But overall, if you -- the primary endpoint
17 isn't the limitation of the effect. The effect can
18 be seen above and below the primary endpoint of the
19 trial at 33 weeks. There's an effect 35. There's
20 an effect that goes back to 28. So it's not
21 limited to the primary endpoint of the trial.

22 Even though we have to pick a primary

1 endpoint and show that we're efficacious there,
2 which we did, the effect still goes above and below
3 that point and addresses some of the concerns that
4 Dr. Murtha was speaking about a moment ago.

5 DR. WESLEY: I would like to respond to that
6 as well. Barbara Wesley, from the FDA.

7 We are charged with looking at clinical
8 endpoints, and the clinical endpoints would be all
9 the morbidities that you see, could be early
10 neonatal or long-term. It's not practical to ask
11 somebody to measure something 20, 10 years later
12 because it just doesn't work. So we do have a lot
13 of early morbidities that are measureable.

14 The thing about that is that you can have
15 different definitions. It's a little bit more
16 cumbersome. So we use a surrogate, which is
17 gestational age. And that is controversial as to
18 which surrogate would be the best predictor. But
19 the lower you go down in gestational age, the more
20 likely you're going to have these morbidities,
21 which also can be measured, and that's really what
22 our charge is, the morbidities.

1 So we recommended 32 weeks because we
2 figured that you would get a certain number of
3 morbidity that we could also look at the clinical
4 outcome in addition to the surrogate outcome, and
5 that's why we recommended. Now, one week above or
6 whatever, we worked with because there is no real
7 hard answer to which week this should be.

8 DR. SOULE: And Lisa Soule, I just want to
9 make one final clarification because there have
10 been several references to the 2006 advisory
11 committee, and I think some of you probably were on
12 that panel.

13 The question posed to the committee was not
14 to recommend a gestational age that should be use.
15 The question was, given three gestational ages that
16 were discussed in that trial, do any of these
17 function as an acceptable predictor of neonatal
18 morbidity, mortality? So they were asked that
19 question for births less than 37 weeks, births less
20 than 35 and less than 32 weeks. And the committee
21 voted that delivery of less than 37 weeks was not
22 an acceptable predictor, but that the other two

1 gestational ages were. But the vote was actually
2 somewhat divided even at 35 weeks. At 32 weeks, it
3 was pretty near unanimous that that was a good
4 predictor.

5 DR. JOHNSON: Did you have another comment?

6 DR. ORZA: I had another question that I
7 would like a little more explanation about the
8 superiority of natural progesterone which is
9 discussed at several points.

10 DR. JOHNSON: Go ahead and ask your
11 question.

12 DR. ORZA: So the difference in
13 bioidentical, natural progesterone.

14 DR. CREASY: So the difference between our
15 micronized progesterone and the other progesterone
16 that's been approved for prevention of preterm
17 birth, the hydroxyprogesterone caproate?

18 From a structural standpoint, the two
19 molecules are different. The natural progesterone
20 form is on the left. This is what is produced by
21 the ovary and then during pregnancy by the
22 placenta.

1 Hydroxyprogesterone caproate here shown on
2 the right has a relatively large side chain on
3 position 17. This is the same spot that side
4 chains are placed for menopausal progesterone like
5 MPA and also for Megace, which is used in breast
6 cancer treatments.

7 So it's a synthetic progestin, and the
8 overall metabolism of this caproate molecule, no
9 natural progesterone is formed in the body so that
10 it goes in as a caproate, it comes out as a
11 caproate, as far as I know, and it isn't converted
12 to natural progesterone.

13 Does that answer your question?

14 DR. ORZA: Partly. So it's not a question
15 of where the progesterone comes from.

16 DR. CREASY: Well, yes, the caproate
17 doesn't --

18 DR. ORZA: The molecule is the -- but it
19 might be synthesized. I mean yours is --

20 DR. CREASY: Yes, well, the body doesn't
21 make hydroxyprogesterone caproate, nor is hydroxy
22 progesterone caproate converted into any natural

1 hormone in the body. It's a synthetic drug,
2 basically, that has a biologic effect, and it's
3 used for that purpose now.

4 Natural progesterone is made by the ovaries,
5 and it's made by the placenta, and it's considered
6 the pregnancy hormone. And that's the form that's
7 used in the 8% gel in the first trimester to
8 support the achievement and maintenance of early
9 pregnancy and in these studies to prevent preterm
10 birth.

11 DR. JOHNSON: Dr. Emerson, did you want to
12 just make a comment? I'm sorry, just one moment.

13 Did you just want to make a comment,
14 Dr. Greene?

15 DR. GREENE: Yes, I just -- please correct
16 me if I'm wrong, but 17 hydroxyprogesterone
17 caproate is not made in the human body, but it is
18 the natural progesterone in the goat; is that not
19 correct?

20 DR. CREASY: You probably know more about
21 that than I do.

22 [Laughter.]

1 DR. GREENE: Yes, and so the reason that
2 it's useful in humans is because that side chain
3 confers long life to the progesterone effect and
4 the caproate is not cleaved -- as you noted, is not
5 cleaved from the molecule. So that gives it a long
6 life in human beings, but it is a natural molecule,
7 just not in humans. It's goats. And we haven't
8 noticed anybody baying from it.

9 [Laughter.]

10 DR. JOHNSON: Thank you, Dr. Greene, for
11 that information.

12 Dr. Emerson.

13 DR. EMERSON: So could you put up CE-43
14 again? So one of the big questions in my mind is
15 about this pivotal trial, what do we have in the
16 way of supporting data beyond just what the primary
17 endpoint is.

18 Now, one of the questions that we can have
19 is with a Type 1 error is that we just saw
20 something by random chance. So let's imagine that
21 a treatment didn't work at all; yet by random
22 chance, we had a decreased incidence of preterm

1 birth in one group. Would we be surprised to see
2 that also that group had a reduction in the
3 frequency of RDS or reduction in birth weight, low
4 birth weight and of the trends and the composite
5 scores would be the same way? And my argument
6 would be no, we wouldn't be surprised. We know
7 that those are correlated and things like that

8 So I guess my question is, what do we have
9 to go on that is an idea that we are seeing an
10 effect of the drug that is something that's
11 supporting beyond -- I will concede that these are
12 the endpoints that we really want. If early term
13 delivery didn't cause any clinical problems, we
14 wouldn't care if we had it.

15 So the question we have is now just more of
16 the scientific evidence. What do we have to go on
17 in this pivotal trial?

18 DR. CREASY: Perhaps what you're looking for
19 is the evidence that we had for the delay in
20 cervical shortening, which is a different factor.
21 But it's a biologic endpoint that we believe is
22 related to slowing the cervical shortening, keeping

1 the pregnancy in utero longer.

2 Slide up. So this is the data from the 300
3 study, and it's data from the trial overall. So
4 it's not in any -- the first row is not in any
5 subgroup. The first row is the delay that was seen
6 overall and among all cervical lengths in the
7 trial. And then we took a look to see what was the
8 effect in the women with the shorter cervical
9 length, those less than or equal to 30 millimeters
10 here. Actually, the effect was greater. So those
11 women who started out with a shorter cervical
12 length actually had more of a delay in their
13 cervical shortening by being exposed to vaginal
14 progesterone. And we believe that it's this effect
15 that is what we're seeing then in the
16 Trial 302 -- well, first of all in the subgroup
17 that was hypothesis generating but also in Study
18 302.

19 Does this answer your question?

20 DR. EMERSON: It certainly goes towards it.
21 And so if you had to -- as you're positioning this
22 treatment -- and this goes to a question I had

1 earlier again about the subgroups stuff. If we had
2 to make a guess in terms of the treatment -- I
3 always wonder is it a treatment that only works if
4 you're really, really sick, and that's who it works
5 in, in the people who are moderate, or is that if
6 you're too far gone, it can't help.

7 Where would you place this, your treatment,
8 along that spectrum?

9 DR. CREASY: Dr. Hassan, do you want to
10 answer this?

11 DR. HASSAN: And, Dr. Emerson, I assume
12 you're saying in what patient population maybe this
13 would be most effective?

14 DR. EMERSON: Looking at these pictures in
15 terms of where that -- as we're trying to guess
16 with particular subgroups. Earlier I asked about
17 the idea that the patients who were enrolled later
18 rather than earlier, and that those patients
19 actually had a better effect than the patients who
20 were enrolled earlier, and that that seemed
21 somewhat paradoxical if you took it at face value,
22 that the longer time you had the treatment, it

1 would seem better, but that I recognize that
2 there's differences in what it means to have a
3 short cervix at different gestational ages.

4 So as we're trying to look at these patients
5 and what their severity is of their condition that
6 maybe your treatment can address, where do you
7 think it is?

8 DR. HASSAN: I think it's certainly in women
9 that are in the mid-trimester, of course, and the
10 range for this study was from 19 to 23 and
11 six-sevenths weeks. So that is what I would speak
12 to, and that's a similar range with related to the
13 Fonseca trial. And based on both the meta-analysis
14 and also of the Fonseca trial and ours, a safe
15 range in terms of cervical length, many of us use
16 is less than 25 millimeters.

17 The gestational age range, as you mentioned,
18 in that study and that particular difference, as
19 you mentioned, it could be likely from the
20 different cause of a person that has a cervix
21 earlier versus later, and there's probably
22 different mechanisms for that, though we don't have

1 a definite answer to that.

2 DR. EMERSON: If we were wanting to use the
3 Fonseca trial as truly independent support for the
4 plausibility of the mechanism.

5 Now, the Fonseca trial, the cutoff was 1.5?

6 DR. HASSAN: Correct.

7 DR. EMERSON: And that your mean was 1.75 in
8 302?

9 DR. HASSAN: Yes.

10 DR. EMERSON: And then we have the question
11 of the different dose and different administration
12 between the two trials.

13 Can you sort of revisit how you feel that is
14 comparable?

15 DR. HASSAN: It is comparable in terms of
16 the reduction. I think they know this already, but
17 the reduction in both trials, as you know, showed a
18 difference or a reduction of 44 percent in less
19 than 33 weeks and less than 34 weeks. The
20 difference between the 302 study and the Fonseca
21 study is we were able to show some difference and
22 improvement in neonatal outcome. And then the

1 discussions about the bioadhesive gel and maybe
2 it's better bioavailability, that's obviously a
3 discussion many people have had and may agree with.

4 So in terms of the patient population that
5 you ask about, again, I would focus that on the
6 mid-trimester as we are doing, anywhere from 19 to
7 24 weeks, and those women with a short cervix are
8 offered the progesterone gel. And less than
9 25 millimeters is often used by physicians, and
10 that is standard, I think, for a lot of us here.

11 DR. EMERSON: In terms of, if you will, the
12 severity of disease as measured as by how short the
13 cervix is, do we need to make some adjustment for
14 these different values in terms of the 1.5 being
15 the upper bound in the Fonseca and it's 1.75 was
16 the average in your study, or is that a point that
17 it doesn't matter anymore?

18 DR. HASSAN: I think the 2-millimeter
19 difference is not substantial in terms of
20 conferring a huge difference in risk. I think both
21 populations are at very high risk.

22 DR. JOHNSON: Yes, I'd like to ask about the

1 original Study 300. You were not able to show
2 effectiveness in patients who had a history of
3 preterm delivery. And tell me why you think that a
4 better use of this product would be with women who
5 have a proven short cervix as compared to those who
6 have a history of preterm labor. Why would it work
7 in one group and not in the other when the approval
8 for the current product is for the history of
9 preterm delivery?

10 DR. CREASY: Well, I'm not really sure what
11 the mechanism is in the treatment of women with a
12 history of preterm birth. As we saw earlier in
13 Dr. Murtha's slides and Dr. Hassan's slides, this
14 is a syndrome. So if a person has a preterm birth,
15 it's not clear what their mechanism is. But
16 Dr. Murtha presented some potential mechanisms in
17 the short cervix, and I think that may be worth
18 revisiting in answering your question.

19 DR. JOHNSON: So is that presuming then that
20 it's a different mechanism in women who have a
21 history of preterm delivery as compared to women
22 who have a short cervix?

1 DR. MURTHA: Slide up. So I think an
2 important difference -- besides the fact that
3 cervical length gives us an opportunity to treat
4 women in their first pregnancies, which the current
5 indication for 17P doesn't give us that
6 opportunity. Besides that fact, if you look at why
7 women deliver preterm, as we said earlier, it's a
8 multifactorial disease. It's people have either
9 ruptured membranes, preterm contractions, their
10 cervix gets short. They have infection and
11 inflammation. When they come to their next
12 pregnancy, we're treating them with 17P, but we
13 don't really know what it was that caused that
14 preterm birth the last time. And so it's a big
15 sort of gmish of things that could have happened to
16 them in their prior pregnancy, and we're trying to
17 treat that with progesterone.

18 In contrast to that, by looking at the
19 cervical length, we're trying to identify a disease
20 process as it's happening as opposed to just
21 identifying a risk factor that we don't know a lot
22 about. Identifying that disease process as it is

1 happening is giving us an opportunity to apply a
2 medication that we know can block that
3 pathophysiologic process as it's going on, and I
4 think that's, to me, why the difference is
5 important besides the fact that it gives us an
6 opportunity to look at first pregnancies.

7 Does that answer your question?

8 DR. JOHNSON: It does, but are you saying
9 then that idiopathic cervical shortening, you do
10 not think that's related to inflammation? You
11 don't think it's related to any other factor that
12 would also cause preterm delivery? You think it's
13 a unique cause of preterm delivery --

14 DR. MURTHA: No, no, I am not saying that at
15 all. In fact, idiopathic cervical shortening is
16 likely an inflammatory process. It's probably also
17 a multifactorial disease, but it's a way of
18 identifying that risk factor that's a process
19 that's happening, that we can apply a medication to
20 try and block that process as it's occurring.

21 DR. JOHNSON: Thank you.

22 Dr. Gillen.

1 DR. GILLEN: Yes, this is a comment in
2 reference to a statement that was made a few
3 moments ago, which was the role of data-driven
4 analyses and how it cuts both ways in terms of
5 looking for particular subgroups. And it was
6 stated that, sure, if you throw out the worst
7 performing sites, then one can lower the p-value
8 that was actually observed in the study. And

9 Dr. Darney actually gave a very, very good
10 presentation on why we should not over-interpret
11 subgroup results, and I agree with much of what he
12 said and most of it, in fact.

13 However, science is adversarial, and the
14 question is really on the burden of proof. And
15 that's how you have to look at this, in my opinion.
16 And since we are in a pivotal trial setting, we
17 need to consider that burden of proof. So if I
18 were trying to prove to the committee that a
19 subgroup was significantly different, then I would
20 be asking myself am I convinced with the data at
21 hand that there is, in fact, modification by
22 region. That's the cutting both ways aspect here.

1 That's where I would have to have a priori
2 hypothesis about such subgroups.

3 There's another burden of proof that's
4 sitting here, though, and that is do we have
5 consistency across key subgroups. And I just need
6 to make this point. And that is begging the
7 question, is there a probable doubt that there may
8 be effect modification by region when considering
9 these. And those are two different scenarios in my
10 mind.

11 So I'm happy to hear an objection to that,
12 but I don't think that the statement that it cuts
13 both ways applies equally depending upon what the
14 scientific goal is.

15 DR. CREASY: Can I respond to that? I think
16 the issue that we're trying to get to here is what
17 kinds of variability, what are the known and
18 unknown factors in this trial that may be
19 contributing to the variability. And I know we
20 discussed two previously. We discussed compliance
21 quite a bit, and I think we understand the
22 compliance was a little lower. We're not sure how

1 that may have impacted entirely, but probably had
2 some effect. The other point was the
3 chorioamnionitis.

4 We had one center in the trial, site 36,
5 that routinely measures -- or assesses placental
6 pathology on all of the births at the institution.
7 And so at that one center, we have a very accurate
8 determination of whether or not there was any
9 evidence of chorioamnionitis.

10 This center had an overall marginal effect
11 at minus .8, but when the cases of chorioamnionitis
12 are removed from the center that assessed it on all
13 of the placentas, the effect size goes to minus 20,
14 and it's statistically significant on its own, at
15 one center.

16 Now, this is not -- I'm not presenting this
17 as the reason or the explanation. I'm just showing
18 that this kind of effect can be contributing to the
19 variability in the trial and that this one center
20 has a big impact. We don't know this kind of data
21 across all the centers in the trial. The adverse
22 events reporting were not as detailed from the

1 other centers as we had from this particular site
2 on this particular issue.

3 DR. WEINSTEIN: The only thing is Benirschke
4 showed years ago that virtually everybody that
5 delivers prematurely will have inflammation in the
6 membranes. So I don't think that's unusual at all.
7 That's exactly what you would expect, and they
8 shouldn't be taken out because they do have -- that
9 is a cause of prematurity, and maybe we can arrest
10 it with progesterone, maybe. But I think if you
11 looked at the other centers, you'd see exactly the
12 same thing, if you believe what the world's
13 authority on placentas says.

14 DR. CREASY: I'm not presenting this as the
15 reason. I'm just suggesting that this is one of
16 the variables of known and unknown factors in the
17 background that can be affecting the results in the
18 trial. That's my point.

19 DR. JOHNSON: Okay. We're going to extend
20 it just for five more minutes for the two last
21 questions.

22 First, Dr. Hoeger.

1 DR. HOEGER: So this goes to the questions
2 that we're going to be discussing after the break,
3 but I think it gets down to in many of the
4 questions, it asks for the differences between the
5 U.S. data and those outside the U.S. And it's my
6 understanding that all of the data we have, the
7 majority is from the Fonseca trial, if we're going
8 to use that, which was Brazilian data.

9 Is that correct?

10 DR. CREASY: No. That primarily was
11 conducted in London, and there were also sites I
12 believe in Chile -- and I forget the other
13 countries, but it was mostly from London.

14 DR. CAMPBELL: London, two centers in the
15 United States and Chile and in London.

16 DR. CREASY: Oh, the U.S. as well?

17 DR. CAMPBELL: Yes.

18 DR. HOEGER: But the majority of this trial,
19 55 percent, were non-U.S. sites, so the majority of
20 data even if you combine those --

21 DR. CREASY: That's correct.

22 DR. HOEGER: -- would be outside the U.S.

1 So the proposal that you've made to explain
2 is the chorioamnionitis, which again, I think we
3 have to consider the fact that that was not -- that
4 was a pathologic diagnosis, not a clinical one made
5 at the time of delivery, and you're not seeing
6 that. It'd be very hard to give labeling
7 indications for something that we can't test for
8 clinically. And then compliance, which again,
9 you're proposing that U.S. subjects are less
10 compliant, which, again, we're talking about
11 prescribing it to the U.S. population when we're
12 looking at FDA approval, so we have to consider
13 that.

14 So in your estimation, this is sufficient to
15 say that in the U.S. population to which this is
16 going to be applied, we should be able to believe
17 the data or use the data from all sites?

18 DR. CREASY: Yes, that's the purpose of a
19 large randomized multinational trial is to create
20 an overall estimate of the treatment effect. If we
21 would believe that somehow -- if we were to believe
22 that there were real differences between pregnant

1 women in the U.S. -- that women in the U.S. were
2 really somehow different from women in the rest of
3 the world in terms of pregnancy, I think we would
4 try and explore that and understand what those
5 differences are. But I'm not aware of any
6 differences, and Professor Campbell presented
7 earlier that he's not aware of any differences.

8 Another way to look at the differences is to
9 actually look at race differences to see if there
10 are any. And these are the race results from the
11 subgroups in the trial, and there don't really
12 appear to be dramatic differences between the races
13 overall.

14 So it doesn't seem like there's a genetic
15 factor involved here. It seems like there are
16 other factors involved, and that's why we were
17 trying to explore, to the extent that we could, the
18 compliance issue and the chorioamnionitis because
19 we had some information about that. But I think
20 the overall result of the trial is the best
21 estimate of what we can expect from the U.S.

22 DR. JOHNSON: We have a comment from the

1 FDA.

2 DR. SOULE: I just want to make one
3 clarification. I may have misunderstood your
4 focus, but when we are talking in the context of
5 the questions, we need to consider the data that
6 was submitted to the NDA and that FDA has reviewed,
7 which is not inclusive of Fonseca.

8 DR. ORZA: And also, according to the
9 meta-analysis that we have, there were no U.S.
10 sites in Fonseca.

11 DR. ROSEN: There are no U.S. sites in
12 Fonseca. There are no U.S. sites.

13 DR. CREASY: Yes, I didn't think so.

14 DR. JOHNSON: We actually have two more
15 people because I had forgot that Dr. Henderson did
16 not get the answer to her question.

17 Did you have the slides to show the answer
18 to Dr. Henderson's question? Do you want to
19 readdress it again?

20 DR. CREASY: We do actually. That would be
21 the question about BMI and age in the U.S.
22 population, yes.

1 So these are the results for BMI. This is
2 data just in the U.S. subgroup and just the BMI
3 above and below the median of BMI in the U.S. and
4 above and below the median for age in the U.S.

5 DR. JOHNSON: Any further questions?

6 DR. HENDERSON: In the two groups, the U.S.
7 and the non-U.S., in the U.S., non-obese women,
8 what was the risk? And in the non-U.S., the obese
9 women, was there a difference?

10 DR. CREASY: So the obese women here would
11 be in the group above 23.9, and their effect rate
12 was minus 2.8. This is the U.S. In the non-U.S.,
13 you're looking for the lower or the upper?

14 DR. HENDERSON: The lower.

15 DR. CREASY: The lower outside the U.S. was
16 minus 6.

17 DR. HENDERSON: I'm sorry. I'm looking for
18 the upper.

19 DR. CREASY: So this is the non-U.S. These
20 are the non-U.S. patient subgroups.

21 DR. JOHNSON: Ms. Aronson.

22 MS. ARONSON: This is a safety question.

1 Is it possible to have Table 4.4-4 put up?
2 It's the adverse events that were greater in the
3 progesterone gel versus the placebo.

4 DR. CREASY: Is this the table you're
5 talking about?

6 MS. ARONSON: Yes. Is there any explanation
7 about the premature rupture of membranes being
8 greater in the progesterone gel arm?

9 DR. CREASY: We don't have an explanation
10 there. The difference is just about, what,
11 1 percent, or just under 1 percent. We would
12 consider this to be probably just the variation of
13 the trial result.

14 DR. JOHNSON: For allowing all to get their
15 questions answered, Dr. Aronson, do you have
16 another question? I'm sorry. Dr. Emerson.

17 DR. EMERSON: I just wanted to return to the
18 chorioamnionitis slide that you had. And my next
19 question is just what's going to have everybody
20 behind me cringing, but what test was done in that
21 no group, that 4 of 20 and zero over 17 would be
22 statistically significant?

1 DR. PHILLIPS: What test was done?

2 DR. EMERSON: Yes.

3 DR. PHILLIPS: I'm pretty sure that's the
4 same primary model, only in this case because it
5 was only on one site, it was risk strata, so only
6 adjusted for risk strata, and then among the
7 subgroup with none and the subgroup with.

8 DR. EMERSON: I would not consider that
9 trustworthy at this sample size.

10 DR. JOHNSON: Last question, Dr. Rosen.

11 DR. ROSEN: I just want to ask the sponsors
12 again about the discussion about the .01 because it
13 was very clear in the FDA initial discussion with
14 you before the pre-NDA that you needed a single
15 multicenter study, you needed a p-value of .01.
16 And you got a relative risk of .56 which is
17 identical to Fonseca's data, but his p-value was
18 .02.

19 So was there some concern on your part or
20 some pushback about the .01 or how you powered for
21 that? I mean, did you take that seriously into
22 consideration when you were discussing the power

1 because I think this is a very important point.
2 Were you adequately powered to the standards that
3 were set by the FDA?

4 DR. CREASY: We believe we were adequately
5 powered for the assumptions that went into the
6 calculation, which was at the time a 22 percent
7 placebo rate which was lower than the other placebo
8 rates that we had observed. And we were very well
9 powered to achieve a level of .01 if we had seen
10 the 22 percent placebo rate.

11 What happened was we got a placebo rate of
12 15 percent, which was quite a bit lower, but the
13 drug still showed an effect. Even with a
14 remarkably lower placebo rate, we still showed a
15 44 percent reduction. So it would seem to me
16 that -- well, I think the data suggests that the
17 drug is working pretty potently if you're getting a
18 .02 p-value with a much lower placebo rate.

19 DR. ROSEN: So Dr. Phillips mentioned,
20 though, in his discussion something about the
21 80 percent power at .01. What was that? How did
22 that come down, and what were the numbers there?

1 Because that was really at the edge of statistical
2 significance for .01.

3 DR. CREASY: I'm not sure --

4 DR. ROSEN: I think he mentioned when he
5 was --

6 DR. CREASY: He did -- well, it was
7 power -- let me ask Dr. Phillips to answer the
8 question.

9 DR. ROSEN: Maybe he can just restate what
10 he told us about the 80 percent power for .01.

11 DR. PHILLIPS: Slide up, please.

12 So the assumptions are given in bullet 1,
13 22 percent, 55 percent reduction which translates
14 to a 12.1 percent difference, absolute difference
15 between the treatment groups. And then the middle
16 paragraph repeats the power calculation.

17 So the 80 percent power for a 1 percent
18 significance level basically uses the same
19 assumptions in terms of the 22 percent,
20 9.9 percent, 12.1 percent difference. And so it's
21 just varying the significance level to then
22 recalculate the power.

1 DR. ROSEN: I understand that, but if the
2 FDA had mentioned to you that you needed to get to
3 .01, then would you have set up any other a priori
4 predictions about numbers? I guess that's my
5 question. If that's what they said was the limit
6 of .01, here we're struggling with you have a
7 statistical value that's .02 but that doesn't meet
8 their criteria. So tell us about how you had to
9 deal with that.

10 DR. CREASY: Well, a suggestion of .01 came
11 in the first trial. We felt that that trial was
12 going to be a little bit more supportive than it's
13 turned out to be. So when we were designing the
14 trial, we were seeing the 300 result as somewhat
15 supportive. So we weren't viewing the .01 as at
16 the same criteria for the second trial as we were
17 told in the first trial. And that's how it came.

18 DR. JOHNSON: A comment by Dr. Montgomery
19 Rice.

20 DR. MONTGOMERY RICE: I just got a little
21 bit confused because I thought that he said that
22 you-all powered the trial at .05, and so when you

1 did the power analysis, that's what you came up
2 with. So just tell me, what would the end have
3 been if you had powered it for .01? How many
4 subjects would you have had to enroll? Because I
5 know you did the calculation.

6 DR. CREASY: What --

7 DR. MONTGOMERY RICE: How many subjects
8 would you have had to enroll in order for it to be
9 powered at .01?

10 DR. PHILLIPS: So while it's not exactly at
11 93 percent power, the middle bullet shows that it's
12 about a 40 percent increase up to 292 per group if
13 we had taken that as the primary calculation.

14 DR. JOHNSON: Any comment, Dr. Emerson?

15 DR. EMERSON: I would just like, I think all
16 of this power question is just this red herring
17 that just doesn't matter. The idea is this is a
18 gamble, right, and this is the concept that if you
19 have to produce two trials that each stand on their
20 own, that's a much higher level of evidence than
21 the FDA has come to accept by a .01.

22 There's a concept that you'd really like to

1 see independent trials to do that, and if you
2 really demanded .05 in two trials, then you need to
3 have .0025 in one. And we don't go there.

4 But the key thing is that a sponsor when
5 they do this trial, if the treatment worked as well
6 as they thought, they had an 80 percent chance that
7 they were going to get away with one trial. It
8 didn't work out. That doesn't negate this one
9 trial. It just says they have to do another one.

10 So that's the only strategy. There's no
11 real statistical issue in the fact that they didn't
12 power it for their imagined thing at some high
13 level.

14 DR. JOHNSON: Any last comments by the
15 sponsor before our break?

16 Okay. Thank you very much.

17 We're going to take just a 10-minute break.
18 We will come back at 2:52. Panel members, please
19 remember no discussion of the meeting topics
20 between ourselves or any member of the audience.
21 We'll return at 2:52.

22 Also, when we return, just to let the

1 members of the advisory committee know, our first
2 item is a vote. Before we do that vote, I want to
3 just allow any further comments, no further
4 questions but any further comments. Thank you.

5 (Whereupon, a recess was taken.)

6 **Questions to the Committee**

7 **Discussion and Voting**

8 DR. JOHNSON: Okay. If we could have our
9 seats, please. So now we will begin our panel
10 discussion portion of the meeting. Although this
11 portion is open to public observers, public
12 attendees may not participate except at the request
13 of the panel.

14 Now, as you look at our questions, we have
15 four questions. The first one requires a vote.
16 The next two are discussion only, and the last one
17 requires a vote and a discussion.

18 So for the voting portion, let me give you
19 explanations. We'll use an electronic voting
20 system. Each voting member has three voting
21 buttons on your microphone, yes, no and abstain.
22 Please vote by pushing the button located

1 immediately below the corresponding statement.

2 Firmly press this button three times.

3 After everyone has completed their
4 vote -- and we'll know if you didn't press hard
5 enough, no -- everyone has completed their vote,
6 the votes will then be locked in. The vote will be
7 displayed on the screen. I'll read the vote from
8 the screen for the record.

9 Then we will follow by going around the
10 room. You will say your name and how you voted,
11 and please give me a reason, if you wish to do, for
12 why you voted in the manner that you did. And this
13 will all go into the record.

14 Now, before we begin with the voting, I
15 wanted to see if there were any other comments or
16 issues that you would like to address to the
17 advisory committee.

18 [No response.]

19 DR. JOHNSON: Seeing none, allow me to read
20 to you the first vote. I'm sorry. So the way that
21 we vote, it's always good to repeat these things
22 several times. Okay. So we will begin by voting

1 on question number 1. We're going to use our
2 electronic voting system for this meeting. Each
3 voting member has three voting buttons, yes, no and
4 abstain. Please vote by pressing the button
5 located immediately below your choice. Firmly
6 press the button three times.

7 After everyone -- it doesn't give you three
8 votes; you just press it three times. After
9 everyone has completed their votes, the votes will
10 be locked in, and then they will be displayed on
11 the screen. I will read the vote from the screen
12 into the record.

13 We will then go around the room, and each
14 individual who voted will state their name and
15 their vote into the record as well as the reason,
16 if they choose to do so, on why they voted in this
17 manner. And that will all go formally into the
18 record.

19 So allow me to read Question 1. Has the
20 applicant provided sufficient information to
21 conclude that progesterone gel reduces the risk of
22 preterm birth in women with a singleton gestation

1 and a short uterine cervical length at
2 mid-trimester of pregnancy, given that
3 statistically significant treatment benefit was not
4 demonstrated in a single pivotal trial,
5 particularly in the U.S. subset of the overall
6 study population?

7 So again, have they provided sufficient
8 information to conclude that it reduces the risk of
9 preterm birth in women with singleton gestation and
10 short uterine cervix at mid-trimester? So you may
11 now post your vote: yes, no or abstain.

12 [Voting.]

13 DR. JOHNSON: The results that I read into
14 the record are yes, four votes; no, 13 votes;
15 abstain, no votes.

16 Now we will go around the room starting with
17 Dr. Davidson. If you would please state your name,
18 how you voted and the reason for your vote, if you
19 wish to explain.

20 DR. DAVIDSON: My name is Ezra Davidson. I
21 voted no. I was very concerned, and I was
22 persuaded with the subgroup analysis and the no

1 difference in efficacy of the progesterone gel.
2 And I was a little bit dismayed with the
3 invalidation of the concerns of subgroup analysis
4 in a general ROCT trial and how this, some external
5 analysis of these concerns could be brought to bear
6 in this comparison, which I did not think was
7 proven to be appropriate.

8 DR. JOHNSON: Thank you.

9 Dr. Greene.

10 DR. GREENE: Mike Greene, I voted yes, and
11 the reason I voted yes is that I believe that the
12 study was demonstrated at the level of significance
13 that was not .01 but nonetheless met standard
14 criteria for significance.

15 The issues with respect to subgroup analyses
16 are as stated by Phil Darney. The questions with
17 respect to modified intention to treat analysis,
18 I'd like to point out that with noncompliance,
19 those who fail to comply with a study protocol tend
20 to do less well than those who don't comply, even
21 if the people who fail to comply fail to comply
22 with the placebo treatment. That is well known in

1 large clinical trials.

2 The fact that the largest -- or the poorest
3 compliance was in the United States I think may
4 help to explain why there was less effect noticed
5 in the United States.

6 I was also -- learned statistics, and was
7 brought up by Ken Rothman, who told us never told
8 us to worship at the altar of .05. And similarly,
9 I wouldn't necessarily worship at the altar of .01.

10 I believe that the treatment progesterone,
11 my assessment of the entirety of the literature on
12 progesterone is that there is a modest treatment
13 effect. It is what I would say is a scratch single
14 in terms of treatment. It's not a homerun. I
15 believe that the results of this study are
16 consistent with that assessment, that there was a
17 modest effect size which is consistent with prior
18 progesterone studies. I think it was less than the
19 sponsor used in their power analysis and sample
20 size calculation. They gambled, hoping that they
21 would be able to reach statistical significance at
22 a higher level, and unfortunately for them, they

1 lost. And thus, from the prespecified significance
2 level from the FDA, this may be perceived as a
3 failure. However, I do think it's consistent with
4 all of the other data with respect to progesterone.

5 DR. JOHNSON: Thank you.

6 Dr. Gillen.

7 DR. GILLEN: Daniel Gillen. My vote was no.
8 I believe that in the standard approval process, we
9 require two independent trials for a reason.
10 That's because we are worried about spurious
11 results that may come up, even if a .05 p-value is
12 met and we're also concerned about subgroups that
13 may, in fact, have deleterious and no effects. And
14 we run the two independent trials for that
15 particular reason. And when we run a pivotal
16 trial, we are doing that. We are raising the
17 standard, and we are raising the bar. And then the
18 question becomes do we have a strong robust
19 treatment effect that is effectively extremely
20 consistent across key subgroups that we're looking
21 at.

22 In my opinion, the study sponsor did not

1 show a strong robust treatment effect across key
2 subgroups that I would be concerned with in the
3 study.

4 DR. JOHNSON: Dr. Emerson.

5 DR. EMERSON: Scott Emerson. I voted no.
6 My major concerns relate to the pivotal trial
7 criteria, that I don't think that this met the
8 standards yet, particularly with the idea of no
9 evidence of effect in the U.S. I don't know that
10 I'd always require that if we had more evidence
11 that it was efficacious overall, but I don't think
12 it's as much of a gamble going with it when the
13 effect isn't quite as strong in the U.S.

14 But I do note that this appears to be quite
15 a heterogeneous disease in the sense of early
16 delivery and that giving people a treatment that
17 doesn't work, does that put them off from looking
18 for treatments that do; at that time, I think that
19 can be actually a dangerous situation. So I think
20 sticking with the usual standards and getting
21 another trial that would confirm the efficacy would
22 be better.

1 MS. ARONSON: I voted no, Diane Aronson, for
2 exactly the same reasons as articulated by
3 Dr. Emerson.

4 DR. BOCKMAN: Richard Bockman. I voted no
5 as well. I just took a very concrete
6 interpretation of the question, and that is that I
7 did not feel that they had provided sufficient
8 information to come to the conclusion that this was
9 sufficiently effective, particularly given that
10 only a single trial was being utilized. I
11 recognize that the need for such an agent is great,
12 but I was not convinced that this is necessarily
13 the right agent.

14 DR. HOEGER: Kathleen Hoeger. I also voted
15 no for similar reasons to those that have been
16 stated previously, recognizing that there is
17 evidence of some benefit across the trial, but as a
18 pivotal trial, insufficient support. And also, the
19 acknowledgment that with such a significant disease
20 where we have such significant morbidity and
21 mortality, we don't want to provide things that
22 aren't truly efficacious.

1 DR. ORZA: Michele Orza. I voted no. I
2 think if this were a clinical guideline committee,
3 I might have been comfortable with giving this
4 somewhere around a 2-B kind of a recommendation.
5 But this is an FDA advisory committee, and I think
6 the regulatory standard is both more specific to
7 this product and higher. And I don't think that
8 the single trial had a robust enough result to
9 support the regulatory question of efficacy.

10 DR. CLARKE: Bart Clarke, I voted no for the
11 same reasons articulated. I think there is
12 suggestion of effect here, but in the U.S.
13 population, there wasn't the effect seen.
14 Certainly would strongly encourage consideration of
15 another trial perhaps powered better to show the
16 effects that are desired.

17 DR. MONTGOMERY RICE: Valerie Montgomery
18 Rice. I voted yes, but I was clearly torn, and I
19 took the concreteness to be a little bit different
20 and reading has the applicant provided sufficient
21 information. And they did provide us information
22 from other trials that I do think point to a

1 benefit. I do not think the benefit, though, is
2 limited to just progesterone gel. I believe that
3 it is progesterone in general, and so that is why I
4 voted yes.

5 DR. HARRIS: Joseph Harris. I voted yes
6 because I thought the data was very compelling and
7 it's consistent with what's being published, both
8 in the meta-analysis from Dr. Romero as well as the
9 review in the American Journal of OB/GYN by
10 Thevenet N. Tita about the evolving concept of
11 progesterone for therapy.

12 I think the issue of this 0.01 is the
13 standard for the trial raises the question of why
14 did we even have the meeting if that's what we're
15 going to be held to. If they were held to that, we
16 shouldn't have had the meeting. The fact that we
17 had the meeting meant that that wasn't a hard and
18 fast criteria, at least that's my interpretation.

19 I think clearly there's more that needs to
20 be done in this area. The problem is not so much
21 treating preterm labor but getting to etiology.
22 The data from the New England paper by Smith about

1 parturition speaks to the multiple etiologies, and
2 not only that, the redundancy in the system. So if
3 you attack the anti-inflammatory component, there's
4 another component or the stretch mechanism. So
5 there's several things going here, and I think this
6 progesterone therapy is a piece of that puzzle,
7 obviously not the complete piece.

8 DR. HENDERSON: Cassandra Henderson. I
9 voted no. I do think that progesterone
10 supplementation probably has some role, but I don't
11 believe that the data supported this formulation
12 used this way primarily because of the
13 subpopulations. I'm really concerned about the
14 young primigravida, the obese population that we
15 have so many of. And if it's not effective in
16 those groups in the U.S., that's my patient.

17 So I'm really uncomfortable with
18 recommending approval because I think it would
19 stray away from further investigation, maybe
20 another formulation, maybe at a higher
21 concentration, maybe more frequent dosing,
22 something to address the needs of that population.

1 And my concern is, is approving something that may
2 be marginally effective, particularly in a large
3 group that I'm interested in that will prevent them
4 from having access to more research to get
5 something more effective.

6 DR. ROSEN: I'm Cliff Rosen, and I voted no.
7 I agree with many of us that .01 is probably not
8 the major issue here. I think it had marginal
9 effectiveness, but I think the concern really is in
10 the U.S. population, there really was nothing and
11 there was a very high noncompliance rate, which
12 means efficacy may be -- and the effectiveness may
13 be much less than the efficacy. And that is
14 troublesome to me. And I think that is probably my
15 most compelling reason and why I voted no.

16 DR. SCHWARZ: Eleanor Schwarz from the
17 University of Pittsburgh. I voted no perhaps
18 because of a concreteness about this high bar being
19 set. But I think it's appropriate when this is a
20 medication that is available to the population that
21 wants to use it as an off-label use. What we're
22 really deciding is whether or not they can

1 advertise that this is a way to use this
2 medication. And I think we need a little bit
3 higher level to go ahead and advertise that this is
4 a better approach than some of the others
5 available. I would ideally like a comparativeness
6 effectiveness trial, but rather than a pure placebo
7 group, a common treatment group.

8 DR. SICALLI: Tony Sicalli. I voted yes. I
9 noted first that the question is biased since it
10 reads, "given that a statistically significant
11 treatment benefit was not demonstrated." And by my
12 reading, a statistically significant effect was
13 demonstrated.

14 I was not convinced that the analysis that
15 departed from the previously developed analysis
16 plan was worth more than the analysis plan that was
17 developed prior to collecting the data. I'm a
18 strong believer that you design your study,
19 including the analysis plan first, and then you
20 stick with it.

21 I also note that while this is being cast as
22 a single pivotal trial, for those of us who read

1 the literature, it's not a single trial. And
2 although FDA did not consider the Fonseca study,
3 because it was not submitted with the FDA, that's a
4 peculiarity of our system of approving drugs. And,
5 in fact, I have to consider that this is not a
6 single trial, but this is one of now several trials
7 with the same results.

8 DR. WEINSTEIN: Lou Weinstein. I voted no
9 for several reasons. I came up in the era when we
10 were using progesterone for almost every patient in
11 the late sixties, early seventies, and it didn't
12 work then. And I think it didn't work because two
13 things. One is we have not been able to identify
14 who really would benefit from progesterone, and I
15 do believe there's a very small group of women who
16 do. But I strongly believe, and have for my whole
17 career, that the bulk of the cause of prematurity
18 is a social disease, and until we value and learn
19 the importance of pregnancy in women in this
20 country, we'll never solve the problem. And I
21 don't think a single drug will ever do that.

22 DR. JOHNSON: Julia Johnson. I voted no for

1 all the reasons that have already been outlined. I
2 do understand the need for this medication, and I
3 would strongly encourage the sponsor to go further
4 in testing this product to demonstrate more clearly
5 that, indeed, there is a benefit to women.

6 I was somewhat concerned that, indeed, their
7 initial trial was not able to show that the history
8 of preterm labor could be an effective use of this
9 medication.

10 I'm also somewhat worried that they were not
11 able to show that there really was a clinical
12 benefit to these infants, no difference overall in
13 how these babies did. And that obviously is the
14 reason to use this medication, is to give benefit
15 to these children, and I did not think they could
16 demonstrate that.

17 So thank you to everyone for voting and for
18 your comments. Now I'm going to open for
19 discussion. I will read this to you, number 2.

20 Do you believe that there is any clinical
21 explanation, based on the data in the NDA, for the
22 difference in efficacy results in the U.S. and

1 foreign populations? If yes, do you believe that
2 the explanation could be adequately addressed in
3 labeling so that the progesterone gel could be
4 safety and effectively used in the U.S. population?

5 So thoughts about the differences between
6 the U.S. and non-U.S. populations in the study and
7 then whether or not this could be explained in a
8 labeling from the FDA.

9 So I'll open it up, Dr. Greene.

10 DR. GREENE: Yes, I'll continue my harangue
11 from when I explained my vote, which is as
12 Dr. Darney has showed in the subgroup analyses, he
13 mentioned several new drugs that had been approved
14 by the agency recently where they addressed the
15 issue of subgroups in whom the drug appeared not to
16 work and they addressed that in the label. It
17 seemed not to work very well in the U.S. population
18 where noncompliance was at its highest, and I would
19 suggest that the label could address that by saying
20 that the drug won't work if you don't use it.

21 DR. JOHNSON: Dr. Davidson.

22 DR. DAVIDSON: Sorry, I really don't want to

1 be heard.

2 [Laughter.]

3 DR. DAVIDSON: Now that I've passed that
4 truth. I don't think there is a satisfactory
5 explanation for this, and whatever is suggested is
6 purely speculative.

7 DR. JOHNSON: Dr. Emerson.

8 DR. EMERSON: I'll just expand on what
9 Dr. Johnson said in her explanation before, and
10 that is that at the level of taking the history of
11 women who've had early delivery before, this
12 apparently was a very small subgroup. Now,
13 recognizing that the cerclage is an open question,
14 still it's a very small subgroup, that it couldn't
15 show through as an effect.

16 Again, the heterogeneity of the disease is
17 such that there are undoubtedly women who are prone
18 to early delivery, and the shortening of the cervix
19 is caused by that. And that perhaps there's other
20 women who the shortening of the cervix is perhaps
21 one of the earliest signs of the disease. And we
22 certainly don't have any sort of mechanisms being

1 put forward to give us an idea as to which is which
2 in this situation. And I think that further study
3 could pick this out better than us just leaping to
4 conclusions in a current indication.

5 DR. JOHNSON: I would just like to make a
6 comment that I did find it somewhat concerning that
7 just 7 percent of the participants, if they are
8 removed, that it was no longer significant. So I
9 certainly would say to the sponsor, as they prepare
10 to do a further trial with this medication, to just
11 look at those sites and assure that there was no
12 potential downside to those sites.

13 Even though I would agree with Dr. Davidson,
14 I do not think that we can find an explanation for
15 this difference, that certainly engaging more of
16 the U.S. population would be reasonable in further
17 study.

18 DR. HARRIS: Thank you. Along the same
19 line, the issue seems to be the U.S. population.
20 Would it be appropriate -- it seems that the
21 question we're begging is that if another study is
22 done, it should be done exclusively in the United

1 States, and it should be powered by a large enough
2 sample size to answer the question. And if the
3 sponsor elects to do that, then the communication
4 with the FDA needs to be better than it apparently
5 was this time around; because what I'm hearing is
6 okay, we've agreed to do this and the data is
7 presented, and the analysis is, no, that's not what
8 we want to look at regardless of what you did and
9 what we agreed to earlier. And I think that's a
10 real communication problem that has left us with
11 more questions than answers here.

12 DR. JOHNSON: Dr. Henderson.

13 DR. HENDERSON: I would like to add to
14 Dr. Harris' point. One of the things, something
15 very simple, basic kind of social science stuff,
16 compliance in the U.S. is clearly a problem, and I
17 would certainly go back to the sites to do a focus
18 group or contact participants to figure out why the
19 compliance was so poor. Was it just that they
20 didn't like the gel? Was it that no one instructed
21 them how important it was? What was the
22 communication at the sites that caused women to not

1 use the gel that they initially thought they
2 needed?

3 DR. JOHNSON: Dr. Montgomery Rice.

4 DR. MONTGOMERY RICE: I was trying to find
5 the slide. I thought that someone showed some data
6 that we were seeing overall, just in the last
7 couple years, a decrease in preterm.

8 Did I miss that? No? So we are --

9 DR. HENDERSON: No, but it's from the
10 indicated preterm delivery, from the March of Dimes
11 pushes and ACOG saying that we shouldn't just for
12 convenience schedule it, like the inductions or
13 C-section.

14 DR. MONTGOMERY RICE: So that is the reason
15 why --

16 DR. HENDERSON: That's the late preterm
17 birth --

18 DR. MONTGOMERY RICE: But it was only in the
19 late preterm birth?

20 DR. HENDERSON: Late preterm, right.

21 DR. MONTGOMERY RICE: Okay. That's what I
22 wanted to make sure.

1 DR. JOHNSON: Dr. Emerson.

2 DR. EMERSON: Just in response, I am not a
3 believer that a future trial would have to be just
4 done in the U.S. I think that the concept is that
5 there are times that just the additional
6 information and having greater precision allows
7 clinicians to know how to use things and recognize
8 that the effect that we're seeing overall is not
9 the same effect that you might see in the U.S.
10 population, but the idea is that it's an
11 efficacious drug and it's safe. And that
12 additional information is needed in order to be
13 able to go with that, to say the idea, is there's
14 some evidence of something going on.

15 I'll also say that I'm not real quick to say
16 that patients who are not compliant are just bad
17 patients. Sometimes their noncompliance is what
18 saves us from having a terrible safety issue, and
19 that sometimes the patients are stopping a drug and
20 the drug is effective in the population precisely
21 because those patients who get in trouble stop
22 taking it.

1 DR. JOHNSON: Dr. Davidson.

2 DR. DAVIDSON: Oh, one final comment. I
3 think that there were enough patients and a
4 sizeable introduction to this drug that if it were
5 really effective at this formulation, it would have
6 been more obvious with the size of this study. And
7 I am concerned that even if they pursued the same
8 study similar to this design, the results would be
9 the same.

10 DR. JOHNSON: Was there any comment from the
11 sponsor?

12 DR. CREASY: Well, I would like to address
13 two things. First, the issue of compliance, there
14 was a remarkable difference between compliance in
15 the 300 trial and the 302 study. Women who have a
16 history of preterm birth know they have a big
17 problem. They've faced it before, and they
18 probably don't want to face it again. And so
19 they're more likely to be compliant with their
20 drug, and in the 300 study, the compliance rates
21 were well over 95 percent.

22 In this trial, short cervix is well known

1 among obstetricians to be a high-risk factor. It's
2 not well known among patients, and most of the
3 patients in this trial were first-time pregnancies.
4 They're the ones who are contributing most of the
5 preterm births in this country. They don't think
6 they have a problem. Their friends didn't have a
7 problem. Their pregnancy is going to be just fine.

8 So even when they're told that they have a
9 high-risk factor that they never heard of before,
10 they're less likely to be compliant. And I think
11 that's what happened in our trial. And we could so
12 some focus groups, but I think what we're going to
13 find is they didn't believe they were at risk to
14 begin with.

15 The second thing that I'd like Dr. Murtha to
16 address is the ability to do another placebo-
17 controlled trial.

18 DR. MURTHA: I think as was suggested by
19 Dr. Platt -- and I can echo some comments that I've
20 heard him say as well, that our societies are
21 currently in the process of evaluating routine
22 intravaginal ultrasound screening for cervical

1 length to implement this strategy. And so we're
2 looking to the American College of OB/GYN and the
3 Society for Maternal Fetal Medicine and others to
4 guide us in how we manage a short cervix.

5 So with that being said, the opportunity to
6 do another placebo-controlled trial in the U.S.,
7 which is what we would all probably like would be
8 virtually impossible.

9 I think the other important thing that I
10 just wanted to clarify is that when we talk about
11 if we give vaginal progesterone to pregnant women
12 with a short cervix, that we might be withholding
13 some other therapy that's effective, we don't have
14 any other therapy that's effective. We have
15 nothing else, and that's basically what we're
16 trying to do, is be able to offer to these women
17 something.

18 DR. JOHNSON: Dr. Montgomery Rice.

19 DR. MONTGOMERY RICE: Can you clarify --
20 you're saying that -- the two societies are about
21 to develop guidelines? Is that what you're saying?
22 And that because you're going to develop

1 guidelines, we cannot do any -- it would be
2 impossible to do another placebo-controlled trial?

3 Please clarify.

4 DR. PLATT: Yes, Dr. Montgomery Rice, that's
5 correct. Society of Maternal Fetal Medicine, a
6 working collaboration with ACOG -- and now what I
7 mentioned earlier, the Pregnancy Quality
8 Foundation, are working at creating guidelines
9 based on the studies that have been published as
10 well as the meta-analysis.

11 If I can have the slide up, I can show you
12 what was recently in the SMFM website newsletter to
13 members, and this is a direct quote from it.

14 "As a result of accumulating evidence, SMFM
15 is collaborating on final guidelines for making
16 cervical length screening and vaginal progesterone
17 therapy a standard part of obstetrical care."

18 Now, it'll take a while before clearly the
19 societies formulate that plan. As we know, it's
20 got to go through ACOG and all the guidelines. But
21 I can tell you that, number one, that will happen
22 before a guideline, there will be an educational

1 program by the Pregnancy Quality Foundation.
2 There's already a task force that's been formed to,
3 again, further educate people on the importance of
4 recognition of short cervix.

5 DR. MONTGOMERY RICE: With all due respect
6 and having served on many of those boards, just
7 because those groups and boards develop guidelines
8 does not usurp good sound practice with randomized
9 placebo-controlled trials. And part of what the
10 role of the FDA is, is to make sure that we are
11 approving therapy that has undergone the rigor that
12 has been put forth, that is going to do the least
13 amount to the patient and the benefits must
14 outweigh that.

15 I'm going to go back to hormone replacement
16 therapy. There were lots of guidelines put out by
17 each of those groups on hormone replacement
18 therapy, and when the randomized placebo-controlled
19 trials came out, there were challenges. And I'm
20 not saying that those trials did not have
21 challenges with those, but we learned a lot more
22 from doing those trials than we would have ever

1 learned from people putting out guidelines. And
2 you don't have -- now, I was flexible, number one,
3 in when I voted initially, but you didn't meet the
4 guidelines as agreed upon with the FDA for .01,
5 okay? But I believe that there is some efficacy
6 here. But that doesn't mean that we stop doing the
7 research to really address the important issues
8 that we may not have even uncovered yet for the
9 patients.

10 DR. PLATT: I would submit to you that I
11 don't think we'll ever stop doing research based on
12 a guideline. I think it's important to continue
13 and continue to evaluate what we're doing as
14 clinical practice always. So I don't think the
15 fact that societies are looking at guidelines will
16 tell people it's the only treatment and the
17 ultimate treatment.

18 DR. JOHNSON: I'd like to go ahead and make
19 a comment, too. It's concerning to hear you say
20 this, that there would be the FDA and an advisory
21 committee, and we advised against approval of this
22 medication, but you're going to recommend it to

1 your members. I think you need to think about this
2 issue and consider the fact that you're
3 recommending something that is not FDA approved for
4 use in your patients based on data that is believed
5 rather than proven. I find this concerning.

6 DR. PLATT: Let me make the following
7 comment. I don't think preparing guidelines,
8 awaiting a panel's report means that they will come
9 out against what the panel had said. I think the
10 guidelines will respect what the panel has to say,
11 and I think, as everyone knows, looking at
12 guidelines, it takes months or often years to
13 formulate an agreement. So I don't think that they
14 would come out against something that's been
15 advised.

16 DR. JOHNSON: Dr. Sicalli.

17 DR. SICALLI: Well, since we're getting far
18 afield, I thought I'd get a little more far afield
19 and just make the comment that I've been involved
20 in a project at Georgetown on the ethical propriety
21 of using placebos at all in research like this.
22 And this is an old story, and FDA has fought this

1 battle for a long time.

2 But after the appearance of the Fonseca
3 study, I would seriously question a trial for
4 vaginal progesterone formulations that used a
5 placebo control rather than a vaginal progesterone
6 control. And we don't need to argue that; it's not
7 in our charge. But I don't think that the points
8 of view being raised at that microphone over there
9 are so outlandish.

10 DR. MONTGOMERY RICE: I agree with you.

11 DR. JOHNSON: Dr. Greene.

12 DR. GREENE: So I'd like to add to those
13 comments. I thank Tony for that. I think that
14 there are several issues about the possibility of
15 doing another trial. One is the assumption of
16 equipoise, which is what Tony was getting to, and
17 is there still the assumption of equipoise that's
18 possible, given all the available data, number one.

19 Number two, whether there is an assumption
20 of equipoise or not, the train is sort of too far
21 down the tracks. I think you're going to have
22 difficulty getting physicians and patients to agree

1 to participate in a trial where there's a placebo
2 arm.

3 And, number three, just to respond about the
4 guidelines with respect to hormone replacement
5 therapy, with all due respect, those were all based
6 on observational studies and not randomized control
7 trials. And when the randomized control trials
8 came in, they said, oops, maybe observational
9 studies had built-in bias. So I think that there
10 is a difference.

11 And finally, the professional societies are
12 not going to recommend this preparation that the
13 committee has just voted down. They're going to
14 recommend vaginal progesterone in available and
15 other preparations.

16 DR. JOHNSON: Thank you for your comments.

17 I would just say that there is no vaginal
18 progesterone that is approved for this purpose.

19 DR. GREENE: Certainly not approved,
20 absolutely right.

21 DR. JOHNSON: Other comments?

22 [No response.]

1 DR. JOHNSON: Thank you for that vigorous
2 discussion. That was very good.

3 Now we shall move on to -- any other last
4 comments on this topic?

5 [No response.]

6 DR. JOHNSON: Thank you very much.

7 Now I'll move on to discussion of point 3,
8 has the applicant provided sufficient information
9 to conclude that the safety profile for
10 progesterone gel is acceptable for the proposed
11 indication? So a safety question.

12 DR. GUT: Yes, I think the applicant
13 provided sufficient safety information for
14 progesterone gel, and I will even refer to the
15 statement from Dr. Lisa Soule when she said a great
16 deal of safety information about progesterone gel,
17 even from early pregnancy treatment, which is, as
18 we know, very important.

19 DR. JOHNSON: Ms. Aronson.

20 MS. ARONSON: This is the area where I feel
21 concern. The issue of two cases, for instance, of
22 the male congenital abnormality of hypospadias,

1 which has been linked to women who have used
2 progesterone in ART cycles, is troubling because
3 there were no cases of hypospadias in the placebo
4 arm. So I'm still -- I would like more information
5 about the cases of hypospadias, and again, the DES,
6 the uses of hormones for women in the past, the
7 long-term studies prove something different.

8 It's just the hormonal connection to -- if
9 this is just seen as okay, broad use, okay if some
10 has preterm risk, that's where I start to come on
11 the precipice about concern that we really don't
12 fully understand yet if there are more safety
13 issues.

14 DR. JOHNSON: Dr. Sicalli.

15 DR. SICALLI: In response about the
16 hypospadias, this product was used several months
17 after hypospadias formed. So those two cases of
18 hypospadias would not have been related to the
19 treatment.

20 My answer to the question generally is yes,
21 but I think that given the wealth of data available
22 on other progestins, granted not progesterone, and

1 the wealth of nonclinical data available on
2 progesterone and non-progesterone progestins, that
3 a fuller presentation would have been possible and
4 might have been desirable. However, the standard
5 safety data were demonstrated, and I think it was
6 sufficient, although perhaps there are some people
7 here who would have felt better with a more
8 detailed presentation.

9 DR. JOHNSON: Dr. Greene.

10 DR. GREENE: So just as Tony said, the
11 formation of the penile urethra is all over by
12 12 weeks, long ago, and so they're not even
13 screening for the condition for this until well
14 beyond that. So the first trimester exposure is an
15 issue but not well into the second trimester.

16 As far as the concern about the analogy,
17 potential analogy to DES, that's always a concern
18 whenever we're talking about using steroid
19 hormones, sex steroid hormones in pregnancy. The
20 differences between natural progesterone and DES
21 are enormous just chemically. So that the DES
22 completely sidestepped the normal carrier

1 mechanisms in the serum for sex steroids so that it
2 reached receptors at levels that were orders of
3 magnitude higher than we're talking about with any
4 natural sex steroid, number one. And number two is
5 that this progesterone is bioidentical to the
6 progesterone that's produced in the human placenta
7 and increases that level of progesterone very
8 modestly. So I'm really not concerned. I don't
9 think there are any safety issues here.

10 We can talk about the efficacy, but I don't
11 think there are really any issues about safety.

12 DR. JOHNSON: Dr. Orza.

13 DR. ORZA: I worry that we're dealing with
14 so little data even to feel like we had enough
15 power on the efficacy side, that there really isn't
16 enough for a lot of the safety questions,
17 especially the ones that will occur at a very low
18 frequency and over a long period of time. And this
19 committee just went through two meetings, one on
20 bisphosphonates and one on fourth generation
21 progestins, where it was on the market for 10 years
22 or more before serious adverse events started to

1 emerge.

2 So I just think when you're dealing with
3 something that is affecting a fetus, you just don't
4 know. And I would feel better if we had in place,
5 or if FDA could put in place as part of its new
6 sort of phase 4 kind of tools that it has to work
7 with, a really good registry of pregnant women.
8 There's a lot that we can learn from something like
9 that.

10 But I worry that -- especially when we're
11 talking about this being in very widespread use and
12 having only really two years of data on a very
13 small number of babies, I just think it's
14 impossible for us to know. I can see this
15 committee, we'll all be different, but in 10 years
16 from now, looking back on this and discovering we
17 just would never have even thought of.

18 DR. JOHNSON: Dr. Weinstein.

19 DR. WEINSTEIN: I think the sponsors have
20 done what they can do as related to the safety
21 issue with the small numbers in this short length
22 of time. But we have over 50 years of synthetic

1 progestins in birth control pills with unintended
2 pregnancies by accidents, and we also have the
3 failure of hydroxyprogesterone acetate with
4 patients who get pregnant. And clearly, if the
5 synthetic progestins -- although they were
6 initially associated with cardiac defects from the
7 English data, which has not been proved to be true.
8 But if they haven't shown to cause congenital
9 anomalies, it's highly unlikely the naturals will.
10 And so I'm very comfortable with the safety aspects
11 of the drug. It's just the efficaciousness that is
12 critical.

13 DR. JOHNSON: Dr. Montgomery Rice.

14 DR. MONTGOMERY RICE: I think for us who
15 have used progesterone for years and progestins for
16 years, I think we are very comfortable with the
17 fact that -- of the safety profile, based on our
18 infertility population and in all of our
19 reproductive age patients who have taken it for one
20 reason or another.

21 But I don't devalue what you're saying here,
22 and I think that one of the things that we should

1 definitely move to -- technology allows us to do it
2 so much more easier now these days is that,
3 definitely, you can set up a registry and have some
4 way that you can track this such that for our
5 children who are sitting on this panel 10, 15,
6 20 years from now, they won't say that we just
7 ignored the obvious use of capturing some
8 information that was of value. I think we can make
9 that recommendation, if nothing else.

10 DR. JOHNSON: Thank you very much for your
11 input, panel.

12 And I would just add to what Dr. Montgomery
13 Rice just said. This has been used, as you stated,
14 as Dr. Soule noted before, infertility patients.
15 If we even can put together a registry, that's a
16 much more robust, larger group, and anything that
17 the company itself could contribute, that may be
18 very reassuring at future advisory committee
19 events.

20 So now we shall move on to our second vote,
21 which is Question 4. Is there an overall
22 risk-benefit profile for progestin gel acceptable

1 to support approval of this product in the U.S. for
2 the proposed indication?

3 So again, you will press yes, no or abstain.
4 Press it three times on whether or not the overall
5 risk-benefit profile is acceptable to approve this
6 product.

7 [Voting.]

8 DR. JOHNSON: So our vote is yes, 4; no, 13;
9 abstain, zero, no voting zero.

10 So as we go around the room and say your
11 name and your vote, if you did vote no, please
12 discuss any recommendations you may have regarding
13 the design of a new study to investigate efficacy
14 and safety in the U.S. population.

15 So let us begin on the other side this time
16 and go with Dr. Weinstein first.

17 DR. WEINSTEIN: I interpreted this as very
18 similar to the first question, so obviously, I
19 voted no again. If I was advising the company to
20 do a study, I think the study needs to be done in
21 the U.S. and it needs to be done in a middle-class
22 population, and it needs to be done in a private

1 setting.

2 Too many times the university setting
3 continues to use lower socioeconomic patients who
4 really are not the same as what happens in the
5 private doctor's office, and so I would strongly
6 advise them -- if we could only identify which
7 group of patients would benefit from progesterone,
8 either gel or intramuscular, I think it would be a
9 major benefit to our women who are reproducing.
10 But I don't think repeating the study as you've
11 done it will do any good, as sort of as Ezra had
12 alluded to.

13 DR. SICALLI: Tony Sicalli. I voted yes for
14 reasons that I've already put on the record.

15 DR. SCHWARZ: Eleanor Schwarz, University of
16 Pittsburg. I voted yes because I think the risks
17 are very, very low. But as I said before, I think
18 more study is warranted.

19 DR. ROSEN: Cliff Rosen. I voted no. I
20 think a comparative effectiveness trial might be
21 warranted compared to the other form of
22 progesterone, and that might be a reasonable

1 approach for the sponsor. But in terms of
2 approval, there really isn't a trial I think that
3 could be done other than what Dr. Weinstein said,
4 which is trying to look in the United States
5 population for individuals that would be more
6 appropriate. So again, I voted no for the reasons
7 I had stated previously.

8 DR. HENDERSON: Cassandra Henderson. I
9 voted no for the reasons I stated previously. I
10 think a future trial would look to address issues
11 of obesity and preterm delivery and also younger
12 women who deliver spontaneously preterm.

13 DR. HARRIS: Joseph Harris. I voted yes for
14 the same reasons I outlined before. In addition,
15 the apparent risk for this intervention in this
16 drug is virtually zero.

17 DR. JOHNSON: Julia Johnson, and I voted no.
18 I do think there is an opportunity to look at this
19 more closely with -- I agree that the U.S.
20 population would make sense, although I do not
21 think it has to be all U.S. population. I
22 certainly would go with what Dr. Henderson said

1 earlier and consider looking at what the issue was
2 with compliance, to see if we can improve
3 compliance because that will be the same issue that
4 will happen once this comes out on the market for
5 the shortened cervix. Thanks.

6 DR. MONTGOMERY RICE: I voted no, and the
7 reason is because although I do believe that there
8 is benefit to progesterone in preventing preterm, I
9 do not think that that benefit is unique to the
10 progesterone gel. And I would like to see a
11 comparative effectiveness trial that would be done
12 with other vaginal progesterone preparations, and I
13 think that the risk was definitely low. But I
14 think this is not something that's unique to this
15 progesterone gel.

16 DR. CLARKE: Bart Clarke. I voted no for
17 the same reasons mentioned before, but I do think
18 that a trial would be useful to try to tease out
19 the differences. Whether you do it with placebo or
20 another comparator drug, I think that's the choice.
21 I think ethically, you can justify a
22 placebo-controlled trial if there's no currently

1 accepted agent to treat this condition. On the
2 other hand, practice is changing, and that's a
3 reality that we face.

4 DR. ORZA: Michele Orza. I voted no because
5 I didn't think the -- I voted no on the efficacy,
6 and I didn't think that there -- if you can't
7 demonstrate the efficacy, it doesn't matter if
8 there are no safety consequences. There's no point
9 in giving it to people.

10 But I also don't feel sanguine about the
11 safety side, and I think the kind of data that's
12 apparently out there with spontaneous reporting on
13 14 years of experience with this drug is not the
14 kind of data I'm looking for. The kinds of
15 concerns I have would not be discovered through
16 spontaneous reporting.

17 DR. HOEGER: Kathleen Hoeger. I also voted
18 no for the same reasons I stated in the first vote.

19 With respect to another trial, I agree with
20 those that have stated earlier that we need a
21 better understanding of what the compliance issues
22 are, as the sponsor believes that this is the

1 reason for the lower efficacy in the U.S.
2 subpopulation. We have to look at what's going to
3 be out there when we approve a drug, and if we
4 can't understand how to do that, we can't label
5 properly compliance. Telling a patient just to
6 take a drug is not the reason they don't take it
7 sometimes.

8 DR. BOCKMAN: Richard Bockman, I voted no.
9 First of all, I am comfortable with the risk
10 aspect. I think it's low to the point where I
11 would support perhaps a larger study. I presume
12 that any study would try to achieve the highest
13 compliance possible. Because I am comfortable with
14 the safety data, I might suggest that in addition
15 to comparison study that some increased doses might
16 be tested as well.

17 MS. ARONSON: Diane Aronson, I voted no for
18 the reasons stated by Dr. Orza. And as far
19 as -- there's been suggestions about a patient
20 registry. I don't know if that's something that
21 can be funded, but certainly, there'd be a lot more
22 gained from safety issues.

1 DR. EMERSON: Scott Emerson. I voted no for
2 reasons stated earlier with the restatement that
3 had I been confronted with two trials that were
4 independent that had these same results, I probably
5 would have then voted yes. So the aspect that I'm
6 not certain they have to do something different; I
7 just want confirmation of their quite similar
8 profile.

9 DR. GILLEN: Daniel Gillen. I voted no.
10 Like many before me, I'm relatively comfortable
11 with the risk profile that I've seen to this point,
12 at least given the data that we have. But as was
13 noted earlier, we're dealing with a heterogeneous
14 population with respect, I believe, to their
15 reaction to the intervention. And so really what I
16 would be seeking in a second confirmatory trial
17 would be looking for higher precision on the
18 overall marginal effect of what we have.

19 DR. GREENE: Mike Greene. I voted yes. And
20 I would like to point out -- and I'd like people in
21 the agency to correct me if I'm wrong, but I do
22 believe this would not be unprecedented to approve

1 this drug with one demonstrative trial. I believe
2 that was done with 17 hydroxyprogesterone caproate.
3 The Mease trial, which was efficacious, was the
4 only trial upon which 17-OHP was approved. So this
5 would not be unprecedented. Please correct me if
6 I'm wrong.

7 Next is that there really are no
8 alternatives that have any evidence of efficacy at
9 preventing preterm birth other than progesterone in
10 its various forms for various indications. We
11 would all love to have 14 years or 15 or 20 years
12 worth of data on 100,000 treated patients to know
13 for sure that there are no safety issues, but we
14 never have that kind of data at the time we make an
15 approval of a product.

16 So that's always an issue. We didn't know
17 about Fen-Phen until it had been on the market for
18 years. There are going to be effects that are seen
19 only after 4 or 5, 10 years of exposure like with
20 bisphosphonates. So you're not going to have that
21 at the time of approval of any drug, as important
22 as it may be.

1 Finally, the other reason that I'd like to
2 see approval is because as happened with Makena,
3 17 hydroxyprogesterone caproate, it would be nice
4 to have some competition in the marketplace that
5 would prevent the outrageous price gouging that
6 occurs with only a single approved efficacious
7 agent.

8 DR. DAVIDSON: Ezra Davidson. I voted no.
9 I'm not sure I have any good advice about another
10 trial. I think a trial has to be done. I
11 certainly would not repeat this trial at the same
12 dose.

13 DR. JOHNSON: Thank you very much.

14 In summary from this last vote, the overall
15 information from the advisory committee is that
16 they voted no. And although they do agree that
17 there may be some potential great benefit with
18 treating this critical disorder, there is not
19 sufficient data to document the efficacy. There is
20 very limited concern about safety, although the
21 long-term effect of using this medication is an
22 understandable concern going forward.

1 Finally, in recommendations for new studies
2 there, I'd say it's a general consensus that even
3 though the exact same study could be done again,
4 that there may be some benefit in doing either a
5 comparative effectiveness study looking at
6 different dosing and perhaps looking at the U.S. or
7 other populations in looking at the nonacademic
8 population, and certainly to try to address the
9 issue of compliance with the subsequent study.

10 So now in that conclusion, I would like to
11 look to the advisory committee for last comments.

12 Dr. Emerson.

13 DR. EMERSON: I just want put the
14 perspective for the statistical bias and the lack
15 of clinical expertise might put on this. But when
16 I'm confronted with the situation where people say
17 but we have nothing else, that over the past years
18 that we've been studying this thing, we have
19 nothing else, I presume we've been studying it.
20 And so you're telling me that we've been doing lots
21 and lots of trials or other studies and we haven't
22 been successful tells me that the prevalence of

1 good treatments out there is relatively low,
2 thereby increasing the chance that the first time
3 we see something that's statistically significant,
4 it's a false positive rather than a true positive.

5 So that's precisely the situation that you
6 have to be more careful in, is that when you start
7 out with a low prevalence, a positive result is
8 less indicative of a good treatment.

9 DR. JOHNSON: Dr. Greene.

10 DR. GREENE: A couple of comments just about
11 a comparative effectiveness trial. I think it's
12 fairly clear that if there is going to be a
13 comparative effectiveness trial, it's going to have
14 to be federally funded. It is extraordinarily
15 unlikely that a sponsor would do such a study for
16 reasons that all of us around the table understand.

17 Then the other, just to address Lou's issue
18 about doing it in private practices, I think that
19 everybody who's tried to do a large study knows the
20 difficulties encountered in trying to recruit
21 patients in private practices. I think it's
22 impractical and unlikely.

1 DR. JOHNSON: Dr. Orza.

2 DR. ORZA: I just wanted to clarify that I
3 don't think that the kind of data I was talking
4 about, long-term safety data, are required for
5 approval, but they're a reason to not take lightly
6 a weak signal for efficacy and say, well, because
7 there's no downside, go ahead and let it through;
8 and also, that as a condition of approval that
9 there be a requirement for some really long-term
10 follow-up on some of the babies.

11 DR. JOHNSON: Yes, Dr. Schwarz?

12 DR. SCHWARZ: While we are talking about
13 things we'd like to monitor for signal, I'd like to
14 also put a call to monitor the effects of
15 medications we administer during pregnancy on
16 women's subsequent abilities to breastfeed their
17 children and whether there's any effect on the
18 lactation experience.

19 **Adjournment**

20 DR. JOHNSON: I would like to very much
21 thank the advisory committee for your hard work.
22 I'd also like to offer my thanks to the sponsors

1 for the information provided as well to the FDA for
2 the excellent information. This meeting is
3 adjourned.

4 (Whereupon, at 3:52 p.m., the meeting was
5 adjourned.)

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