

FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH
 ADVISORY COMMITTEE FOR REPRODUCTIVE
 HEALTH DRUGS

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Monday,
 April 20, 1998

Ballroom
 Holiday Inn
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

IN ATTENDANCE:

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IN ATTENDANCE: (Continued)

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 Urologic Drug Products
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 Research Institute for NDA 20-797 Antocin
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 Premature Labor**

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P R O C E E D I N G S

(8:30 a.m.)

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DR. PETITTI: Good morning. Welcome to the advisory committee meeting for reproductive health drugs. We are here today to consider the issue of the New Drug Application No. 20-797 for Antocin (atosiban). I'd like to begin the meeting by having introductions of the people sitting around the table.

I'll start. My name's Diana Petitti. I am the director of research and evaluation for Kaiser Permanente of Southern California, and I'd like Dr. Rarick to introduce herself, and then we'll go around the table this way.

DR. RARICK: Hi, I'm Dr. Rarick. I'm the division director for reproductive and urologic drug products at the Center for Drug Evaluation and Research.

DR. VAN MARTER: I'm Linda Van Marter. I'm a neonatologist and epidemiologist at Children's Hospital and Brigham and Women's Hospital in Boston.

DR. HAMMOND: I'm Mary Hammond. I'm a reproductive endocrinologist. I'm in private practice in Raleigh, North Carolina.

DR. LEWIS: I'm Vivian Lewis. I'm director of reproductive endocrinology at University of Rochester.

DR. BROWN: I'm Haywood Brown. I'm director of obstetrics at Wishard Hospital, at Indiana University

1 School of Medicine in Indianapolis.

2 DR. AZZIZ: I'm Ricardo Azziz, professor of
3 obstetrics and gynecology and medicine at the University of
4 Alabama at Birmingham.

5 MS. TOPPER: I'm Kimberly Topper. I'm exec sec
6 for this committee.

7 DR. HARRIS: I'm Joseph Harris in maternal-
8 fetal medicine at King/Drew Medical Center, Los Angeles.

9 MS. SCOTT: Julia Scott, National Black Women's
10 Health Project.

11 DR. D'AGOSTINO: Ralph D'Agostino, statistician
12 from Boston University.

13 MS. NARRIGAN: Deborah Narrigan, nurse-midwife
14 from Nashville, Tennessee.

15 DR. OH: I'm Bill Oh. I'm a neonatologist and
16 chairman of pediatrics at Brown University in Providence,
17 Rhode Island.

18 DR. DATTEL: Bonnie Dattel, professor of
19 obstetrics and gynecology, Division of Maternal-Fetal
20 Medicine, Eastern Virginia Medical School.

21 DR. PETITTI: The first order of the day is to
22 have some opening remarks by Dr. Rarick.

23 DR. RARICK: And I'll be brief. As you'll see,
24 the next order will be our conflict of interest statement,
25 and for those of you wondering who at the table is going to

1 be voting, et cetera, we'll be hearing from Kimberly next.
2 But I do want to say good morning and welcome to all of you
3 who have joined us today and some who will be showing up
4 soon, I'm sure.

5 Today, as you know, we're here to discuss a new
6 drug application for atosiban, which is an oxytocin
7 antagonist, for the management of preterm labor. It's been
8 a very interesting drug development process and review
9 process, and we're very pleased that the sponsor has joined
10 us this morning and is going to be discussing their
11 perspectives on the review, and you'll be hearing the FDA's
12 also. It's an incredibly important condition, preterm
13 labor, with dire and important and difficult consequences,
14 and we'll be anxious to hear all of your deliberations.

15 I'm always allowed one groaner joke per
16 advisory committee. Of course, my staff has been very poor
17 at giving me groaner jokes these days, because they're all
18 interested in erectile dysfunction now and contraception,
19 so I had to turn to my third-grader, my 8-year-old, and she
20 told me this morning from her cereal box, "Now, we all know
21 that April showers bring May flowers, but what do May
22 flowers bring? Pilgrims."

23 (Laughter.)

24 DR. RARICK: I'm sorry. That's it for groaner
25 jokes, and, yes, she is 8, and I'll have to thank her later

1 today.

2 Why don't I let Kimberly go ahead and let us
3 know who's going to be voting and what the conflicts might
4 be today, and I will remind those who speak during the open
5 public hearing and other folks who may get up to ask
6 questions to always identify yourselves and declare or
7 disclose any conflicts you may have.

8 Kimberly?

9 MS. TOPPER: The following announcement
10 addresses the issue of conflict of interest with regard to
11 this meeting and is made part of the record to preclude
12 even the appearance of such at this meeting:

13 Based on the submitted agenda for the meeting
14 and all financial interests reported by the committee
15 participants, it has been determined that all interests in
16 firms regulated by the Center for Drug Evaluation and
17 Research present no potential for an appearance of conflict
18 of interest at this meeting.

19 With respect to FDA's invited guest speaker,
20 Dr. Linda Van Marter has reported an interest which we
21 believe should be made public to allow the participants to
22 objectively evaluate her comments. Dr. Van Marter would
23 like to disclose for the record that her employer, the
24 Brigham and Women's Hospital, might have been a trial site
25 for Antocin.

1 In the event that the discussions involve any
2 other products or firms not already on the agenda for which
3 an FDA participant has a financial interest, the
4 participants are aware of the need to exclude themselves
5 from such involvement, and their exclusion will be noted
6 for the record. With respect to all other participants, we
7 ask in the interest of fairness that they address any
8 current or previous financial interests with any firm whose
9 products they may wish to comment upon.

10 Everyone who is seated at the table, with the
11 exception of the FDA and Dr. Linda Van Marter and Dr.
12 William Oh, has been cleared for voting.

13 Thank you.

14 DR. PETITTI: I'd like to move along now with
15 the next section of the presentation, which is the
16 presentation by the Robert Wood Johnson Pharmaceutical
17 Research Institute. Each of the speakers for this section
18 will be introduced by the sponsor, and we'll move right
19 along in the agenda.

20 Dr. Dunton?

21 DR. DUNTON: Good morning. I'm Dr. Alan
22 Dunton, vice president of global clinical research and
23 development for the R.W. Johnson Pharmaceutical Research
24 Institute, referred to today as PRI. I'd like to thank Dr.
25 Diana Petitti and the committee for being here to consider

1 Antocin, a new and novel therapeutic agent for the
2 treatment of preterm labor. I'd like to request that we do
3 hold all questions until the end of the formal
4 presentations.

5 Antocin, or atosiban, as it is generically
6 known, is a 9 amino acid peptide. It is an oxytocin
7 antagonist that was discovered by Ferring Pharmaceuticals,
8 located in Sweden. PRI licensed atosiban for development
9 in the U.S., while Ferring conducted development of the
10 drug outside the U.S.

11 Oxytocin is the most potent known stimulator of
12 myometrial contractions. It stimulates both the frequency
13 and force of contractions. Oxytocin is used
14 therapeutically for inducing labor at term and is the most
15 widely used agent for labor induction worldwide. Oxytocin
16 also stimulates the production of prostaglandins, which are
17 potent stimulators of uterine contraction.

18 Let's now review the rationale for the
19 development of atosiban for use in preterm labor. In in
20 vitro studies, atosiban blocked the effects of oxytocin on
21 human myometrial contractions. In studies in rats and in
22 rhesus monkeys, atosiban has been shown to delay the
23 initiation and progression of labor in a dose-dependent
24 manner. In early clinical studies, a majority of patients
25 with preterm labor experienced either complete or partial

1 inhibition of uterine contractions when atosiban was
2 infused intravenously, thus providing further evidence that
3 oxytocin and its receptors are involved in the etiology of
4 preterm labor.

5 A final but important part of the rationale for
6 investigating atosiban as a treatment for preterm labor is
7 the fact that it has been shown to have significantly less
8 maternal adverse effects that have been associated with the
9 only currently approved tocolytic. The actions of atosiban
10 are specific. Other tocolytics are non-specific and are,
11 therefore, associated with numerous and often serious side
12 effects.

13 At present in the United States, less than 10
14 percent of the patients who receive tocolytic therapy
15 receive a drug which has been proven safe and effective to
16 the satisfaction of the FDA. The most widely used
17 therapies are magnesium sulfate and terbutaline, which have
18 not received regulatory review and approval in the U.S.
19 Atosiban, therefore, offers an important option for the
20 majority of patients who could benefit from tocolysis, with
21 significantly less maternal side effects than those
22 normally seen for beta-mimetics or magnesium sulfate.

23 The clinical program consisted of 27 studies.
24 Eight of the studies were randomized clinical trials
25 designed to evaluate the efficacy and safety of atosiban in

1 preterm labor. The remaining 19 studies were clinical
2 pharmacology studies. In all, we enrolled more than 2,300
3 pregnant women; more than 1,600 pregnant women received
4 atosiban. Over 1,000 women received atosiban in the U.S.
5 Phase II/III studies, and over 600 in ex-U.S. Phase III
6 trials.

7 It is now well accepted by the perinatology
8 community that a prolongation of gestation by 48 hours is
9 not only meaningful, but desirable, and it is the expected
10 goal of tocolysis. It gives the obstetrician enough time
11 to administer antenatal steroids and/or to transfer the
12 mother to another facility if necessary.

13 In our briefing book, we recommended the use of
14 atosiban for the management of preterm labor in suitable
15 patients. We stated that the data to support the efficacy
16 and safety of atosiban under 28 weeks of gestational age
17 are inconclusive. We also know that antenatal steroids are
18 most effective at greater than or equal to 28 weeks of
19 gestation. Therefore, we have concluded that atosiban is
20 indicated as follows: Antocin, or atosiban, is indicated
21 for the acute treatment of preterm labor for up to 48 hours
22 in patients who are at least 28 weeks of gestation to
23 facilitate therapies designed to hasten fetal lung
24 maturation and/or for maternal transfer to more appropriate
25 facilities.

1 I mentioned earlier that only 10 percent of
2 patients receiving tocolysis in the U.S. receive FDA-
3 approved drug treatment, while the other 90 percent are
4 using drug therapies which have not been the subject of
5 FDA's NDA review process and/or an NDA advisory committee
6 evaluation. Having been involved with the Antocin project
7 for the last 2 years, the reasons for this are clear to me:
8 this is a very difficult indication to study, the diagnosis
9 is only made with certainty at delivery, causative factors
10 are many, the endpoint for proving efficacy is open to
11 debate, and there is need to consider both mother and baby.
12 However, as a physician and as a father, it's also clear
13 that the issues associated with prescription drug
14 development for complications of pregnancy and childbirth
15 can -- and I add, may appropriately -- become emotional,
16 losing sight sometimes of logic and scientific rigor.

17 Many companies have shied away from developing
18 products in this area. We are here today not because we
19 believe atosiban is the complete answer to the problem of
20 preterm labor. We are here because we have an obligation
21 as a responsible company to have a full, open, and public
22 discussion of the data. More importantly, we believe that
23 we do have a safe and effective option for physicians to
24 use in appropriate patients in preterm labor.

25 Today's agenda will include the following:

1 After my introduction, there will be a presentation on
2 preterm labor and the available treatments by Dr. Steven
3 Caritis, professor at the University of Pittsburgh School
4 of Medicine. Dr. Caritis is a practicing perinatologist
5 and a Phase III investigator.

6 Next, a presentation of the preclinical safety
7 and pharmacokinetics by Dr. Robert Wills, vice president of
8 preclinical development at PRI.

9 Dr. George Creasy, director of clinical
10 research at PRI and the medical monitor of the Antocin
11 project, will present a portion of the clinical program.
12 Additional clinical results will be presented by Dr. Per
13 Bengtsson, director of medical research from Ferring.

14 Because infant outcomes are an important aspect
15 to this project, we have asked Dr. Robert Ward to analyze
16 and interpret the infant safety data. Dr. Ward is
17 professor at the University of Utah School of Medicine. He
18 is a practicing neonatologist and a pediatric clinical
19 pharmacologist.

20 Dr. Roberto Romero, a noted perinatologist,
21 will review the data generated on Antocin and provide the
22 rationale for why Antocin is needed and why it should be
23 approved for the treatment of preterm labor. Dr. Romero is
24 a professor at Wayne State University School of Medicine.
25 He is a practicing perinatologist and was also the lead

1 investigator in our pivotal Phase III study. He is also
2 chief of the Perinatology Branch at the NICHD, and I should
3 add that Dr. Romero is here today as a private citizen.

4 Dr. George Creasy will wrap up the formal
5 presentations with a brief summary, as well as our
6 conclusions.

7 In addition, we have several experts from
8 outside of PRI with us today to address any questions which
9 may arise, and these experts include Dr. Robert Brent of
10 the A.I. DuPont Children's Hospital, Dr. Lewis B. Holmes of
11 Harvard University, Dr. Cassandra Henderson of the Albert
12 Einstein College of Medicine in the Bronx, Dr. Marc Keirse
13 of the University of South Australia, Dr. Peter Nathaniels
14 of Cornell University, and Dr. Baha Sibai of the University
15 of Tennessee Medical Center in Memphis.

16 I thank you for your attention, and I'll invite
17 Dr. Caritis to take the podium.

18 DR. CARITIS: Dr. Petitti, members of the
19 advisory committee, members of the Food and Drug
20 Administration, and guests, today I would like to provide
21 you with a contemporary perspective of labor inhibition
22 therapy.

23 The approach to labor inhibition therapy has
24 changed substantially in the last 5 to 10 years because our
25 understanding of the parturitional process has evolved. In

1 the past, we tended to equate the process of parturition
2 with the onset of contractions and cervical changes.
3 Consequently, strategies for dealing with preterm birth
4 included home uterine activity monitoring to detect
5 contractions, preterm birth prevention programs to detect
6 cervical changes, and the use of pharmacologic agents to
7 abolish uterine contractions. Expectations of labor
8 inhibition therapy were simplistic and, in retrospect,
9 unrealistic. We assumed that by abolishing contractions,
10 we abolished the parturitional process. We anticipated
11 that pregnancy could be prolonged for weeks or months, and,
12 therefore, perinatal mortality could be reduced.

13 Our current perspective on parturition suggests
14 that the parturitional process, shown here in blue, begins
15 long before clinically detected preterm labor. The
16 parturitional process is heralded in increases in gap
17 junctions, oxytocin receptors, and enhanced uterine
18 contractility. With this perspective in mind, the use of
19 labor inhibiting agents and expectations of what such
20 therapy can accomplish has changed. None of the currently
21 utilized agents appears to alter the fundamental process of
22 parturition. However, several agents can stop uterine
23 contractions for 24 to 48 hours to enable administration of
24 glucocorticoids to the mother and, if necessary, to
25 transfer the mother to a tertiary center.

1 The benefits of short-term pregnancy
2 prolongation have been emphasized by the 1994 NICHD-
3 sponsored consensus conference on the benefits of antenatal
4 steroids. Corticosteroid administration reduces the odds
5 of neonatal death by 63 percent, the odds of respiratory
6 distress syndrome by 30 percent, and the odds of
7 intraventricular hemorrhage, a risk factor for cerebral
8 palsy, by 46 percent. These effects of corticosteroids are
9 greatest when the pregnancy is prolonged for at least 24
10 hours; the benefits continue for at least 7 days.

11 The impact of corticosteroid therapy appears to
12 differ according to gestational age. After the 28th week,
13 both the incidence of death and RDS are significantly
14 reduced. Between 24 and 28 weeks, the incidence of death
15 and IVH are significantly reduced. Although the incidence
16 of RDS is not significantly reduced, the severity of
17 disease is.

18 Thus, in contemporary practice, labor
19 inhibition therapy has relatively modest objectives: the
20 prolongation of pregnancy for 24 to 48 hours so that mother
21 can receive corticosteroids and, if necessary, be
22 transferred to a tertiary center. Based on placebo-control
23 trials, three classes of pharmacologic agents appear to be
24 capable of achieving this objective: the beta-adrenergic
25 agents ritodrine and terbutaline, the prostaglandin

1 synthase inhibitor indomethacin, and the oxytocin
2 antagonist atosiban. Only ritodrine is currently approved
3 by the Food and Drug Administration for the treatment of
4 preterm labor. Despite this approval and proven short-term
5 effectiveness, this agent is seldom used to treat preterm
6 labor because it causes many maternal side effects and is
7 generally viewed as unsafe by the obstetric community.

8 This slide lists the frequency that ritodrine
9 treatment was discontinued due to severe maternal side
10 effects. Discontinuation rates as high as 38 percent have
11 been reported, and this accounts for the loss of confidence
12 in ritodrine by the obstetric community. Based on the data
13 gathered by the sponsor, the only FDA-approved agent is now
14 used in less than 10 percent of cases.

15 The usefulness of indomethacin as a tocolytic
16 agent is also limited because of fetal safety concerns.
17 Indomethacin appears to increase the risk of necrotizing
18 enterocolitis, intracranial hemorrhage, and patent ductus
19 arteriosus. These serious effects severely limit the use
20 of prostaglandin inhibitors in the treatment of preterm
21 labor.

22 In summary, based on proven efficacy in
23 placebo-control trials, the current pharmacologic options
24 for achieving short-term pregnancy prolongation are
25 ritodrine, which is rarely used because of maternal safety

1 concerns; indomethacin, whose use is limited because of
2 fetal safety concerns; and atosiban, which appears to be
3 both effective and safe.

4 I would like to turn the podium over to Dr.
5 Robert Wills, vice president of preclinical development at
6 PRI, who will present the preclinical safety and
7 pharmacokinetics of atosiban.

8 DR. WILLIS: Good morning. I'm Dr. Robert
9 Wills, vice president of preclinical development. I'm
10 going to present a summary of the preclinical safety and
11 pharmacokinetics of atosiban.

12 On the first slide is a comprehensive list of
13 the preclinical safety studies that were conducted in
14 support of the atosiban NDA. You see listed the type of
15 studies in the far left-hand column, the species in the
16 middle column, and the route of administration in the far
17 right. Both acute and chronic studies were conducted in
18 rodents and non-rodents. The number of studies identified
19 are within the parentheses.

20 I want to spend a few minutes describing the
21 peri/postnatal studies in more detail, as they are germane
22 to the intended clinical use of atosiban and address FDA
23 concerns.

24 On the next slide is a listing of the five
25 peri/postnatal studies that were conducted. We have the

1 route of administration in the left-hand column, the dose
2 regimen in the next column, the gestational days over which
3 the animals were dosed, and some comment on outcome. I'm
4 going to concentrate on the last two studies, as these
5 studies were conducted to better reflect the clinical
6 setting and have companion plasma concentration data.

7 These studies accomplished three important
8 outcomes. The first was a demonstration of toxicity at
9 doses of 200 and 300 milligrams per kilogram, which are 40-
10 and 60-fold the doses being used in the clinic. The major
11 toxicological finding was a significant decrease in food
12 consumption and body weight in the dams, resulting in
13 decreased survival in the offspring. The second outcome,
14 of equal importance, was a demonstration of a no-
15 observable-adverse-effect level at a dose of 100 milligrams
16 per kilogram per day. The third outcome was the
17 availability of plasma concentrations in both the dams and
18 fetus that can be compared to the human as indices for
19 margin of safety.

20 On the next slide is a comparison of atosiban
21 exposure in rats and humans that I will use to illustrate
22 the safety margin. Let me orient you to this slide. The
23 top half of the slide contains the maternal comparisons.
24 The bottom half contains fetal comparisons. If we look at
25 the dose column, we have the clinical dose listed here, we

1 have the lower of the toxicological doses in the rat, and
2 we have the no-effect dose in the rat. Now, if you look at
3 the dose comparisons, the toxic dose was 40 times the
4 clinical dose, the no-effect dose in the rat is 20 times
5 the clinical dose. These are external dose comparisons,
6 which would indicate a sufficient margin of safety.

7 However, if we want to be more precise, we can
8 then move to an internal dose comparison, of which plasma
9 concentrations are one such index. Here we have listed the
10 maximal concentrations found in each of these situations.
11 Over here, that's one measure of internal dose. In this
12 column, the area under the curve, which essentially is
13 looking at the time course over which plasma concentrations
14 are measurable, that's another internal dose measure. And
15 likewise to comparing external dose across rat to human, we
16 can compare the values at the toxic dose or at the no-
17 effect dose to those in the human and result in ratios for
18 comparative purposes. The maximal concentration ratios are
19 in this column, the area-under-the-curve ratios are in this
20 column.

21 Now, let's focus on the fetal comparisons to
22 illustrate the point. If we look at the toxic level line
23 here, what the four and the five signify is that fetal
24 concentrations in a human are four- to five-fold less than
25 the fetal concentrations in a rat exposed to toxic doses.

1 More importantly, if you look at the no-effect comparison,
2 this signifies that the human fetus is exposed to one and a
3 half to three times less atosiban than the rat fetus at a
4 no-effect dose. Collectively, these data signify an
5 adequate margin of safety in extrapolating from animals to
6 humans.

7 To ensure that we designed, conducted, and
8 interpreted these studies correctly, we assembled a panel
9 of experts, listed on the next slide, who independently
10 provided their assessment. Both Drs. Brent and Holmes are
11 present today to answer any questions that you may have
12 regarding their assessment. Now, I've abstracted a quote
13 from their written conclusions that I will read to you on
14 the next slide: "State-of-the-art Segment III-type studies
15 in rats have not shown developmental toxicity independent
16 of maternal toxicity, and have not shown developmental
17 effects that are not explained on the basis of maternal
18 toxicity and impairment of lactation."

19 So let's summarize the preclinical safety. We
20 believe that based on the results of the preclinical safety
21 studies, a sufficient margin of safety exists for both
22 human maternal and fetal safety.

23 Now, that concludes what I have to say on the
24 preclinical safety. I'd like to now turn our attention to
25 clinical pharmacokinetics.

1 The clinical pharmacokinetics of atosiban are
2 straightforward. The kinetics are linear. Both the
3 within- and across-patient variability is low, at less than
4 20 percent. The clearance is rapid, and the half-life is
5 short. Importantly, the placental transfer is low, at 12
6 percent, and in particular if we compare this to the value
7 of the placental transfer values reported for other
8 products used to treat preterm labor, which range from 30
9 to 100 percent. Taken together, the kinetic behavior of
10 atosiban combined with the need to saturate the oxytocin
11 receptor quickly and until uterine quiescence, this
12 provides the rationale for the dosing regimen of a loading
13 dose followed by a constant infusion.

14 I would now like to introduce Dr. George
15 Creasy, who will discuss the clinical safety and efficacy
16 of atosiban.

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

18 Dr. Petitti, members of the committee, I am
19 pleased to begin the presentation of the clinical trials of
20 atosiban. As we begin, let's keep in mind two points.
21 First, even though long-term endpoints were included in the
22 atosiban studies, the clinically relevant endpoint is 48
23 hours, as Dr. Caritis has just pointed out. Second, as Dr.
24 Dunton mentioned in his opening remarks, a target
25 population has been identified for the use of atosiban.

1 The target population is the group greater than or equal to
2 28 weeks, and this group has been identified, as you will
3 see, through both biologic justification and through the
4 results of more than one randomized clinical trial.

5 The clinical trials to be discussed are shown
6 here. I will begin the review with two studies that formed
7 the basis for our dose selection, a placebo-control
8 subcutaneous study and an intravenous active-control study.
9 I will follow that by a discussion, then, of the two
10 placebo-control Phase III studies of safety and efficacy.
11 The dose-ranging studies and the two placebo-control Phase
12 III studies clearly demonstrate a biologic effect of
13 atosiban in contracting patients, an effect also
14 demonstrated in the primate work of Dr. Peter Nathaniels,
15 who's with us today. Dr. Per Bengtsson will then present
16 the results of the active-control Phase III studies,
17 comparisons of atosiban to ritodrine, to terbutaline, and
18 to salbutamol.

19 Let's turn now to the dose-ranging studies,
20 studies that show a biologic effect of atosiban on
21 contraction reduction. M92-065 was a placebo-control study
22 of single atosiban injections. Four doses of atosiban and
23 a placebo dose were studied in threatened preterm labor
24 patients or in patients who had just completed an acute
25 preterm labor treatment. L91-049 was a ritodrine-control

1 study that involved the intravenous infusion of four dose
2 regimens of atosiban in actual preterm labor patients. The
3 atosiban infusions lasted 6 to 12 hours.

4 We will review the subcutaneous study first.
5 On this slide is a graph of the results for the mean number
6 of contractions per hour in the subcutaneous single-dose
7 study, M92-065. What you see is a plot of the mean number
8 of contractions per hour versus steady time. Steady time
9 began 3 hours prior to the single dose and ended 12 hours
10 after the single subcutaneous dose. The placebos plot is
11 in the open circles, and as you can see, after the single
12 subcutaneous dose of placebo, the mean rate of contractions
13 drifted down, but never went below five contractions per
14 hour. On the other hand, the high-dose plot, signified by
15 the open diamonds, experienced a rapid decline after dose,
16 which declined to nearly one contraction per hour by 7
17 hours. The middle doses reduced contractions better than
18 placebo, but not as well as the high dose. Treatment
19 differences for the change in mean number of contractions
20 per hour were not statistically significant, but the plasma
21 level data behind this response supported the subcutaneous
22 maintenance dose selection.

23 Let's move now to the intravenous dosing study.
24 Shown here are the mean number of contractions per hour for
25 L91-049 by dose regimen. The high dose of 300 micrograms

1 per minute was included in two of the dose regimens. The
2 first was preceded by an appropriate loading dose, the
3 second had no loading dose. The other two treatment
4 regimens each had an appropriate loading dose, the middle
5 dose being 100 micrograms per minute and the low dose being
6 30. Ritodrine was the control.

7 As you can see by the bars on the right in each
8 pair, all treatment arms were effective in eventually
9 bringing down the contraction rate to a target level of
10 about zero to four contractions per hour. What you cannot
11 tell from this data is the very important point that the
12 high-dose arm with the loading dose accomplished this much
13 faster than the other three regimens of atosiban.

14 Shown here is the mean time to the last
15 contraction for those subjects in whom contractions
16 stopped. As you can see, the mean time to contraction
17 cessation for the high-dose regimen preceded by a bolus was
18 3 hours, similar to the ritodrine rate of 2.6. The other
19 three atosiban dose regimens had a mean rate of between 4
20 and 5 hours.

21 We believe, after reviewing all of the data
22 from this study, that the data justifies elimination of the
23 lowest-dose regimen as a candidate for the treatment of
24 acute preterm labor. We believe that the data justifies
25 preceding study dosing and treatment with a bolus, and it

1 justifies the use of a biphasic regimen, initiating
2 treatment with the high dose and a bolus for the most rapid
3 control of contractions, followed by optimal completion of
4 the control of an acute preterm labor episode with the
5 lowest effective dose.

6 An assessment, shown here, is the percent of
7 subjects who discontinued therapy due to adverse events
8 from this intravenous study L91-049. You will note that
9 for the ritodrine subjects, 26 percent discontinued
10 treatment for an adverse event. This is consistent with
11 the results shown by Dr. Caritis just a moment ago, where
12 his data ranged from 6 percent to 38. In all of the
13 atosiban arms, only a single patient discontinued treatment
14 for the report of an adverse event. An important advantage
15 of atosiban is demonstrated here: strikingly better
16 maternal safety.

17 Let's move on from the dose selection studies
18 to the Phase III studies, and we'll begin with PTL-096.
19 PTL-096 was a randomized, double-blind, multi-center study
20 where patients could be enrolled as early as the 20th week
21 of gestation, but no later than 33 weeks and 6 days.
22 Patients were not to be included with dilatations of more
23 than 3 centimeters, nor were patients to be included with
24 rupture of the membranes. There was a 2-year infant
25 follow-up, but the results that you will see over the next

1 couple of slides are all data through the delivery
2 hospitalization. The 2-year follow-up data for the program
3 will be summarized a little later.

4 The study population described here was similar
5 in all of the Phase III studies, with the exception that in
6 the active-control studies, the lower limit of inclusion by
7 gestational age was 23 weeks, and the upper limit of
8 inclusion was 32 weeks and 6 days.

9 The acute I.V. dose was also similar in all of
10 the Phase III studies, beginning with a bolus dose to bring
11 patients to an immediate steady state for the ensuing high-
12 dose infusion of 300 micrograms per minute, which was
13 continued for 3 hours. Subsequently, the dose was reduced
14 to 100 micrograms per minute for the completion of the
15 acute preterm labor treatment in this study, up to 45
16 additional hours. The maintenance dose in this study was
17 30 micrograms per minute, which was to be continued to the
18 end of Week 36. There was, of course, a matching placebo
19 regimen. The primary endpoint for this trial was time to
20 delivery or therapeutic failure, defined as progression of
21 labor requiring alternate tocolytic therapy.

22 In this study, 531 patients were randomized to
23 receive either placebo or atosiban. An equal number of
24 patients in both arms did not receive study drug, 15 in
25 each. The most common reason for this was also similar for

1 both treatment arms, and that was progression of labor
2 beyond 3 centimeters during the time of subject screening
3 to the mixing of the drug in the pharmacy, so that the
4 patient progressed beyond the protocol allowable 3
5 centimeters before the drug could actually be administered.

6 The baseline demographics for the randomized
7 groups was also similar, as you can see here, for the mean
8 age, race, and the percentage of singleton pregnancies
9 included. Although the baseline labor characteristics
10 appeared similar, as shown here, for the mean gestational
11 age, mean contractions per hour, mean dilatation, and mean
12 effacement, there was an imbalance in both the number of
13 patients and the severity of their labor for the subgroup
14 enrolled below 26 weeks. This imbalance favored placebo
15 over atosiban, and this will be addressed later by Dr.
16 Romero and Dr. Ward.

17 For the entire study population and for the
18 clinically relevant short-term endpoint of 48 hours, the
19 percent of patients undelivered and not in need of
20 alternate tocolysis was highly significant in favor of
21 atosiban over placebo, P value .008. However, as stated
22 previously, our request is for atosiban use greater than or
23 equal to 28 weeks. The justification for this suggested
24 use is shown on the next slide.

25 The rationale for the identification of the

1 greater than or equal to 28 week group includes a biologic
2 plausibility and is also based on the efficacy findings
3 from two studies. The biologic justification for the use
4 of atosiban greater than or equal to 28 weeks includes the
5 high incidence of infection in patients below 28 weeks, a
6 condition where atosiban could not be effective. In
7 addition, oxytocin receptor concentrations and uterine
8 responsiveness to oxytocin are known to be markedly reduced
9 at the lower gestational ages.

10 The rationale is also based on the findings
11 from two placebo-control trials. In one Phase II study,
12 atosiban was only superior to placebo in contraction
13 reduction -- that would be PAT-U01, included in the back of
14 your briefing book -- above 28 weeks gestational age. In
15 the Phase III study PTL-096, part of the planned analysis
16 of the primary endpoint was a statistically significant
17 treatment-by-gestational-age interaction finding. Atosiban
18 was consistently better than placebo for the clinically
19 relevant short-term endpoint of 48 hours only in the group
20 greater than 28 weeks gestational age.

21 Finally, efficacy for this subgroup of greater
22 than or equal to 28 weeks gestational age lines up with the
23 gestational age effect of antenatal steroids to reduce the
24 incidence of respiratory distress syndrome, the group who
25 deliver between 29 and 34 weeks.

1 This slide shows the results for the clinically
2 relevant short-term endpoint of 48 hours in the target
3 population greater than or equal to 28 weeks for the
4 percentage of patients who are undelivered and not in need
5 of alternate tocolysis, and as you can see, the results are
6 highly significant in favor of atosiban. Please note that
7 this population of 203 patients in atosiban and 226
8 patients for placebo represents 85 percent of the entire
9 study population.

10 The results of the long-term endpoint for the
11 target population are shown here, time to delivery or
12 therapeutic failure. Shown are the Kaplan-Meier survival
13 curves, which, as you can see, separate early, with
14 atosiban above placebo until about Day 45, when the curves
15 come together and remain together until the last patient
16 fails. This distribution of data is not statistically
17 significant, as you can see by the results of the
18 stratified log-rank test, where the P value is .4. The
19 early separation, however, is consistent with the somewhat
20 better P value on the Wilcoxon test, which values early
21 successes more than later, and is also consistent with the
22 finding of statistical significance at the 48-hour
23 endpoints shown on the previous slide.

24 The safety in this study is the safety of study
25 drug plus any alternate treatments that may have been

1 given. In the target population, the rates of maternal and
2 fetal adverse events were comparable between the atosiban
3 group and the placebo group. As you can see here, the only
4 exception is the occurrence of subcutaneous injection site
5 reactions, which are higher for atosiban than placebo.
6 These reactions occurred during the maintenance treatment.
7 This includes similar rates of the troublesome reactions
8 typical of adrenergic agents, such as chest pain and
9 tachycardia, which here are comparable between atosiban and
10 placebo and much lower, especially for tachycardia, than
11 rates typically seen with adrenergic agents.

12 I should emphasize that the rates of fetal
13 distress, even with more than 10 days of continuous
14 exposure to atosiban infusion, are no different from
15 placebo.

16 This is a very important point regarding the
17 PTL-096 study. PTL-096 is not a placebo-control comparison
18 for infant outcomes. The use of alternate tocolytics
19 confounds the comparison of infant outcomes for efficacy
20 purposes. Study drug was required only for 1 hour in this
21 protocol. Subsequent to that, alternate tocolytics could
22 be used at any time to permit aggressive treatment of all
23 preterm labor patients toward the best possible infant
24 outcome, and as you can see, for those randomized to
25 atosiban, after the first hour 42 percent of the patients

1 subsequently received an alternate tocolytic, and for the
2 placebo group, 51 percent after the first hour subsequently
3 received an alternate tocolytic.

4 I should point out that this 51 percent of
5 patients were actually in need of their initial treatment
6 of preterm labor, and in fact one out of every five of
7 these patients received for their initial treatment a
8 tocolytic cocktail of between two and three tocolytic
9 agents at once.

10 Let's look now at the infant outcomes from the
11 target population. For the target population, fetal and
12 infant mortality and morbidity is comparable for atosiban-
13 initiated tocolytic care versus placebo-initiated tocolytic
14 care with regard to fetal and infant mortality, where it
15 was 1 percent for atosiban-initiated care and 2 percent for
16 placebo-initiated care. The various morbidities -- mean
17 gestational weight, mean weight at delivery -- and the
18 various mortalities -- respiratory distress syndrome,
19 intraventricular hemorrhage, patent ductus arteriosus, and
20 necrotizing enterocolitis -- were also similar between the
21 groups.

22 The results for the infants less than 28 weeks
23 where infant morbidity and mortality favored placebo over
24 atosiban will be discussed by Dr. Ward and Dr. Romero
25 during their presentations.

1 Our conclusions, then, from the PTL-096 placebo
2 regimen study are that atosiban is superior to placebo for
3 delay in delivery or use of alternate tocolytic at 48 hours
4 in preterm labor patients greater than or equal to 28 weeks
5 gestational age. Atosiban is well tolerated compared to
6 placebo, and atosiban has similar infant mortality and
7 morbidity to placebo-initiated standard care for patients
8 greater than or equal to 28 weeks gestational age. The
9 value of atosiban is safe tocolysis for 48 hours in
10 patients greater than or equal to 28 weeks, which includes
11 all patients where a reduction in the incidence of
12 respiratory distress syndrome would be expected from the
13 use of antenatal steroids.

14 Let's move now to PTL-098, the placebo
15 maintenance study. Although we're not requesting approval
16 for the maintenance indication, as a placebo-control study,
17 this study shows a biologic effect and provides additional
18 safety data which is supportive of the intravenous use of
19 atosiban. Since this study is of maintenance treatment
20 rather than acute treatment, I will present all of the
21 data, focusing on the safety results.

22 As you may recall, all patients presenting for
23 this study with their acute preterm labor episode were
24 treated with open-label atosiban. Those who achieved
25 uterine quiescence were then randomized to receive a

1 maintenance of either atosiban or placebo. Any subsequent
2 episodes of preterm labor were to be treated for at least 1
3 hour with open-label atosiban.

4 All together, 649 acute preterm labor patients
5 were treated with open-label atosiban, and 80 percent
6 achieved uterine quiescence. Five hundred and thirteen
7 were subsequently randomized to their respective regimens.
8 For the target group of greater than or equal to 28 weeks,
9 the percent of uterine quiescence was actually 82 percent,
10 or 455 out of 557, of those who presented at greater than
11 or equal to 28 weeks. The baseline demographic features
12 were similar in this study for both treatment groups.

13 This slide shows the results for the primary
14 endpoint, time to the next episode of labor. It's a plot
15 of the Kaplan-Meier curves, and you can see that the curves
16 separate early, with the atosiban curve above the placebo
17 curve until the last patient fails. This distribution of
18 data is consistent with the finding of statistical
19 significance in the stratified log-rank test, where the P
20 value was .02.

21 The maternal and fetal safety data being
22 presented for this study is the safety data for the
23 continuous subcutaneous treatment, which is up to the first
24 recurrence of labor. This view of the data does exclude
25 safety data following a re-treatment with intravenous

1 atosiban.

2 Even though the difference in the amount of
3 atosiban infusion to the mother and her fetus was on
4 average more than 3 weeks, the rates of adverse events
5 between randomized groups was quite similar, once again,
6 with the exception of the subcutaneous injection site
7 reactions during the maintenance treatment. Reactions
8 typical of the adrenergic agents, once again, were
9 comparable and low, and in spite of the continuous infusion
10 of atosiban, fetal distress rates were the same.

11 The fetal and infant mortality and morbidity
12 were the same between the treatment groups. The mean
13 weight, rates for RDS, intraventricular hemorrhage, patent
14 ductus arteriosus, and necrotizing enterocolitis were all
15 similar.

16 Our conclusions from this study, then, are that
17 atosiban showed comparable maternal and fetal adverse
18 effects to placebo, with the exception of the injection
19 site reactions, and that there is no adverse effect on
20 infant outcome from the continuous atosiban administration.

21 I mentioned earlier that there was a 2-year
22 infant follow-up in some of our studies. Three large
23 studies included a 2-year infant follow-up, and the results
24 of this follow-up program are summarized on this slide.
25 Infant development during the follow-up program was

1 comparable between atosiban and ritodrine and atosiban and
2 placebo for Bayley mental and motor assessments, for
3 neurologic examinations, for growth parameters, general
4 physical findings, and the occurrence rates of illnesses
5 and accidents that were reported during the follow-up
6 period.

7 The data you've seen so far consistently shows
8 a biologic activity for atosiban in reducing contractions,
9 and this activity has been extended in a placebo-control
10 Phase III study to time, time which can be used for the
11 administration of steroids or transfer to a tertiary
12 center.

13 The target population makes sense from a
14 biologic standpoint and is consistent with the efficacy
15 findings in two placebo-control trials. The target
16 population includes all patients where a reduction in the
17 incidence of respiratory distress syndrome would be
18 expected from the administration of antenatal steroids.

19 The evidence for efficacy, then, from the
20 placebo studies is superiority to placebo in providing time
21 for the administration of steroids or transfer for patients
22 greater than or equal to 28 weeks, and comparable maternal,
23 fetal, and infant safety to placebo during intravenous use
24 greater than or equal to 28 weeks, as well as comparable
25 maternal, fetal, and infant safety with prolonged use.

1 Dr. Per Bengtsson will now present the results
2 of the active-control study.

3 DR. BENGTSSON: Thank you, Dr. Creasy.

4 I would like to arrange for the microphone,
5 because I know that this has to be heard all the way to
6 Europe.

7 (Laughter.)

8 DR. BENGTSSON: Dr. Petitti, committee members,
9 my name is Per Bengtsson, and I'm medical director at
10 Ferring Pharmaceuticals. I've been responsible for the
11 Phase III clinical program on atosiban since the beginning
12 of 1997. I'm very pleased to be here this morning, because
13 I think I can show you some data that you will find both
14 interesting and useful.

15 The study I'm going to present is an active-
16 control study in which the efficacy and safety of atosiban
17 is compared with that of beta-mimetic treatment. The study
18 is called the CAP-001 study. Using the names "active-
19 control" and "placebo-control" is perhaps a little bit
20 misleading for preterm labor studies, as pointed out by Dr.
21 Creasy, because active treatment can, for ethical reasons,
22 only be withheld for 1 hour at maximum. In our study, all
23 mothers received active treatment already from the start in
24 a standardized way, because they were given beta-mimetic
25 treatment if they were not randomized to atosiban.

1 The study was conducted in Europe, North
2 America, and Australia. It was planned as one single study
3 under the same protocol, and three different beta-mimetics
4 were chosen because they are approved and used in these
5 countries. I would like to point out that the effective
6 dose of each beta-mimetic was titrated, which made the
7 dosing of the beta-mimetic agents consistent across all
8 three studies. The overall results across all three
9 studies were planned to be provided in a pooled analysis.
10 Each individual part was also to be analyzed and reported
11 separately.

12 The study was randomized and employed a special
13 double-blinding technique. Each mother received two
14 parallel infusions, one in each arm. In one arm the active
15 drug was infused, and in the other a placebo infusion was
16 given just to blind which type of active treatment the
17 patient was randomized to. The fact that all patients
18 received treatment from the very first minute of the study
19 made the doctor and the mother confident that adequate
20 treatment was given.

21 Atosiban treatment was for the acute preterm
22 labor episode only and any necessary re-treatments up to
23 Week 34. After this time point, study drug could not be
24 given. The purpose was to re-treat if symptoms appeared
25 again, so no maintenance therapy was included in the

1 protocol.

2 And please note that the beta-mimetic agents
3 were used according to the label, which included a
4 titration to an effective dose; therefore, each mother
5 received an effective beta-mimetic treatment, or,
6 alternatively, she could not tolerate the high doses that
7 were needed to control the preterm labor episode.
8 Therefore -- and this should be emphasized -- the titration
9 procedure made the beta-mimetic treatment consistent across
10 all three individual studies, which, as you will see later
11 -- or you will not see it, but I can tell you that the
12 tachycardia rate is equal in all three studies.

13 The diagnosis of preterm labor was based upon
14 contraction rate and cervical status, and mothers from 23
15 up to 33 weeks of gestational age could be included in the
16 study. The results in the lower gestational age strata
17 were very good, but because we want to be consistent with
18 the presentation of U.S. data here this morning, I'm only
19 going to show data from mothers of gestational age above 28
20 weeks at randomization. But I would like to emphasize that
21 in contrast to the U.S. placebo-control study, our trial,
22 comprised of 838 infants, had comparable infant outcome
23 data below Week 28. All together, 552 mothers with a
24 gestational age higher than 28 weeks were included in the
25 efficacy population. As can be seen on the slide, the

1 individual studies included about the same number of
2 patients.

3 The primary efficacy objective of the study was
4 the percent of mothers who do not deliver within 7 days and
5 who do not receive alternate tocolytic therapy. Perhaps I
6 should spent one more minute on this endpoint, because I
7 think it could be useful when looking at our data. Each
8 mother can fail on this endpoint because of either delivery
9 or because an alternate tocolytic was given. Now, if a
10 mother did not respond on atosiban, the dose was not
11 increased and the patient was labeled therapeutic failure.
12 In contrast, and because the beta-mimetic dose was to be
13 increased in a step-wise fashion, the mothers that were
14 poor responders on beta-mimetics would receive a higher
15 dose of the beta-mimetic drug, which consequently, then,
16 became more difficult to tolerate. An adverse event might,
17 therefore, be provoked because lower doses could not be
18 used for efficacy reasons.

19 This slide demonstrates the primary efficacy
20 outcome of the study. As can be seen, atosiban treatment
21 was statistically significantly superior across all three
22 studies, with a numerical favor in two of the studies and a
23 statistical significance in the ritodrine study. On the
24 pooled-data level, you see that there is a 10 percent
25 advantage, which is highly statistically significant.

1 For the 48-hour endpoint, atosiban was again
2 numerically superior in all three studies, and because of
3 this numerical superiority on the pooled-data level, the
4 results became statistically significant, with a 6 percent
5 advantage.

6 In the remaining part of my presentation, I'm
7 going to talk about safety of atosiban. This slide shows
8 the infant and fetal deaths that occurred in the study, and
9 as you can see here, on the bottom line, there were two
10 death cases in both treatment groups. One of these was a
11 fetal death which occurred 11 weeks after study drug
12 infusion with atosiban, so it was, therefore, unlikely
13 caused by atosiban. So there is no difference here with
14 regard to deaths. Birth weight was comparable between the
15 treatments, with only a 3-gram difference on the pooled-
16 data level. Overall, no difference was seen with regard to
17 hyaline membrane disease, occurring at the rate of 9 and 8
18 percent, respectively, for atosiban and beta-mimetic.

19 Further safety data of clinical significance is
20 shown on this slide, and as you can see, the results are
21 comparable between both treatment groups. So there is no
22 obvious difference with regard to cerebral hemorrhage -- I
23 think there should be cerebral hemorrhage here -- and
24 necrotizing enterocolitis, PDA, or hypertension.

25 Now, I have nearly come to the end of this

1 presentation, but before I make the overall conclusions, I
2 would like to draw your particular attention to this slide
3 showing the most prominent difference between these two
4 drug regimens, and it's the maternal adverse events. As
5 you can see, for the more serious medical conditions, there
6 are more problems in the beta-mimetic-treated mothers, with
7 chest pain and myocardial ischemia to be the most serious
8 one on this slide. Pulmonary congestion was also noted in
9 one woman.

10 I think it is appropriate to point out here
11 that for the other subgroup, below Week 28, there were
12 three cases of pulmonary edema. Two of these occurred in
13 mothers randomized to beta-mimetics, and the third followed
14 7 days of rescue therapy with beta-mimetics.

15 As can be seen on this slide, there is also a
16 high rate of tachycardia, which was between 74 and 78
17 percent in all three studies, and this produced a lot of
18 inconvenience as well as palpitation to the mothers.

19 So here is the conclusion. Atosiban
20 intravenous treatment is statistically significantly
21 superior to beta-mimetics in terms of the percent of
22 mothers not delivered and not requiring alternate tocolytic
23 at 7 days and 48 hours, with a 61 to 51 percent, it should
24 be here -- sorry for that typo -- after 48 hours, 77 to 71
25 percent. Atosiban is much better tolerated than beta-

1 mimetic, and infant outcome data is comparable, not only in
2 this group.

3 Thank you very much. Now I would like to turn
4 the podium to Dr. Ward, who will discuss the safety of
5 atosiban.

6 DR. WARD: Good morning, Dr. Petitti,
7 committee, FDA. I'm Bob Ward, a neonatologist and clinical
8 pharmacologist. During the 20 years that I've worked in
9 neonatology, I've watched the survival of the extremely
10 preterm newborn increase significantly so that we're
11 challenged daily in the intensive care unit with their
12 problems. During 9 of those years, I served as medical
13 director of a tertiary care newborn intensive care unit,
14 involved with review of morbidity and all the mortalities
15 in that clinical population, and it will be that same type
16 of review that I'll bring to the case of atosiban. In
17 addition, I'm a clinical pharmacologist. I've studied and
18 written about maternal-fetal drug transfer and effects of
19 maternal drugs upon the fetus and the newborn.

20 The FDA has raised several issues. I would
21 summarize those with these two questions. First, is
22 atosiban toxic to the fetus? Secondly, does atosiban
23 antagonize the effects of prenatal steroids? I would pose
24 another question, and that is, are the differences in
25 mortality and respiratory distress syndrome a study outcome

1 due to disproportionate distribution of the most immature
2 cases to atosiban?

3 In the PTL-096 trial of atosiban plus or minus
4 an alternate tocolytic and placebo plus or minus an
5 alternate tocolytic, patients were not stratified by
6 gestational age at enrollment. This led to a
7 disproportionate number of the most immature cases in the
8 atosiban group. The group of 28 weeks and above, however,
9 is balanced and is an appropriate subgroup for comparison.

10 Let me provide two definitions that we
11 generally use for the extremely preterm newborn, and that
12 is either a birth weight less than 1,000 grams or
13 gestational age less than 28 weeks.

14 This slide shows the imbalance in the atosiban
15 enrollment by gestational age, the atosiban column here,
16 placebo here, beginning at 20 weeks gestation up through 23
17 weeks gestation. There's a roughly five-fold predominance
18 of patients in the atosiban group, or 19 to 4, at these
19 most immature gestational ages.

20 As you would predict, if there's a
21 disproportionate number of immature patients at enrollment,
22 there will be a disproportionate number at delivery. The
23 atosiban patients are shown in the middle two columns.
24 There are 20 patients under 1,000 grams birth weight in the
25 atosiban group, and there are two patients under 1,000

1 grams birth weight in the placebo group.

2 Let me point out some of the problems that this
3 leads to in the extremely preterm newborn. The predominant
4 problems are listed on this slide. In the most immature
5 patients, Roberta and Phil Bower have reported respiratory
6 distress syndrome occurring in over 90 percent of those
7 patients. Infections are common as well, because their
8 immune function is immature. Necrotizing enterocolitis,
9 intraventricular hemorrhage, PDA are all increased in the
10 most immature patients.

11 I think you'll find that the explanation for
12 the mortalities under 28 weeks illustrates these problems:
13 a disproportionate number of non-viable infants, an
14 increased frequency of infection due to this imbalance at
15 the early gestational ages. In the group of 28 weeks and
16 above, however, they have comparable mortality.

17 This is the result of my analysis of causes of
18 death. The atosiban deaths are shown on this column,
19 placebo over here. I'll draw your attention first to the
20 top row. Five infants were judged pre-viable and received
21 either no resuscitation at birth or limited resuscitation,
22 with one being intubated at 17 hours. One child in the
23 placebo group failed resuscitation. One in each group had
24 lethal congenital anomalies. Let me also draw your
25 attention to these last four cases in the atosiban group.

1 These are children who died in the intensive care unit with
2 late-onset infections: necrotizing enterocolitis, candida
3 sepsis, bronchio-pulmonary pneumonia with intrapulmonary
4 abscesses, and one with staphorius endocarditis. These
5 represent problems of the extremely premature newborn. I
6 don't see a link to a tocolytic in these deaths.

7 Let me now change and discuss respiratory
8 distress syndrome. Prenatal steroid treatment has been
9 effective at increasing surfactant production and advancing
10 structural maturation of the lung. In 1981 Alan Jobe
11 pointed out, however, that despite prenatal steroid
12 treatment, 50 percent of infants will continue and go on to
13 develop respiratory distress syndrome, so it's not
14 universally effective. Some of the reasons are listed
15 below. Lung enzymes may be too immature at the time of
16 maternal treatment for the infant to respond. Delivery may
17 occur before the maturation process can proceed, and I'll
18 show you some data from Dr. Crowley's meta-analysis about
19 that. And, finally, what we diagnose as respiratory
20 distress syndrome may not only reflect surfactant
21 deficiency, but we still have trouble separating the Group
22 B strep pneumonia from RDS radiographically.

23 This is my analysis of the cases of RDS in
24 infants in PTL-096 under 28 weeks gestation. Let me begin
25 by pointing out that there were 19 cases in the atosiban

1 group and 11 cases in placebo, so twice as many in the
2 atosiban group. I think this slide also, though, provides
3 some of the explanation for this difference. Enrollment at
4 less than 24 weeks occurred in none of the placebo
5 patients, and almost one-half of the atosiban group was
6 enrolled at gestations under 24 weeks. Again, early
7 enrollment leads to early delivery, and delivery at less
8 than 26 weeks occurred in only one in the placebo group,
9 yet about a third of the atosiban group delivered at under
10 26 weeks gestation.

11 The sum of that is shown down below in these
12 patients with RDS. The average gestational age at birth
13 was 29.5 weeks in the placebo arm and 27.3 weeks in the
14 atosiban arm. That 2-week difference in maturation has a
15 tremendous effect on neonatal problems such as RDS.

16 If we look at the PTL-096 trial and the
17 frequency of respiratory distress syndrome and steroid use
18 at 28 weeks and above, those data are shown on this slide.
19 The atosiban group is in the top row, the second row is the
20 placebo group. You can see that the frequency of
21 respiratory distress syndrome is essentially the same in
22 the two groups. I find from this no evidence that atosiban
23 antagonizes the effects of prenatal steroids.

24 This is work from Dr. Crowley in her meta-
25 analysis that shows the time course of the response to

1 prenatal steroid treatment. It's a busy slide. The left
2 column here shows infants who delivered at less than 24
3 hours after maternal treatment with steroids and the
4 frequency of respiratory distress syndrome; middle column,
5 those infants delivering at 24 hours to 7 days after
6 treatment; and in the far right column, beyond 7 days after
7 treatment. You can see that within the first day there is
8 a reduction in respiratory distress syndrome, but it's
9 modest compared to the dramatic reduction seen at beyond 24
10 hours and less than 7 days after delivery, when the
11 frequency has been reduced from 24 percent to 9 percent.

12 I think the work of Dr. Crowley in that meta-
13 analysis helps to illustrate an optimal use for steroids
14 and, in turn, leads us to an optimal time for delivery --
15 that is, at 28 to 34 weeks, as was pointed out in the
16 consensus conference, exposure to steroids beyond 24 hours
17 and less than 7 days. If we apply again those criteria to
18 the patients in PTL-096 and look at the frequency of
19 respiratory distress syndrome, that's shown at the bottom
20 of this slide. In the atosiban group, the frequency was 55
21 percent; in the placebo group, the frequency was 58
22 percent, or not different.

23 When we look at a larger population, this is
24 the result of the comparison of atosiban to the beta-
25 mimetics, and it presents data for 28 weeks and above for

1 fetal and infant death, birth weight, need for NICU
2 admission, frequency of hyaline membrane disease, infants
3 needing mechanical ventilation, frequency of cerebral
4 hemorrhage, PDA, necrotizing enterocolitis. There's no
5 difference between these two groups.

6 This slide presents data for the entire group
7 in PTL-096, not just those of 28 weeks and above, and what
8 you'll see again, scanning down the columns -- death, birth
9 weight, NICU admission, respiratory distress syndrome, IVH,
10 PDA, necrotizing enterocolitis -- there is no difference
11 between the two groups in those frequencies.

12 In summary, the group of 28 weeks gestation and
13 above is the appropriate subgroup for reduction in the
14 incidence of RDS. Atosiban is comparable to beta-mimetics
15 at 28 weeks and above. In my analysis, I feel that extreme
16 prematurity is the most likely explanation for the findings
17 under 28 weeks. I find no evidence that atosiban adversely
18 affects infant outcome at 28 weeks and above.

19 Thank you. I now turn the podium over to Dr.
20 Romero, who will provide the perinatologist perspective.

21 DR. ROMERO: Good morning. Thank you, Dr.
22 Ward, Dr. Petitti, members of the committee,
23 representatives of FDA, ladies and gentlemen. I would like
24 to begin my presentation with a review of the rationale for
25 exploring the use of an oxytocin receptor antagonist as a

1 tocolytic agent.

2 The rationale is several-fold. First, oxytocic
3 plasma concentrations are elevated in patients in premature
4 labor in comparison to women who are not in labor. Second,
5 the concentrations of the oxytocin receptor measured with
6 binding studies are increased in myometrium and decidua in
7 women who deliver preterm. Third, patients who are
8 sensitive to endogenous oxytocin, as determined by a
9 mammary stimulation test, are more likely to have both
10 premature labor and premature delivery.

11 In addition, the administration of an oxytocin
12 receptor antagonist, atosiban, to both non-human primates
13 and women in premature labor suppresses uterine
14 contractility. This is the administration of atosiban to
15 pregnant baboons. In the vertical axis, uterine
16 electromyographic activity; in the horizontal axis, time.
17 These represent episodes of low-frequency, low-amplitude
18 uterine activity the equivalent of Braxton-Hicks
19 contractions. At this point, at 11:00, there is a switch
20 to higher-amplitude, higher-frequency contractions, which
21 are the hallmark of labor. The administration of atosiban
22 suppresses this electrical activity in myometrium, which
23 then reappears after discontinuation of the agent. Similar
24 findings are observed in clinical medicine.

25 With this rationale, I would now like to

1 address the issues of safety and efficacy of atosiban in
2 the treatment of premature labor, beginning with the safety
3 issues raised in the FDA briefing book. The question is,
4 is atosiban a safe agent? The concern stems from the
5 result of the PTL-096 study in which the fetal and infant
6 death in the overall population was 4.5 percent in patients
7 randomized to atosiban, 1.7 percent for those allocated to
8 placebo, yet for patients at or below 28 weeks, no
9 difference between those allocated to atosiban and those
10 allocated to placebo.

11 Why a difference below 28 weeks of gestation?
12 I'll propose to you that the reasons for this are four-
13 fold: first, an imbalance in gestational age at entry
14 between the study groups; second, a more advanced degree of
15 premature labor in patients at early gestational ages
16 allocated to the atosiban group; third, an excess of non-
17 viable infants in the atosiban group; and, fourth, the role
18 of intrauterine and neonatal infection.

19 Now let me provide in the next set of slides
20 the scientific evidence for each one of these conclusions.
21 The first one is evidence for imbalance at enrollment in
22 the PTL-096 study. In this column, gestational age, the
23 number of patients allocated by each stratum into atosiban
24 and placebo. We begin with 20 weeks, because this is the
25 criteria for enrollment into the trial. The gestational

1 age has been cut at 24 weeks, because this is the age of
2 viability. There were 19 patients enrolled into atosiban
3 at less than 24 weeks in this trial, only four in the
4 placebo group, a nearly five-fold difference. Now, this
5 would not be meaningful if being enrolled at an early
6 gestational age did not have clinical consequences --
7 namely, adverse clinical consequences. Is that the case?

8 The second reason that I invoke as an
9 explanation for this is that women allocated to atosiban at
10 early gestational ages were in more advanced premature
11 labor, and this is the data to support that conclusion.
12 This is cervical state expressed as a modified Bishop score
13 according to gestational age at enrollment. In the
14 vertical axis, the percentage of patients with a modified
15 Bishop score of equal or greater than 4, an expression of
16 advanced premature labor. I'd like to ask you to focus
17 your attention to the less than 26 weeks of gestation. The
18 frequency of patients with a Bishop score equal or more
19 than 4, 48 percent in the group allocated to atosiban, only
20 17 percent of those allocated to the placebo group. So
21 they were in more advanced premature labor.

22 The third explanation is the frequency of non-
23 viable infants. This and the next slide describe the
24 clinical characteristics of the fetal and infant death in
25 cases enrolled at less than 26 weeks of gestation and who

1 received atosiban. This is the case number, gestational
2 age at entry, gestational age at delivery, birth weight,
3 and the occurrence of chorioamnionitis or neonatal sepsis.
4 The first observation is that consistently in most
5 patients, the gestational age of entry was very similar to
6 the gestational age of delivery, confirming what I said
7 before, that the patients were in more advanced premature
8 labor.

9 The three observations that are circled in
10 black is the delivery at 21 and at 20 weeks of three non-
11 viable infants who would not be expected to survive. Less
12 than 500 grams, 21 and 20 weeks. The fourth infant,
13 delivered at 540 grams, 23 weeks. The fifth infant,
14 delivered at 24 weeks, had evidence of infection, and so
15 was the case in four of the infants. Consistently, all
16 deliveries shortly after entry into the trial, all were low
17 birth weights, and four of the five with evidence of
18 infection.

19 Should that evidence of infection be
20 surprising? Well, this slide illustrates the frequency of
21 intra-amniotic infection established by amniocentesis and
22 amniotic fluid culture as a function of gestational age.
23 This is the data of Dr. Watts from the University of
24 Washington in Seattle. Our group has similar data. In the
25 vertical axis, the frequency of infection; in the

1 horizontal axis, gestational age. The earlier gestational
2 age at presentation, the higher the frequency of infection.
3 In patients at less than 24 weeks, 67 percent will have a
4 positive amniotic fluid culture.

5 Now, that in and of itself would not be
6 sufficient. Patients with infection will have to have more
7 advanced premature labor and a higher frequency of
8 complications. Is that the case? The frequency of death,
9 RDS, EPD, and neonatal hospital stay longer in patients who
10 have positive amniotic fluid cultures. In addition, our
11 data indicates that patients with positive amniotic fluid
12 cultures present with a greater degree of cervical
13 dilatation, have a shorter interval to delivery, and have a
14 higher frequency of clinical chorioamnionitis, as was the
15 case in this trial, and most patients will have no clinical
16 evidence of infection and can be detected only by culture
17 of the amniotic fluid.

18 The central question is, is atosiban fetotoxic?
19 Well, if atosiban were fetotoxic, one would expect
20 an increased rate of fetal and neonatal death in all
21 infants exposed to atosiban. This is not the case. Here
22 is the frequency of fetal and infant death in the PTL-096
23 study and the active trials conducted in Europe. In the
24 PTL-096 study, the frequency is 5 percent; in the active
25 trials conducted in Europe, 2 percent, significantly lower.

1 So unless we postulate that infants in Europe have a
2 predisposition to death when they receive atosiban, this is
3 a most implausible result on its face, so we need to look
4 at what are the potential explanations between the
5 observation in the PTL-096 study and the active-control
6 trials.

7 I believe that the answer to that question is
8 two-fold. First, the gestational age at entry in the PTL-
9 096 is 20 weeks; in the European trials, 23 weeks. I told
10 you that the limit of viability is 24 weeks, so we have a
11 greater window for the delivery of non-viable infants in
12 the PTL-096 study. The second one is in the execution of
13 the trial. There was an actual imbalance in patients
14 allocated to atosiban in the PTL-096 study. That imbalance
15 was not observed in the CAP-001 study.

16 So my conclusions in terms of fetal and infant
17 safety are that atosiban is as safe as beta-adrenergic
18 agents, based on the data of the CAP-001 study, and that
19 the safety issues in the PTL-096 can be attributable to the
20 design and the imbalance between the two groups.

21 What about maternal safety? You have heard
22 from Dr. Caritis that one of the problems with the approved
23 agent, ritodrine, is the frequency of side effects. It is
24 an important problem, because at least 25 maternal deaths
25 have been reported in the literature with tocolysis with

1 beta-mimetic agents, and most of these deaths have occurred
2 in the context of intractable pulmonary edema. Although no
3 death has been reported due to intravenous magnesium
4 sulfate administration, pulmonary edema has been certainly
5 reported in this context.

6 This table demonstrates the frequency of
7 pulmonary edema in patients who received atosiban only for
8 tocolysis and those who received beta-mimetic agents in the
9 European trial. No case of pulmonary edema occurred in
10 patients tocolyzed only with atosiban, and the denominator
11 is 1,632 patients. There were two cases in the group
12 allocated to beta-mimetic agents of 430 patients, a
13 difference that is statistically significant.

14 So in terms of maternal safety, I conclude that
15 atosiban has less adverse events than beta-mimetic agents,
16 CAP-001, and the pulmonary edema has not been reported in
17 patients receiving only atosiban for tocolysis.

18 Well, is atosiban an effective tocolytic agent?
19 This is the proportion of patients who are undelivered and
20 have no rescue tocolysis by 48 hours, 24 hours, 7 days, at
21 or greater than 28 weeks, but the significance maintained
22 for the entire study. Clearly, at 48 hours the group of
23 patients who met this secondary endpoint, which was pre-
24 specified before the conduction of the trial, is
25 statistically significant. The primary endpoint of the

1 trial was overall prolongation of pregnancy, and there was
2 no significant difference between these two.

3 One, then, would ask, is atosiban an effective
4 tocolytic agent, and I would conclude that it is, because
5 the objective of tocolysis today, contrary to what it was
6 15 years ago, and the expectation is to achieve short-term
7 prolongation of pregnancy. This is consistent with the
8 recommendations of the American College of Obstetricians
9 and Gynecologists in this technical bulletin issued as
10 recently as June 1995. The technical bulletin concluded
11 that because of the clear benefit of corticosteroid
12 administration before 34 weeks of gestation, the use of
13 tocolytic agents for short-term prolongation of pregnancy
14 is justified.

15 Now, the question may be asked, why settle for
16 short-term prolongation of pregnancy? Why not demand and
17 insist on long-term prolongation of pregnancy as a goal of
18 tocolysis? My answer is that we have tried this. We have
19 tried for nearly 25 years with ethanol, a wide range of
20 beta-adrenergic agents, magnesium, intravenous and oral,
21 indomethacin and other prostaglandin inhibitors, and
22 atosiban, and none of these agents can achieve long-term
23 prolongation of pregnancy. I believe that the fundamental
24 problem is with the concept of disease that we have and the
25 expectations of tocolysis.

1 So my conclusion is that atosiban in terms of
2 efficacy is as effective as beta-adrenergic agents, a
3 conclusion based on the results of the CAP-001 studies, but
4 in terms of safety, the safety profile is superior to beta-
5 mimetic agents, and the fetal safety is comparable to beta-
6 mimetic agents.

7 I'd like to thank you very much for your
8 attention, and I'd like to turn the podium to Dr. Creasy to
9 close the presentation.

10 DR. CREASY: Thank you very much, Dr. Romero.

11 We have now finished with our part of the
12 presentation today, but before moving on to the question-
13 and-answer period, I would like to very briefly summarize
14 what you've heard over the past 75 minutes.

15 The goal of the management of the preterm labor
16 patient is a good infant outcome, but a good infant outcome
17 is dependent on several interventions, not just tocolytic
18 intervention. Forty-eight hours of tocolysis has a place
19 in the practice of obstetrics. This conclusion is based on
20 the data from three analyses of randomized, placebo-control
21 tocolytic trials, the King meta-analysis -- actually, that
22 should be 1988 -- the Canadian labor study, and the Keirse
23 meta-analysis. This conclusion has also formed the basis
24 for the recommendation of beta-mimetic tocolytic use in the
25 United States in 1990, in 1992, and in 1993. And as Dr.

1 Romero just pointed out, the recommendation of the American
2 College of Obstetricians and Gynecologists is for the
3 short-term prolongation of pregnancy so that antenatal
4 steroids can be administered.

5 From the data presented today, we have shown
6 that the oxytocin antagonist atosiban is both safe and
7 effective for the target population of preterm labor
8 patients greater than or equal to 28 weeks gestational age.
9 This subgroup is justified both on biologic rationale and
10 by the results of two placebo-control trials. To achieve
11 safe and optimal exposure to steroids or for transfer,
12 atosiban has efficacy that is superior to placebo and at
13 least similar to beta-mimetics, maternal safety that is
14 superior to beta-mimetics and similar to placebo, and
15 infant safety that is similar to beta-mimetics.

16 Our proposed indication for the use of
17 atosiban, therefore, is that it be used for the acute
18 treatment of preterm labor for up to 48 hours in patients
19 who are at least 28 weeks gestation to facilitate therapies
20 designed to hasten fetal lung maturation and/or for
21 maternal transfer to more appropriate facilities.

22 Thank you.

23 DR. PETITTI: And thank you to all the
24 presenters for keeping on your time, and for such nice,
25 readable slides and the concise presentation.

1 We now go to the portion of the agenda when we
2 have a discussion, and this is a discussion for committee
3 members, but might include some addressing of questions to
4 the presenters or to their consultants.

5 We do also have a break scheduled at 10:15.
6 We're running a little ahead of schedule, and with the
7 agreement of the committee, what I'd like to do is have the
8 break now, a 20-minute break, come back at 10:25, and that
9 way we can have the discussion of the committee
10 uninterrupted, without having to think of breaking up that
11 discussion.

12 So we will break now, return at 10:25 exactly,
13 have our 20-minute discussion, and then move on to the FDA
14 presentation and further discussion.

15 (Recess.)

16 DR. PETITTI: I'd like to keep us on time and
17 moving along. There are two things that I'd like to do
18 before we return to the discussion and question-and-answer
19 session. First of all, we have two members of the
20 committee and one of the FDA staff who joined us, and I'd
21 like Dr. Lockwood, Dr. Greene, and Dr. Bilstad to introduce
22 themselves.

23 DR. LOCKWOOD: I'm Dr. Lockwood, and I'm at NYU
24 in New York.

25 DR. GREENE: Mike Greene, Massachusetts General

1 Hospital.

2 DR. PETITTI: Would you just say briefly what
3 department you're in, both Dr. Lockwood and Dr. Greene?

4 DR. GREENE: Obstetrics and gynecology.

5 DR. LOCKWOOD: Same.

6 DR. BILSTAD: Jim Bilstad, FDA. I'm director
7 of the Office of Drug Evaluation II.

8 DR. PETITTI: And we have one note for the
9 record.

10 MS. TOPPER: Dr. Haywood Brown has elected to
11 recuse himself from the rest of the meeting. He realized
12 that his office and he participated in this study, and he
13 feels it would be incorrect for him to participate at all,
14 so he is going to remove himself from the table, and he's
15 more than welcome to stay in the general audience.

16 Thank you.

17 DR. PETITTI: I would like Dr. Creasy to take
18 the podium, and he will direct any questions to members of
19 the sponsor group. This is the time for a 20-minute
20 discussion among the committee members.

21 Ralph?

22 DR. D'AGOSTINO: I'm just trying to get a
23 setting for myself in terms of interpreting the
24 presentation and the data. Was there a single study with
25 the requested indication -- that is, the 48-hour effect for

1 gestational age greater or equal to 28 weeks -- was there a
2 single study with that requested indication actually
3 planned and performed?

4 DR. CREASY: Actually, there was more than a
5 single study that had the 48-hour endpoint --

6 DR. D'AGOSTINO: No, no. Maybe I should have
7 said as the primary endpoint.

8 DR. CREASY: As the primary endpoint? No,
9 there was not a study that had the primary endpoint of 48
10 hours.

11 DR. D'AGOSTINO: So what we have is that there
12 were some studies where, upon a post hoc analysis, a subset
13 analysis, we pulled out a plausible explanation for
14 proceeding with interpretation of the data, or we used a
15 post hoc subset analysis procedure to identify something
16 for an indication? Is that correct?

17 DR. CREASY: It wasn't a post hoc analysis.
18 The 48-hour endpoint was a prospectively planned endpoint
19 for all of the studies.

20 DR. D'AGOSTINO: But the gestational age of
21 greater than or equal to 28 weeks and the --

22 DR. CREASY: Oh, that's correct. We didn't
23 anticipate ahead of time the target population of 28 weeks.

24 DR. D'AGOSTINO: Let me ask another question.
25 I understand the discussion -- or I think I understand the

1 discussion of the 48 hours, but are we saying that the time
2 to failure is not an appropriate endpoint at all, and are
3 we -- see, I guess I'm stuck that I see the mother, the
4 fetus, and the child as all sort of important aspects of
5 this, and the time to failure followed by looking at the
6 child's status all sounded kind of reasonable, but now
7 we're focusing and saying that it's a sensible indication
8 just to do the 48 hours so that we can delay things and
9 give steroid medication and so forth. Does that mean that
10 we don't look at the other things?

11 I just don't know how to discard or to
12 interpret all the other aspects of these studies if I focus
13 very much on this indication that wasn't pre-planned.

14 DR. CREASY: Can I invite Dr. Marc Keirse --
15 we've heard from Dr. Romero and we've heard from Dr.
16 Caritis. Dr. Marc Keirse is with us today. He's a
17 perinatal epidemiologist. He was responsible for one of
18 the first meta-analyses of the effect of steroids and of
19 tocolysis, and I'd like to ask him to address that
20 question.

21 DR. KEIRSE: I think it's actually a very good
22 question. It goes back to when we first started analyzing
23 the various studies which have been done on beta-mimetics,
24 realizing that all of the trials were actually too small to
25 show significant results, and I'm now talking back to 1985,

1 when we actually started that process, and at that moment
2 in time we made a very conscious decision not to look at
3 prolongation per se, for the very simple reason that most
4 of the studies were done in academic institutions, but
5 that's not where the patients are treated. Most of the
6 patients are treated not in academic institutions, and we
7 wanted to figure out and measure by which one could across
8 studies look at an outcome that was likely to be beneficial
9 if it was used properly.

10 That's when we came up with 24 hours, because
11 you would need -- as a clinician working elsewhere, you
12 would need some guarantee for 24 hours, or you would not
13 put someone on transport if that requires a lot of time,
14 and we took the 48 hours because it corresponded to the
15 corticosteroids.

16 And as Dr. Creasy says, I've been responsible,
17 together with King, for the first beta-mimetic meta-
18 analysis, and together with Patricia Crowley for the first
19 corticosteroids meta-analysis, and it's not an accident
20 that those two items of 48 hours are related. You will
21 also notice that the Canadian multi-center trial of
22 ritodrine actually adopted the same outcomes that we had
23 introduced in our beta-mimetic analysis, and I think it's
24 because it's a clinically relevant and useful outcome.

25 DR. PETITTI: Did that answer your question?

1 Perhaps we can come -- I think there will be a fair amount
2 more discussion of this topic. I'd like to make sure that
3 we have time for the members of the committee to ask other
4 questions.

5 DR. D'AGOSTINO: Can I just ask one more? Then
6 I'll move on. Given the results and the way it was
7 extracted and so forth, isn't there a need for a
8 confirmatory study where the protocol is designed
9 specifically to get at this and the primary endpoint is in
10 fact what you're asking for the indication, a nice
11 confirmatory study to make sure it all does fall in place?

12 DR. CREASY: Dr. Titi from our biostatistics
13 department.

14 DR. TITI: Dr. James Titi, vice president of
15 biostatistics and clinical data management, PRI. Before
16 addressing that question, I think one other factor that is
17 important to point out, Dr. D'Agostino, is that when we
18 looked at this data and looked at the endpoints relative to
19 treatment, we found that there was a significant
20 interaction related to gestational age at enrollment into
21 the trial, and when we did some modeling of this
22 information, we found that in fact the 28-week point is
23 where the response curves crossed, so that we then looked
24 at the response data beyond 28 weeks as the point where we
25 felt it was appropriate to look at the information, and I

1 think as was mentioned in the presentations earlier, that
2 represents about 85 percent of the patients that were
3 enrolled in the trial.

4 DR. PETITTI: While you're up there, I have a
5 question that I believe you probably would be the best
6 person to answer, and it specifically relates to some
7 greater amount of detail about the randomization procedure.
8 Now, this was a double-blind study, and I presume by that
9 that the people who were blinded were the patient and the
10 physician. Could you talk a little bit about the actual
11 procedure whereby the drug was prepared by the pharmacist
12 and whether the pharmacist was in fact blinded?

13 DR. TITI: I would really have to ask Dr.
14 Creasy or Ms. Roseanne Lane, who were actually the people
15 involved in the trial, to address that specifically.

16 DR. CREASY: I think I can best answer that
17 question. The drug was sent to the pharmacy in bulk
18 supply. The pharmacist also received sealed envelopes,
19 with the randomization code contained therein, in
20 sequential order for the patients that were to be enrolled
21 for that center. The pharmacist was to receive a call from
22 the floor when a patient passed through the screening
23 procedures and select the next envelope for randomizing
24 that patient, for mixing the drug, and sending the drug to
25 the floor.

1 We have done a check of the randomization order
2 and the date of dispensement in the PTL-096 study, and
3 there's no aberration in that order with regard to the
4 dates of enrollment and the order of randomization. They
5 are all in the correct order.

6 DR. PETITTI: Have you discussed the imbalance
7 in the number of patients in the less-than-1,000-gram
8 group? Because 20 to 2 is a very striking anomaly in that
9 -- you know, you either have to believe that the drug
10 caused low birth weight or low birth weight caused the
11 drug. Could you explain -- is there any chance that this
12 randomization in the lower-birth-weight, low-gestational-
13 age groups could have been tampered with?

14 DR. CREASY: The best that I can say is that we
15 looked through all of the records, and we actually --
16 during the conduct of the study, the group of individuals
17 that were responsible for monitoring the pharmacy records
18 was a separate group from the group that was responsible
19 for monitoring the clinical records. That was to ensure
20 that there would be no chance of them bumping into each
21 other or divulging information between those two functions
22 that should not be divulged.

23 On a review of all of the records from the
24 pharmacy and from the floor, there just is no evidence that
25 sites were somehow defeating the randomization. All of the

1 randomization numbers were given in the proper sequence,
2 and we simply have no evidence, although we did look.

3 DR. PETITTI: Dr. Oh?

4 DR. OH: I have two questions related to the
5 infant outcome. One actually relates to the issue raised
6 by Dr. D'Agostino in terms of the sample size. Since the
7 event rate of almost all of your infant outcomes -- their
8 death rate, RDS, NEC, et cetera -- are relatively low, 2
9 percent, 1 percent, I just wondered if someone would
10 comment on the power of analysis, given the low event rate.

11 And the other question has to do with the
12 infant follow-up, which has never been delved into in
13 detail. Looking at the data that was presented to us prior
14 to the meeting, you have a 50 percent attrition rate. At
15 least, that was the data that was shown. Out of 250-plus
16 infants that were being followed, only 144 have been
17 followed to date. I just wondered if someone could comment
18 on the validity of the results on having a 50 percent
19 attrition rate for the neurodevelopmental outcome.

20 DR. CREASY: The first question has to do with
21 the power of detecting differences in the neonatal
22 outcomes?

23 DR. OH: Right.

24 DR. CREASY: Ms. Lane, can you address that,
25 please?

1 MS. LANE: Roseanne Lane from clinical
2 biostatistics. We did not power the study to look at
3 infant outcomes. We powered the study to look at time to
4 delivery or therapeutic failure.

5 DR. OH: I realize that, and that was the
6 problem with the post hoc analysis, as was pointed out. My
7 question really is, how valid is it to analyze data with a
8 low event rate, both in the positive and negative sense?
9 In other words, negative sense, you can't really say that
10 there's no bad effect if the sample size is inadequate, and
11 in fact one of the arguments that you have in terms of a
12 48-hour prolongation of labor is that the prolongation
13 would benefit the infant, but, again, you're limited by the
14 power to demonstrate that prolongation indeed will impact
15 the outcome of the baby, which you haven't shown.

16 That's my question, and I don't think you can
17 answer that --

18 DR. CREASY: Dr. Sibai?

19 DR. SIBAI: I think the biggest problem --

20 DR. CREASY: Do you want to state your name?

21 DR. SIBAI: Baha Sibai. I'm one of the
22 investigators who recruited most of the patients in the
23 United States. The problem with studies dealing with
24 preterm labor is that it's not a diagnosis that's so
25 accurate where a lot of the babies will deliver preterm.

1 Given an incidence of IVH of 2 percent, it's very unlikely
2 that any study will ever be done to prove whether a
3 tocolytic will affect the incidence of IVH in a preterm
4 labor population, because the sample size to show even a
5 difference of 50 percent will mean at least 5,000
6 deliveries.

7 The second point really I want to address
8 regarding the 28 weeks. Despite the fact that the sponsor
9 is requesting approval for the 28 weeks, if one looks at
10 all the benefits for everybody enrolled in the study
11 between 20 and 33 weeks, there was a significant pregnancy
12 prolongation for 48 hours. So really the 28 weeks, even
13 though it was a post hoc analysis, was still believed for
14 everybody from 20 to 33 weeks that there was a significant
15 benefit regarding pregnancy prolongation for 48 hours.

16 In response to the second point, should we do
17 another study, my answer would be it's impossible, and the
18 mere reason is, at the present time it's unethical to do
19 any randomized trial with a placebo, and this is why in our
20 recommendations for using steroids, the medico-legal
21 environment as well as ethical environment would preclude
22 anyplace in the United States to conduct a study to say
23 they were going to compare a tocolytic versus a placebo.
24 So we are left at the present time with a need for a
25 tocolytic agent that at least is as good as what's

1 available in this country, because I don't think any
2 company will ever come back and say, "We're going to do a
3 study to introduce a new tocolytic, with this proviso."

4 DR. PETITTI: Dr. Harris?

5 DR. HARRIS: Could I just follow up with Dr.
6 Sibai on the diagnosis of preterm labor in the placebo-
7 control trial, where the therapy was for 1 hour and then
8 defaulted into another therapy? Unless I misread the
9 slide, in the placebo group it looked like only about half
10 of the patients required active intervention after an hour
11 of placebo. Is that correct?

12 DR. SIBAI: For about 51 percent of the
13 patients.

14 DR. HARRIS: Okay. Could you comment, then,
15 about the diagnosis and how you decided to treat or not
16 treat an individual patient?

17 DR. SIBAI: Well, you know, the diagnosis was
18 based on the standard definition that's used by clinicians
19 in the United States, which is a certain number of uterine
20 contractions over a certain time period plus the presence
21 of effacement and/or cervical dilatation. Now, the
22 requirement for using an alternate tocolytic was based on a
23 patient demonstrating significant uterine contractions plus
24 a change during the step which required the practicing
25 obstetrician to use an alternate tocolytic.

1 DR. CREASY: Dr. Harris, I should say that the
2 investigator meeting that was conducted in the fall of 1993
3 to discuss just the criteria that you're referring to was a
4 debate that settled on criteria that the group felt would
5 identify patients who really needed a tocolytic agent. But
6 as you can see, even waiting so long as to identify
7 cervical change in contracting patients still results in a
8 number of patients who, in a posterior view, may not have
9 needed the tocolytic at all. But if you wait any longer,
10 those who would need it may become unrescuable.

11 DR. PETITTI: I have another question about the
12 trial per se. Did you keep a log of patients who were
13 eligible for the study and who declined randomization, and
14 if so, was there any difference in the proportion declining
15 randomization by estimated gestational age at time of
16 eligibility?

17 DR. CREASY: We did keep a log. The study was
18 very difficult to enroll, and we wanted to be sure that all
19 patients were being screened and evaluated for the study,
20 and a review of those logs was done as the study went on to
21 encourage the sites to keep enrolling patients, and the
22 patients who were not being included were patients with
23 ruptured membranes, patients with other complications who
24 didn't meet the criteria. Those were the patients included
25 on the logs of the patients not randomized to the study.

1 They were patients who didn't fit the criteria.

2 DR. PETITTI: Was there a specific analysis
3 done of patients who might have fit the criteria, but who
4 declined participation by gestational age?

5 DR. CREASY: No, there was not.

6 DR. PETITTI: Go ahead.

7 DR. DATTEL: I just have a question about the
8 issue of multiple gestation in the study. In my review of
9 the deaths and the data, it seemed that twin gestations
10 were separated out. I wondered if you had any analysis on
11 multiple gestations, because there seemed to be a
12 disproportionate amount of adverse outcomes in the atosiban
13 group with twins.

14 DR. CREASY: Was there a disproportionate
15 number of adverse outcomes on the twin gestations for the
16 atosiban patients?

17 DR. DATTEL: And did you break out twins
18 separately from singletons in your analysis? Because I
19 don't see that represented anywhere, and it seems to me
20 that that may be a separate group with a different set of
21 issues and potential adverse maternal and fetal or neonatal
22 problems.

23 DR. CREASY: As a group, the twin gestations
24 did deliver earlier, and as a group, they did have more
25 complications because of the expected earlier delivery. I

1 don't think I have a slide to show you today of the
2 outcomes specific to that group.

3 Ms. Lane?

4 MS. LANE: Roseanne Lane, clinical
5 biostatistics. Are you referring to the efficacy analyses
6 by singleton and multiple?

7 DR. DATTEL: Both efficacy and adverse outcome
8 for singleton and multiple.

9 MS. LANE: We do have a slide that has the 24,
10 48, and 7-day endpoints by singleton and multiple, if I
11 could have Slide 73 in the back-ups. I also did some
12 logistic regression analyses on these endpoints and
13 included treatment by singleton/multiple interaction. That
14 was not statistically significant at the .1 level, although
15 singleton/multiple was a significant covariate, with
16 singletons doing better than multiples. But there was no
17 treatment interaction.

18 DR. DATTEL: The adverse event for multiples
19 for the infants?

20 MS. LANE: Right. I believe we have RDS by
21 singleton/multiple. Actually, I don't have a -- let's see.
22 I don't actually have a slide for it, but I know that there
23 was more RDS in the multiples on atosiban than in the
24 multiples on placebo.

25 DR. CREASY: We may have some data from the

1 active-control study.

2 DR. PETITTI: Dr. Azziz?

3 DR. AZZIZ: Ms. Lane, can I ask you a question?

4 On the Slide 73 that you just had here, just to very
5 quickly make sure that I interpreted this correctly, it
6 does not look like atosiban is effective in multiple
7 gestations.

8 MS. LANE: As I said earlier, I had done some
9 logistic regression looking at the treatment by
10 singleton/multiple interaction, and that was not
11 statistically significant at the .1 level.

12 DR. CREASY: There is a very strong effect in
13 the singleton gestations.

14 DR. AZZIZ: And there's no effect, it looks
15 like, on multiples.

16 DR. CREASY: The subgroup of multiples is quite
17 a bit smaller, and it wasn't a study designed to look
18 specifically at multiples. But there is a strong effect
19 shown here on the singletons.

20 Dr. Bengtsson --

21 DR. PETITTI: Excuse me. We have a question
22 from the committee here.

23 DR. CREASY: Oh, okay.

24 MS. NARRIGAN: I have a question on
25 pharmacology. In some of our materials handed out prior to

1 the meeting, your drug is characterized not only as an
2 oxytocin receptor antagonist, but also as a vasopressin
3 receptor antagonist, and, again, in some of our pre-meeting
4 materials, I understood that you were going to be
5 presenting some preliminary information on another animal
6 model, the sheep or the lamb. Is that going to be
7 forthcoming or not?

8 In what I've read, I still have tremendous
9 concerns about the actual effect on the fetus, either
10 animal or human, and I really haven't heard much from you
11 this morning addressing that question.

12 DR. CREASY: Well, as you know from your
13 briefing books, there is an ongoing fetal sheep study, but
14 the results of that study have not yet been concluded and
15 delivered to the reviewing division. We could bring -- I
16 mean, there is some data that's been published, and if I
17 could have Slide 517 and ask Dr. Peter Nathaniels to come
18 and comment on this slide.

19 DR. PETITTI: Briefly.

20 DR. NATHANIELS: I can do it with the hand
21 mike. My name is Peter Nathaniels. I'm from Cornell
22 University. The non-human primate data which we have is
23 published in the public domain, and what we did was to
24 infuse pregnant baboons with up to 24 micrograms per
25 kilogram per minute, which is about five times the normal

1 dose intended for the human, and this is the fetal
2 oxygenation, the P02. The open symbols are the fetal
3 baboons before the atosiban, and the solid symbols are
4 during the atosiban. So it had no effect on fetal
5 oxygenation.

6 In addition, if I could have Slide 677 and 678,
7 we did a study a long time ago in the rhesus monkey in
8 which we infused rhesus monkeys for 12 hours a day,
9 starting at 157 days of gestation, and normal gestation is
10 about 162. Normal gestation is about 162 in the rhesus
11 monkey. So we started at 157 days, which is 5 days before
12 gestation normally ends, and you'll see from the left-hand
13 series that control animals infused just with vehicles
14 actually delivered at 162 days, but we had 15 days of
15 infusion of atosiban, so these animals went about 9 days
16 post-mature, which is the basis for the claim that atosiban
17 will in fact prolong gestation. So these animals went
18 about 9 days post-mature.

19 These are some data from the Oregon Regional
20 Primate Center's additional set of controls. So the first
21 thing we noticed in -- these animals were born alive. We
22 weren't going to study any other parameters, but the
23 newborns were alive, well, and the organ weights were no
24 different from controls. So certainly 15 days of infusion
25 12 hours a day of atosiban to the pregnant rhesus monkey at

1 the end of term gave us no gross indications of reduction
2 in organ weight or any abnormality in the newborns.

3 DR. PETITTI: We have a number of other
4 discussion sections in this discussion, and we can address
5 other questions along the way to your group, so I'd like to
6 move on to the presentation by the FDA, and we have talking
7 today Sandra Kweder, Division of Reproductive and Urologic
8 Drugs.

9 DR. KWEDER: Good morning. Some of the things
10 that I'm -- this is just a list on the slide of who's going
11 to be speaking from the FDA this morning. I'm going to
12 start out with some regulatory history, much of which has
13 already been referred to, but I thought it might be useful
14 for the committee to go into a little bit more detail of
15 how we've gotten to this point from a regulatory
16 perspective. I'll be followed by Dr. McNerney, who will
17 talk about some of the preclinical toxicology data, and
18 after lunch we'll have a pretty extensive presentation on
19 the data itself in the NDA by Joy Mele, our statistician.
20 I'll come back at the end for 5 minutes to sort of wrap up
21 and get you all started on the questions of the day.

22 Now, I am going to talk about the regulatory
23 context of tocolytics, and I always find when I confront a
24 difficult issue or a difficult decision from a regulatory
25 standpoint that it's often useful to go back and read the

1 old literature and read the old minutes of meetings and
2 figure out how did we get to this point. I'm going to talk
3 a little bit about the original approval of ritodrine, I'll
4 say very little about the very early years of terbutaline,
5 and I'm going to talk about hexaprenaline, which we haven't
6 heard too much about today. Some of you may remember the
7 discussions of hexaprenaline sulfate before a committee
8 like this; others of you may not be familiar with that.

9 I'm not going to say much about -- or anything
10 about indomethacin or magnesium sulfate, because those data
11 have never been reviewed by a committee such as this, nor
12 ever submitted to FDA in any shape or form. I'll say some
13 things about some of the medical literature and its
14 evolution that have already been mentioned today, and then
15 try to summarize and give you a feel for how this NDA came
16 to be and how FDA's perspective on this NDA came about.

17 To start with ritodrine, the original ritodrine
18 application was in the late 1970s, and the basis upon which
19 that drug was approved was really four controlled trials.
20 There were other trials, but they were even smaller than
21 the ones that you see up on the slide. You can see that
22 the largest one was 150 patients. The control agent used
23 in those randomized trials were alcohol, librium, or
24 placebo, depending on the study.

25 Overall, in looking at the data in each of

1 those four major trials, which were state-of-the-art at the
2 time, there was demonstrated a significant gain in days to
3 delivery. There wasn't talk at that time -- remember, this
4 is the late 1970s. There wasn't talk about a 48-hour
5 endpoint. They were looking at days to delivery. Also
6 evaluated were, well, were the infants of similar
7 gestational age at birth? Was there a prolongation of
8 gestational age? And the answer was no. In control and
9 ritodrine patients, the gestational age of the infants was
10 similar.

11 That data was taken to an advisory committee
12 much like this one in May of 1979, and, interestingly, the
13 committee stated -- and this is a quote from the record --
14 that the data do not substantially support ritodrine's
15 efficacy, which came as a great surprise to the FDA. The
16 committee sent the FDA and the company back to reanalyze
17 the data. The committee wanted to know, does this
18 obstetric benefit that we see translate into benefit to the
19 infants, because that's what we really care about. They
20 specifically noted that they wanted to see analyzed infant
21 and neonatal mortality, incidence of respiratory distress
22 syndrome, and achievement of gestational age of 36 weeks
23 between the ritodrine and control patients. And because
24 they were concerned that there perhaps might be differences
25 in why patients go into preterm labor at early gestational

1 ages compared to later and thereby perhaps a differential
2 effect of a drug, depending on gestational age at the time
3 it was administered, they wanted to see these data
4 stratified by gestational age at entry.

5 That committee reconvened several months later,
6 and the analyses presented were, on the pooled data from
7 those four studies, infant mortality, respiratory distress
8 syndrome, birth weight, and achievement of 36 weeks
9 gestation. For all of those endpoints, there was a
10 statistically significant benefit to ritodrine compared to
11 the controls shown, and, interestingly, the benefit was
12 most dramatic for infants of mothers who entered the trials
13 at less than 33 weeks gestational age, the younger
14 gestational age patients.

15 The committee did recommend approval, and in
16 June 1980, ritodrine was approved for marketing by Merrill-
17 Dow.

18 In hindsight, it's interesting to go back to
19 those transcripts and recognize that there was really no
20 discussion at the time, at least from what I could see in
21 the notes that were taken at the time, of possible neonatal
22 harm by the sedative control agents of librium and alcohol.
23 That's just something I found interesting.

24 Now, here's my one slide on terbutaline. I
25 mentioned that ritodrine was marketed to Merrill-Dow, and

1 at the time of ritodrine's approval, Astra held the INDS
2 for terbutaline. In 1982 Merrill-Dow traded ritodrine to
3 Astra for terbutaline, and the reason was that Merrill-Dow
4 was in the throes of the Bendectin controversy and
5 basically wanted to divest itself of drugs that had an
6 obstetric indication, and really tried to make it very
7 clear right from the beginning that they had no intention
8 of developing an NDA for terbutaline, and they've held to
9 their word. There has never been an NDA for terbutaline.

10 The FDA has looked at much literature data, but
11 we've never had the opportunity to see source data on the
12 drug. Most of what we've had to do has been to address
13 off-label use issues, and that's been done at a number of
14 advisory committee meetings, and I'm not going to go into
15 detail on that.

16 But that brings us to another beta-mimetic,
17 hexaprenaline. This drug was studied predominantly in the
18 1980s. There were no placebo-control trial data ever
19 submitted to the FDA on hexaprenaline sulfate. The pivotal
20 study for this drug that was presented to us in an NDA form
21 was a ritodrine comparison, an active-control trial. It
22 was basically a trial that was designed to show the
23 superiority of hexaprenaline over ritodrine, and it did not
24 demonstrate superiority of hexaprenaline over ritodrine.
25 The study was not large enough to say with confidence

1 statistically that the drugs had similar efficacy. There
2 was no additional benefit to the infants shown, but there
3 was not much question that the hexaprenaline did have a
4 much better maternal safety profile than ritodrine did in
5 that study.

6 There were a number of concerns at the FDA, in
7 the division, at the time of the NDA. One of the questions
8 was, well, do we simply have here a low-potency beta-
9 agonist, and is that why they couldn't show superiority to
10 ritodrine? Is that why it seemed to be less toxic to the
11 mothers? And there was concern, based on really going back
12 to that 1979 advisory committee discussion about infant
13 benefit, that there was no definitive demonstration of
14 infant benefit from hexaprenaline.

15 Because of those concerns, that drug and an NDA
16 was taken to an advisory committee meeting in 1990, just
17 about 10 years after ritodrine, and the committee voted 10
18 to 0 to recommend approval, and in going back through the
19 transcripts of that meeting, I think there were several
20 reasons why. One is that indeed the drugs did look to be
21 similar, and although the active-control trial didn't have
22 the statistical robustness to show equivalence, there was
23 pharmacologic plausibility that two beta-mimetic agents,
24 two drugs in the same class, we could generally conclude
25 that there was a rationale to consider that they were

1 probably equivalent.

2 The committee was happy to see that there was
3 less maternal toxicity from hexaprenaline, and,
4 interestingly, infant benefit was discussed, but I could
5 not find any evidence in the transcripts that there was
6 ever any specific or pointed discussion of infant benefit
7 as a mandatory requirement for a tocolytic.

8 Now, hexaprenaline, as you know, was never
9 marketed in this country, and we're not going to go into
10 all the reasons for that.

11 While all this was going on, the medical
12 literature in the area of tocolysis was evolving, and I'm
13 going to just talk about two major studies, the King meta-
14 analysis and the Canadian study that have been referred to
15 here. The Keirse meta-analysis following the Canadian
16 study simply extended the original one, and although
17 important, I don't think we have time to go into it in much
18 detail.

19 To start with the King meta-analysis, that was
20 published in the British Journal of Obstetrics and
21 Gynecology in 1988. It was a meta-analysis of 16
22 randomized, controlled trials involving 860 patients. Most
23 of the trials were ritodrine trials. There were several
24 terbutaline trials, but the vast majority were ritodrine.

25 This was a very carefully conducted meta-

1 analysis. What that study showed was that the positive
2 effects of ritodrine seemed to be in delaying delivery for
3 24 to 48 hours. Now, that analysis -- at least, the
4 published version of it -- did not look beyond that, so I
5 can't say if there were -- you can't tell from the data if
6 there was additional benefit to that. The other positive
7 effect was that ritodrine did seem to reduce the frequency
8 of preterm birth and low birth weight, but there appeared
9 to be no effect of ritodrine compared to controls on
10 perinatal mortality or neonatal respiratory distress
11 disorders or other measures of neonatal morbidity.

12 So why was the study important? I think for
13 several reasons. One, it questioned the premise for
14 ritodrine's original approval, which was neonatal benefit,
15 or at least began to raise questions about that. Second,
16 it confirmed the original data on ritodrine's effect in
17 delaying delivery. In the obstetric community, it was
18 already pretty well recognized that most of the benefit of
19 that drug was in the first 48 hours, although it was
20 certainly not likely to be completely limited to that. And
21 I think that it probably affected -- it did come out in
22 1988. I think that these data probably did affect to some
23 extent the advisory committee's discussions on
24 hexaprenaline.

25 The second major event, and probably the most

1 important one, was the Canadian study that was published in
2 1992 in the New England Journal of Medicine. This was a
3 multi-center trial conducted at tertiary care centers in
4 Canada. It was double-blinded, ritodrine versus placebo.
5 Seven hundred patients were randomized, and that
6 randomization was stratified by gestational age at entry.
7 Most important about this trial was that it set out to
8 definitively answer the question of infant benefit from the
9 tocolytic ritodrine. That study was designed specifically
10 to capture neonatal endpoints looking at morbidity and
11 mortality. They did look at obstetric endpoints as well,
12 but they were considered secondary -- important, but
13 secondary to the neonatal issues.

14 The results of that trial showed that there was
15 no difference in birth weight, neonatal mortality, or
16 differences in neonatal morbidity on multiple measures of
17 ritodrine compared to placebo. Ritodrine did reduce the
18 percent of patients delivered at 24 and 48 hours, and that
19 was highly statistically significant. And if you look at
20 the number of days that pregnancies were prolonged, the
21 mean number of days between ritodrine and placebo, the
22 difference, the delta, was about 3 days, although that was
23 not statistically significant. And, again, interestingly,
24 much like all of the data to that point had shown for
25 ritodrine, the most benefit seemed to be in the younger

1 gestational age patients. It wasn't limited to it in the
2 study, but most of it seemed to be in the younger ones.

3 So why did this study matter? Well, it was the
4 largest controlled study ever done of this drug or any
5 tocolytic, and it showed no measurable infant benefit from
6 ritodrine, which was seen by many as a great
7 disappointment, and, again, confirming that most of the
8 benefit is brief, but in earlier gestational age
9 pregnancies.

10 There are a few considerations and subsequent
11 discussions about this trial. I think one of the most
12 important caveats is that despite the fact that the study
13 was done in the late 1980s, antenatal steroids were not
14 required in this study, so their use was highly variable
15 from patient to patient and center to center, which many
16 people felt could have influenced the inability to show a
17 neonatal benefit. And many folks, I think -- if you read
18 the literature and have been around any discussions of
19 this, I think a lot of people after this trial began to
20 think, well, what are we doing here anyway, and have a very
21 nihilistic view of beta-mimetic tocolytics.

22 On the other hand, I think that the real issue
23 that comes out in reading the literature further on,
24 several years out from this, is that what's important is
25 what is done in those first 48 hours, and the Canadian

1 study was performed at tertiary care centers, and perhaps
2 it's unrealistic to expect to show true neonatal or
3 measurable neonatal benefit in tertiary care centers unless
4 you have a very, very dramatic obstetric endpoint.

5 Now, since the Canadian study, there has been
6 very little discussion by FDA advisory committees of
7 specifically requiring infant benefit demonstration or
8 infant benefit at all in terms of tocolytics. FDA has
9 maintained the desirability of at least looking for that
10 data, and that brings us to the atosiban development and
11 our participation in discussions of that.

12 The INDs for this drug started in 1988, the
13 initial trials in humans. In 1993 we met with the company
14 for a Phase III planning meeting, and the company did
15 indeed initially propose that what they really wanted to
16 look at in their Phase III studies was a 48-hour endpoint,
17 and that was based on the history that I've just described.
18 The FDA felt that 48 hours was an interesting endpoint, but
19 it probably wasn't enough to simply do a trial that stopped
20 looking at 48 hours, that we wanted a broader picture of
21 the efficacy and clinical effectiveness of a tocolytic
22 agent, not limited to this narrow window of time. The
23 agency did stress the importance of evaluating perinatal
24 morbidity or improved gestational age, and the agency also
25 specifically stated that it would be important to be able

1 to evaluate independently the effect of acute treatment and
2 prolonged maintenance in the total tocolytic picture.

3 So from there the agreed NDA plan was pretty
4 much as you've seen already and as I have listed here, that
5 the 096 study would be a study of acute and maintenance
6 therapy together, randomized from the beginning, and this
7 study was felt to be the best bet to capture a variety of
8 important endpoints, both obstetric and neonatal. It was a
9 very rigorously designed trial by the time it was
10 implemented, and the placebo nature of it avoided the
11 active-control analysis issues that we had struggled with
12 so greatly with hexaprenaline.

13 The 098 study was the answer to having an
14 independent randomization and analysis for maintenance
15 therapy. As you know, this was a responder analysis, so we
16 felt that its value essentially rested on 096 or was
17 intimately linked to the results of acute treatment that
18 would be seen in 096.

19 And the CAP studies, or the active-control
20 comparisons, were from the beginning really felt likely to
21 be supplemental. They involved controls. Two of the
22 control agents did not have NDA approval in this country,
23 and so we felt like they could be helpful, but were not
24 likely to carry the weight of 096 and 098.

25 So, in summary, the ritodrine approval was

1 based on neonatal benefit, although obstetric benefit
2 existed as well, but what really got it over the threshold
3 for approval was the drug's demonstration of infant
4 benefit. This, unfortunately, was not upheld by more
5 definitive studies of the drug. Although obstetric
6 endpoints for ritodrine do consistently show benefit, most
7 of it seems to be in the first 48 hours for the majority of
8 patients. No tocolytic trial of any drug, to our
9 knowledge, has demonstrated neonatal benefit from
10 tocolysis, and I think it is important to consider that it
11 might be unrealistic to expect that we're going to be able
12 to show that, given the realities of neonatal care today.
13 And we've been the route before of using active controls as
14 the foundation for concluding efficacy, and they create
15 some difficult statistical and comparative issues.

16 So I have two conclusions. One is that the
17 history of tocolysis is why we at the FDA have focused this
18 NDA review on the 096 study. This was a very large, very
19 rigorously conducted trial. It was designed to capture
20 many potentially important pieces of information or
21 variables, and it was also not likely to be blinded or have
22 the blind broken by beta-agonist side effects.

23 History is also why, in light of 096, we find
24 the 098 and CAP data less compelling. The 098 is a
25 responder analysis that really rests on 096, although there

1 is some important safety information to be gained from that
2 study. The CAP studies were conducted much differently
3 than 096 and 098, as I think you'll see in Joy's
4 presentation this afternoon. Unblinding is certainly
5 likely, simply given the reality of beta-mimetic side
6 effects. And in active-control trials, if you don't show
7 superiority when that's what you set out to show, we don't
8 have, as we had in hexaprenaline, the pharmacologic
9 plausibility for similarity.

10 So I'm going to stop there and let Mary Ellen
11 McNerney take over.

12 DR. MCNERNEY: Good morning. My name is Mary
13 Ellen McNerney. I would like to address the preclinical
14 studies of atosiban in maternal-fetal unit.

15 Preclinical studies of the reproductive and
16 developmental effects of atosiban have been completed in
17 rats. Additionally, as was raised earlier, developmental
18 pharmacology studies in the chronically instrumented fetal
19 lamb are ongoing. All protocols for the peri- and
20 postnatal evaluation of atosiban toxicology in rat
21 specified that atosiban be administered to pregnant females
22 from gestational days 15 to 20, inclusive.

23 One of the five studies was designed and
24 executed to permit dose-related evaluations of adequate
25 numbers of dams and their litters. This study, which I

1 refer to as the definitive rat study, I will describe in
2 detail. Remaining studies will be summarized subsequently.

3 In the definitive study, as I have indicated,
4 atosiban was administered to pregnant rats from gestational
5 day 15 through gestational day 20, inclusive. Treated
6 dams, with the exception of satellite animals that were
7 assigned for toxicokinetic evaluation, were permitted to
8 litter and rear their F1 generation. The F1 generation is
9 the progeny. These dams reared their F1 generation through
10 weaning. The F1 generation, in turn, was permitted to
11 mature to about 12 to 13 weeks and then mated. Their
12 progeny, the F2 generation, were subsequently evaluated
13 through weaning.

14 Dose selection for the definitive study was
15 based on the sponsor's stated aim to achieve multiples of
16 previously measured human cord blood concentrations.
17 Specifically, the doses that were administered to rat dams
18 were calculated to deliver rat fetal plasma concentrations
19 that ranged from 60 to 180 nanograms per mL. These
20 concentrations exceed the estimated human fetal
21 concentrations associated with the proposed clinical
22 treatment regimen by factors of about 2.5 to 7.5.

23 Now, unlike the human placenta, the rat
24 placenta is very poorly permeable to atosiban. The sponsor
25 has estimated that relative fetal plasma concentrations in

1 rats are only about 1 percent of maternal plasma
2 concentrations, and this is contrasted with the human
3 placenta, where concentrations measured in cord blood from
4 human third trimester fetuses are estimated to be about 12
5 percent of concurrent maternal concentrations. The upshot
6 of this is that in order to achieve the desired pup
7 concentrations, it was necessary to administer very large
8 doses ranging from 100 to 300 milligrams per kilogram per
9 day to the rat dams.

10 This is a slide depicting the maternal atosiban
11 concentrations. Maternal plasma levels were evaluated on
12 gestational day 20 in three dams at each dose level. The
13 mean maternal plasma atosiban concentration increased as a
14 function of maternal dose, although these increases were
15 not linear. Further, there was considerable variability
16 such that one or more dams at a given dose level would
17 exhibit concentrations in excess of the mean at the next
18 dose level, and recall that there were only three dams per
19 dose group. Finally, the maternal rat-to-human exposure
20 ratios ranged from 10- to 140-fold the average
21 concentrations in third trimester women after the proposed
22 48-hour treatment period.

23 Now, in the definitive rat study, fetal plasma
24 atosiban concentrations in rat pups were in fact within the
25 ranges estimated by the sponsor in its calculation of

1 maternal dosages. Specifically, they ranged from two- to
2 six-fold the predicted human fetal concentrations that
3 would be achieved with the proposed clinical regimen. The
4 mean fetal plasma levels examined at the maternal Tmax --
5 that's the time of maximal concentration after dose
6 administration -- increased with maternal dose, although
7 there was considerable variability in the individual
8 determinations.

9 However, distribution data gathered in a
10 previous pharmacokinetic study suggests that atosiban is
11 sequestered in the fetal compartment, from which it is
12 released more slowly than the maternal plasma elimination
13 half-life would predict. Thus, it is likely that fetal AUC
14 is a better metric of developmental exposure in this animal
15 model. Unfortunately, while data were presented this
16 morning showing us fetal AUC, they were not made available
17 to the FDA for review prior to this time, so I cannot
18 comment on those.

19 While maternal plasma atosiban levels in rats
20 were high relative to those anticipated clinically, there
21 was no serious maternal toxicity reported. Findings, apart
22 from injection site lesions, were limited to dose-related
23 reductions in maternal body weight and dose-related
24 reductions in maternal food consumption over gestational
25 days 18 to 20.

1 This graph depicts the maternal body weights
2 over the course of gestational days 16 to 21. Mean dam
3 body weight in the control population on day 21 was 420
4 grams, while the mean body weight in high-dose dams was 390
5 grams. This represents a decrement of 7 percent. The mean
6 weights of low-dose and mid-dose dams, as you can see, were
7 also reduced as a function of dose.

8 Now, when this parameter is transformed as body
9 weight gain, high-dose females gained 15 percent over their
10 gestational day 15 body weights over the period extending
11 to gestational day 21. This is compared to vehicle control
12 dams, who gained about 21 percent over their gestational
13 day 15 body weights. Thus, when maternal body weight gains
14 are examined this way, the difference between control and
15 high-dose dams is a 6 percent decrement in body weight gain
16 -- that is, the difference between 21 percent and 15
17 percent.

18 Further, dose-related reductions in food
19 consumption were observed among treated dams over the
20 course of 3 days of pregnancy, gestational days 18 to 20.
21 These reductions ranged from 18 to 37 percent, relative to
22 the mean quantities consumed by control dams over the
23 corresponding gestational interval.

24 However, when the overall impacts of atosiban
25 administration on dam and fetus are compared, it is clear

1 that the degree of toxicity is far more extensive in the
2 developing animal. Specifically, the magnitude of findings
3 in the dam at their maxima, which is to say at the high
4 dose, depicts a degree of maternal toxicity which is
5 generally associated with minor reductions in pup weight
6 and perhaps some increase in fetal wastage. These findings
7 do not suggest catastrophic maternal toxicity.
8 Nonetheless, significant developmental mortality and
9 morbidity were observed.

10 First, atosiban administration to rat dams over
11 the interval of gestational day 15 to 20 was associated
12 with a dose-related increase in the incidence of litters
13 with one or more stillborn pups per litter, a trend that
14 was evident in all doses. These data are reproduced here.
15 The values associated with this parameter, the incidence of
16 litters with one or more stillborn pups per litter, at the
17 control, low dose, mid dose, and high dose were 20 percent,
18 30 percent, 33 percent, and 46 percent.

19 More alarmingly, there was 100 percent
20 lethality observed in pups born to 16 of 25 dams treated
21 with the high dose. This lethality was cumulative over the
22 interval spanning postnatal days 1 to 14. This finding
23 represents an extraordinary magnitude of developmental
24 toxicity and cannot be explained by the observed reductions
25 in body weight, nor was there evidence that these dams

1 experienced a significant degree of dystocia.

2 Now, it is conceivable that pup deaths were
3 secondary to interference with maternal lactation and/or
4 perturbations to nurturing behavior. Unfortunately, the
5 available data do not permit this determination to be made.
6 In fact, several lines of evidence refute this
7 interpretation as the sole explanation. First, the
8 pharmacokinetics of atosiban in the rat, a species in which
9 the elimination half-life is estimated to be 3 hours, imply
10 that the drug was completely eliminated in the interval
11 between the last dose administered on gestational day 20
12 and parturition, which is approximately gestational day 22.
13 This argument is bolstered by data which demonstrated no
14 difference in durations of gestation or parturition among
15 control and treated groups.

16 Further, there was milk present in the stomachs
17 of about 50 percent of the dead pups. Finally, clinical
18 observations did not document any evidence of maternal
19 moribundity or failure to nurture, and decrements in
20 maternal weight gain were reversed in the postpartum
21 interval, suggesting no lasting adverse effect to the dams.

22 In summary, we are concerned that maternal
23 toxicity is not the sole cause, nor even the principal
24 cause, of neonatal mortality in this study. Our concern is
25 based on three lines of reasoning: first, that the extent

1 of maternal toxicity is not commensurate with the degree of
2 developmental mortality; second, that signs of maternal
3 toxicity, such as weight decrements and reductions in food
4 consumption, were reversed almost immediately after
5 parturition, while six entire litters perished between
6 postnatal days 5 and 14; finally, there were no clinical
7 observations which documented that dams were too sick to
8 nurse and nurture.

9 Peri- and postnatal pup mortalities were not
10 the only evidence of developmental toxicity. Dose-related
11 reductions in pup weights were also reported. The dose-
12 related discrepancies among experimental groups were first
13 evidenced in the birth weights. These disparities actually
14 increased in magnitude over the course of postnatal days 1
15 to 4. The maximal mean weight decrement first observed on
16 postnatal day 4 was 38 percent in the high-dose group and
17 persisted at this magnitude through postnatal day 28. Some
18 catch-up growth was observed between postnatal day 28 and
19 maturation, but decrements of 10 to 12 percent persisted in
20 mid-dose and high-dose progeny for the lifetimes of the F1
21 generation.

22 Further, transient neurobehavioral morbidity in
23 the F1 females was associated with maternal atosiban
24 administration. There is an error on this slide. It
25 should read that increases in motor activity and learning

1 latencies, as well as reductions in learning retention
2 latencies. That word "latencies" is missing in the
3 learning retention. These findings were observed in F1
4 females on postnatal day 21. These findings again
5 correlated with dose-related reductions in pup body weight.
6 The discrepancies were not apparent when the F1 animals
7 were tested on postnatal day 60.

8 These findings were confirmed and extended in
9 two additional studies, which were considered to be
10 adequate in design and implementation, although it did not
11 provide the numbers of evaluable litters, which would be
12 desirable in a standard test of reproductive toxicity.
13 Specifically, increases in peri- and neonatal mortality
14 were also observed in these studies, as were reductions in
15 birth weight. I'm going to talk about these briefly.
16 Unfortunately, I don't have slides for them.

17 In one of these studies, atosiban was
18 administered by I.V. infusion through in-dwelling canulas
19 at rates of 4, 12, or 40 milligrams per kilogram per minute
20 for 16 hours a day from gestational days 15 through 20.
21 Cumulatively, the high dose in the study delivered a dose
22 of 38.4 milligrams per kilogram per day, a dose
23 considerably lower than the doses that were administered in
24 the definitive study, which you will recall ranged from 100
25 to 300 milligrams per kilogram per day.

1 The numbers of evaluable litters were low.
2 They were 13, 11, 10, and 12, respectively, from vehicle
3 through low-, mid-, and high-dose infusion rates. There
4 were no reports of maternal toxicity at any dose.
5 Nonetheless, in this study, the numbers of litters with
6 dead pups and the numbers of pups affected were increased
7 among atosiban-treated animals. Further, the trend toward
8 fetal and neonatal wastage was extended when examined in
9 the postnatal period between delivery and postnatal days 1
10 to 4.

11 Additional dams were affected by pup loss, and
12 some additional pups were lost to dams that had delivered
13 more than one dead pup initially. In this study, the
14 incidence of litters affected by peri- or neonatal loss
15 ranged from 40 to 58 percent among atosiban-treated dams.
16 This is contrasted with about 23 percent among the vehicle-
17 treated dams.

18 Now, in a second ancillary study -- and it was
19 a bridging study -- atosiban was produced by one of two
20 synthetic methods and administered once daily by
21 subcutaneous injection on gestational days 15 to 20 in
22 doses of 50 or 100 milligrams per kilogram per day. The
23 design of the study was quite similar to that of the
24 definitive study, although lower doses were used. Maternal
25 findings were limited to minor dose-related reductions in

1 food consumption over a 48-hour interval during treatment.
2 These reductions ranged from 8 to 18 percent.

3 When all pups for a given dose group were
4 pooled, the percent mortality was increased among progeny
5 born to drug-treated dams, although in this study the
6 incidence of affected dams was not increased. Total pup
7 mortality between birth and postnatal day 14 ranged from 4
8 to 10 percent among the pups born to atosiban-treated dams,
9 and only 2.5 percent among pups born to dams that were
10 treated with vehicle.

11 Notably, pups in the high-dose groups in each
12 of these studies also weighed less than those born to
13 vehicle-treated dams. These decrements persisted among
14 pups observed in the infusion studies, but were overcome in
15 pups observed in the bridging studies.

16 Now, it is important to acknowledge that for
17 each of these studies, one or more confounding issues
18 exist. Dams from each treatment group in the infusion
19 study, including the controls, showed signs of immune
20 stimulation and/or frank infection. This is not unusual in
21 animals with in-dwelling catheters. This was true for dams
22 with large litter losses that were drug treated. Notably,
23 however, it was also true for control dams and true for
24 dams who delivered normal litters. Likewise, two drug-
25 treated dams in the subcutaneous study lost about 30 grams

1 of weight over a 24-hour interval during treatment.
2 Historically, however, this is not associated with complete
3 litter loss.

4 Considered together, we find that three of the
5 five studies of peri- and postnatal toxicity yielded some
6 evaluable data; that in each of these three studies,
7 excessive developmental mortality was observed in progeny
8 born to atosiban-treated dams; that the extent of mortality
9 was better correlated with the dose administered than any
10 maternal toxicity; that decrements in birth weight were
11 observed in all three studies; and that despite the
12 presence of confounding influences in each study, the most
13 parsimonious explanation for these findings is attribution
14 to drug treatment.

15 So the question we would like to raise for
16 discussion is whether developmental lethality reflects
17 atosiban pharmacology. We are concerned by the concordance
18 between the preclinical and clinical findings with regard
19 to developmental mortality. Our statistical reviewer, Joy
20 Mele, will present her findings in detail this afternoon.
21 For the moment, however, I would like to direct you, in the
22 event you want to look, to findings presented in Tables 21
23 and 29 in the FDA statistical review that were included in
24 your FDA briefing book. They're on pages 33 and 44. I'm
25 not going to discuss these. They're simply something there

1 that you could look at, were you interested.

2 Briefly, data from the pivotal studies 096 and
3 098, during which atosiban was administered to pregnant
4 women with ongoing preterm labor, demonstrate that
5 mortality among atosiban-exposed infants under 28 weeks was
6 significantly greater than among placebo-exposed infants.
7 This was particularly true among those infants whose labor
8 progressed despite atosiban administration in both studies.

9 The explanation for this excess in mortality is
10 presently unclear to those of us at FDA. One suggestion
11 has been that repeatedly and due to unfortunate
12 randomization, more critically impaired infants were
13 assigned to atosiban treatment than placebo in study 096.
14 However, this may not account for a similar adverse event
15 profile among infants who failed to complete maintenance
16 treatment during study 098. Thus, we feel compelled to
17 examine alternative explanations for the observed
18 developmental mortality both clinically and in the animal
19 studies.

20 One such alternative is drawn from the
21 pharmacology of atosiban itself. We know that atosiban is
22 an antagonist at both oxytocin and vasopressin receptors.
23 We know that the placenta is permeable to atosiban in the
24 human fetus. You will recall that plasma concentrations
25 are about 12 percent those of maternal concentrations. We

1 know that the third trimester fetus has functional
2 vasopressin receptors, activation of which evokes the renal
3 regulation of fetal plasma osmolality in response to water
4 deprivation, hypovolemia and hypotension, the maintenance
5 of fetal arterial pressure, particularly in response to
6 challenge by stressors such as hypoxia and hemorrhage --
7 and this is a very important point, because a number of
8 studies have demonstrated that there are very few effects
9 of atosiban administration when it is simply infused; it
10 requires the presence of a challenge by a stressor in order
11 to see an effect -- I'm sorry, of vasopressin, not atosiban
12 -- finally, the stimulation of pituitary ACTH secretion in
13 response to stressors.

14 So we find ourselves asking, what are the
15 consequences of fetal vasopressin receptor blockades for
16 developing physiology? It is likely that vasopressin-
17 mediated physiologic events are blocked in the fetus during
18 maternal atosiban administration. Unfortunately, the
19 developmental consequences of continuous fetal vasopressin
20 receptor blockade during mid- to late gestation have not
21 been adequately characterized. Thus, one concern we have
22 is whether atosiban prevents the fetus from mounting
23 compensatory responses to stressors such as hypoxia and
24 hypovolemia. In the absence of an experimental model to
25 test these hypotheses, we assume that vasopressin receptor

1 blockade during development is deleterious to the fetus.

2 Moreover, we do not know whether maternal
3 atosiban treatment may adversely affect fetal renal
4 development, renal concentrating ability, amniotic fluid
5 volume and composition, and, secondarily, fetal pulmonary
6 development. It was not possible to assess this in the
7 peri- and postnatal rat studies which were conducted,
8 because the development of renal function occurs prenatally
9 in humans, but postnatally in rats. These consequences of
10 fetal renal hypoperfusion have already been noted
11 clinically in infants born to women treated with classes of
12 drug which elicit renal hypoperfusion in adults, most
13 notably the ACE inhibitors.

14 We have suggested to the sponsor that studies
15 be undertaken in an animal model which permits examination
16 of these concerns. The sponsor has complied with the
17 protocol design to examine in the chronically instrumented
18 fetal lambs the consequences of physiologic responses to
19 stress and regional blood flows with atosiban infusion.
20 These studies are ongoing, although preliminary data are
21 not ready for discussion at present.

22 Now, clinically, the signs of fetal vasopressin
23 receptor blockade could present as changes in maternal
24 amniotic fluid volume, alterations to fetal renal
25 development, secondary alterations to lung development, et

1 cetera. Unfortunately, amniotic fluid volumes were not
2 rigorously assessed for pre- and post-treatment values in
3 the clinic. Further, soft tissue dysmorphologies were
4 generally not assessed among infants who died, as autopsies
5 were infrequent. Thus, whether infants whose outcome was
6 impaired following atosiban administration demonstrate
7 signs of intrauterine vasopressin receptor antagonism
8 remains to be determined.

9 Thank you.

10 DR. PETITTI: Thank you very much. Perhaps you
11 could stay at the podium in case members of the committee
12 would like to address questions. As you know, we will have
13 a detailed discussion this afternoon from Dr. Mele of the
14 actual studies from the FDA's point of view.

15 Dr. Oh?

16 DR. OH: A comment and a question. The comment
17 is that the difference between the -- I'm trying to be fair
18 and look at two sides of the picture. To compare what you
19 see in animal data with humans is probably not the best way
20 of doing the analysis, mainly because the duration of
21 exposure in the model is almost 25 percent of the gestation
22 -- it started 10 days through 21 days -- while all the
23 human data that we've seen so far does not exceed 7 weeks,
24 as I recall. So that's one point.

25 The other point I wanted to make -- or the

1 question is, do you have a way of comparing the area under
2 the curve, or do you derive from the fetal plasma atosiban
3 concentration the projected or calculated area under the
4 curve on the human infants, given the dose that was given
5 to the mother?

6 DR. McNERNEY: We discussed this at length, the
7 reviewer and myself, and determined that fetal AUC in
8 humans, because of the dosing schedule, may be difficult to
9 look at, because you have this first 3-hour infusion at 300
10 mics per minute, and then that's subsequently reduced to
11 100 mics per minute. So as a first approximation for the
12 fetal levels, we simply multiplied the study state
13 concentration by the number of hours that it was infused.
14 Unfortunately, I did not have the AUC data from the rat in
15 order to look at this information, so I'm stuck for your
16 question right now.

17 DR. OH: So in other words, you can't really
18 make a comparison between the two situations.

19 DR. McNERNEY: No. I need to get a look at
20 the --

21 DR. OH: It's well known in interpreting any
22 toxicity data that you need to know the duration exposure
23 to the developing fetus as well as the concentration of the
24 drug that you're looking at, because --

25 DR. McNERNEY: Well, we have the concentration

1 levels. They were two- to six-fold higher in the rat
2 fetus. We don't have the AUCs, but we have the
3 concentrations. They were two- to six-fold higher --

4 DR. OH: But you already said that the
5 concentration is a pulse level or value. So you don't know
6 what the exposure really is.

7 DR. McNERNEY: No, I don't. I wish I had had
8 that data to look at.

9 DR. PETITTI: Other questions, comments,
10 discussion by members of the committee?

11 DR. LOCKWOOD: I actually have a series of
12 questions that impact not only the toxicology arguments,
13 but the basic biology. I guess this is an appropriate
14 interval to discuss them, and I guess what I'm trying to
15 understand is the possibility that atosiban may promote in
16 certain subsets of patients preterm deliveries rather than
17 prevent, and particularly, obviously, in the early
18 gestational age group, and I would be very relieved if I
19 could be convinced that this was not a possibility.

20 Given the heterogeneity of the preterm delivery
21 process that was outlined by several of the speakers, what
22 I would like to do is sort of ask four targeted questions
23 that may sort of resolve this in my mind one way or the
24 other.

25 Now, the first issue is the potential that its

1 anti-ADH effects could actually induce a mild form of DI in
2 the fetus, sort of the opposite of your argument, and maybe
3 they cancel each other out and that's why it's not an
4 issue. But it would be very useful for me, at least, to
5 know whether or not any of the centers collected amniotic
6 fluid indices values, were there differences in AFIs
7 between the two groups at any point, and particularly after
8 a long maintenance therapy, and as a less rigorous way of
9 looking at that, were there differences in ultrasound
10 detection of pyelectasis? These are directed more, I
11 think, at the manufacturer than they are necessarily at the
12 FDA.

13 So that's the first set of questions, and the
14 second set of questions reflect the possibility, from sort
15 of my review of all the material that was sent, that
16 atosiban may be associated with a higher risk of abruption
17 and bleeding, which is another mechanism that can enhance
18 preterm delivery to a completely separate set of
19 biochemical pathways, as might be associated with
20 polyhydramnios.

21 So the second set of questions were -- and I
22 was very unclear in my mind one way or another whether this
23 is true -- was there a higher incidence of clinical
24 abruption in the atosiban versus placebo-control group, and
25 was there a higher incidence of postpartum hemorrhage?

1 Were there differences in the rate of transfusion
2 postpartum between the two groups? And were there
3 differences in postpartum hematocrit values?

4 Now, the last issue is the possibility that the
5 atosiban -- this was alluded to -- may actually promote
6 ascending genital tract infections or other kinds of
7 infections that lead to preterm delivery through either its
8 effects on the maternal or fetal immune system and
9 lymphocyte production, et cetera, or perhaps by other
10 mechanisms not understood. So my question there was, were
11 good placental pathology studies done? Was there an
12 increased incidence of histological chorioamnionitis in the
13 two groups?

14 So just to sort of summarize those three
15 issues, because I'm sure no one can remember what I just
16 asked, number one, were there differences in amniotic fluid
17 index or pyelectasis between the two groups? Were there
18 differences in the occurrence of abruption, postpartum
19 hemorrhage, postpartum hematocrit, or transfusions between
20 the two groups? And then was there a difference in the
21 degree of histological evidence of chorioamnionitis in the
22 two groups?

23 DR. PETITTI: What I'd like to do first,
24 perhaps you can answer that question from the point of view
25 of the animal studies, and then we can go back to the

1 sponsor and clarify that from the point of view of the 096
2 trial.

3 DR. MCNERNEY: Most of these are not things
4 that people look at in animal studies. The question has
5 been raised whether there was any evidence of placental
6 infarcts in the animal studies, and if you just envision --
7 first of all, they don't do that kind of histopathology in
8 animal studies generally, but, second, if you can envision
9 that a rat dam has 15 or 16 individual placentas
10 corresponding to the number of pups that she's carrying,
11 it's pretty unlikely to envision multiple simultaneous
12 infarcts in all 16 placentas.

13 DR. LOCKWOOD: It's actually the opposite
14 question. Not infarcts, but bleeding. Did the rats bleed
15 more?

16 DR. MCNERNEY: We don't have any data --

17 DR. LOCKWOOD: Did they have postpartum
18 hemorrhage?

19 DR. MCNERNEY: There were no reports of
20 postpartum hemorrhage.

21 DR. LEWIS: What about placental weight or
22 histology?

23 DR. MCNERNEY: They did not do any of that.

24 DR. PETITTI: Could the four questions,
25 actually, that I heard be specifically answered for the 096

1 trial that related to amniotic fluid index, pyelectasis,
2 postpartum hemorrhage, and abruption of placenta, and
3 whether there were measures of infection?

4 DR. McNERNEY: Do you want the FDA or the
5 sponsor?

6 DR. PETITTI: This is for the sponsor. I think
7 it would be appropriate to -- you had your hand up earlier
8 in the morning, so --

9 DR. CREASY: I can answer some of these
10 questions. With regard to the routine collection of
11 amniotic fluid index data, unfortunately, we don't have
12 that. If I can have back-up 408, I can show the reporting
13 of oligohydramnios in the study. I'll tell you that the
14 number of cases of oligohydramnios was not many, and was
15 not in excess in the atosiban treatments.

16 The slide that you'll see is the number of
17 cases of oligohydramnios by the various treatment arms
18 across the studies. It's the top row of this slide. The
19 first column is the cases from the atosiban PTL-098 study,
20 where there was continuous and prolonged exposure to
21 atosiban throughout that study. All of the patients in
22 that arm received an initial treatment, any necessary re-
23 treatments, and continuous infusion of atosiban until the
24 end of Week 36. That's followed, then, by the cases and
25 percents in the atosiban arm from the PTL-096 study, and

1 the next to the last column is the placebo arm from the
2 PTL-096 study.

3 So you can see that the placebo had a 2 percent
4 incidence of oligohydramnios, 2 percent in PTL-096, 1
5 percent in PTL-098.

6 DR. LOCKWOOD: Actually, I'm a little bit more
7 interested in the polyhydramnios. Do you have a slide that
8 shows that?

9 DR. CREASY: I don't. But it's similar low
10 results, and no excess in any of the treatments. But I
11 don't have those numbers.

12 You were interested in renal findings. Let me
13 try 410. Let me see what 410 is. This is the infant
14 urinary system disorders, total disorders reported at
15 delivery, at the 6-month follow-up, at the 12-month follow-
16 up, and this data was interim data from the 2-year follow-
17 up program, so we don't have the complete 24-month data
18 there. But there doesn't seem to be an excessive number of
19 urinary system disorders reported for those who were
20 continuously exposed to atosiban versus those who were
21 exposed to placebo.

22 If we go back to 409, I think that's a list of
23 the kinds of problems that were seen at delivery and during
24 the follow-up, and I think you had asked about pyelectasis
25 and -- I don't have it.

1 DR. LOCKWOOD: How about renal distension?

2 DR. CREASY: Oh, yes. There were two cases
3 reported at delivery, none during the follow-up. These are
4 all the cases only in the atosiban arm, so I don't -- this
5 is all of the infants that were in the follow-up program
6 exposed to atosiban.

7 DR. LOCKWOOD: To be honest with you, I'm more
8 interested in the ultrasound diagnosis of pyelectasis sort
9 of as a marker for increased urine output, rather than that
10 there would necessarily be any possibility even, given the
11 lateness of the therapy, to cause an obstruction. I'm
12 looking for a surrogate of polyhydramnios.

13 DR. CREASY: Well, we don't have consistent
14 ultrasound examinations on the fetuses.

15 You had asked about evidence of clinical
16 abruption and postpartum hemorrhage, transfusion and the
17 postpartum hematocrits. We didn't collect information
18 about transfusions. The number of cases of postpartum
19 hemorrhage in the whole program were few. There were also
20 just a few cases reported of clinical abruption and no
21 imbalance between the arms. The postpartum hematocrits
22 were pretty much the same, though I don't have the data to
23 show you. And, unfortunately, we did not consistently do
24 placental pathology on all of the infants in the program.

25 DR. PETITTI: Did you have data on infection or

1 some marker for infection? I think that was the third
2 general area that --

3 DR. CREASY: For the infants or the mothers? I
4 mean, what was the --

5 DR. LOCKWOOD: Well, I was giving you, I guess,
6 the most rigorous possible predictor of infection with the
7 histological chorioamnionitis, but what about clinical
8 chorioamnionitis?

9 DR. CREASY: Well, as was shown in the slides
10 by Dr. Romero and Dr. Ward, there were a number of cases in
11 that lowest gestational age group where there was either a
12 diagnosis of clinical chorioamnionitis, there was a case of
13 a positive amniotic fluid culture, there was a case of
14 infection based on placental pathology.

15 DR. LOCKWOOD: But what about the entire
16 population?

17 DR. CREASY: Well, there were very few cases --
18 I'm not saying that there were none, but there were very
19 few cases above 24 weeks.

20 DR. PETITTI: Yes?

21 DR. VAN MARTER: I was just curious to follow
22 up that second question. In the materials provided by the
23 sponsor, there's reference to a high rate of female
24 reproductive disorders in the atosiban-treated group, and
25 included in the parentheses it talks about placental

1 disorders. I thought at one point it mentioned hemorrhage.

2 And then on the slide that you showed first
3 with the oligohydramnios, at the bottom of the slide, it
4 looked as though there was a comment about hypotension, a
5 higher rate in the atosiban-treated group. Am I reading
6 that correctly?

7 DR. CREASY: Let's go back to 408, just to look
8 at that bottom line, but I have another slide to show for
9 -- you're referring to the bottom line here of hypotension,
10 which came at 6 percent in 098, 3 percent in 096, and 4
11 percent for the placebo patients, I believe. I don't think
12 that those rates are really remarkably different between
13 the placebo of 4 percent and the finding of 3 or 6 percent
14 in the other arms.

15 DR. VAN MARTER: Could you tell us a little bit
16 more about what the female reproductive disorders were that
17 were relevant in the atosiban-treated?

18 DR. CREASY: Where are you referring to these?

19 DR. GREENE: It's at the bottom of page 37, top
20 of page 38 in your briefing book. Sort of a quaint
21 reference to female disorders.

22 DR. CREASY: Yes. This is in the CAP-001
23 terbutaline study, I believe. "In the atosiban group, the
24 most frequently reported maternal adverse events during the
25 entire study period were GI system disorders, female

1 disorders."

2 DR. DATTEL: That phrase is actually repeated
3 through each one of the studies, because I circled it each
4 time, because I didn't understand what it meant.

5 DR. CREASY: Dr. Bengtsson, can you comment on
6 these findings in the CAP-001 studies, please?

7 DR. BENGTSSON: Could you please repeat the
8 question? I didn't hear exactly --

9 DR. PETITTI: I think we're looking for some
10 kind of summary that would describe the comparison between
11 the atosiban and other group for the category of disorders
12 that are described on page 38 as female disorders, which
13 includes uterine hemorrhage, vaginal hemorrhage, and
14 placental disorders. Is that correct?

15 DR. GREENE: Yes. And also on page 30, again
16 it refers to, "In the atosiban group, the highest number of
17 events were gastrointestinal disorders, headache, fever,
18 and reproductive disorders, while in the ritodrine group,"
19 etc. This comes up as a theme several times. It says
20 "reproductive disorders" or "female disorders," and it's
21 not totally clear what that means.

22 DR. BENGTSSON: We have to code that way to use
23 some kind of common code for different things, and I'm
24 afraid I cannot give you the details of the percentages, if
25 that's your question, if you want exactly what these

1 things --

2 DR. GREENE: Well, what are they?

3 DR. CREASY: I was just reminded as Per
4 mentioned the coding, that's a code that covers all the
5 female reproductive disorders, and some of the most common
6 ones in the program were things like vaginitis that were
7 reported during the study. So anything that had to do with
8 the female reproductive tract was included under there.

9 But may I ask if we can check into this and
10 bring an answer back after lunch? Because I think we have
11 the answer, but it's a detail that we don't have at our
12 fingertips.

13 DR. LOCKWOOD: Just so you're clear what we're
14 worried about, what's written in your briefing book is,
15 under female disorders, mainly uterine hemorrhage, vaginal
16 hemorrhage, and placental disorders, and I guess having
17 this as an interest academically, I focused on that right
18 away, but it is ominous. Vaginitis isn't ominous. An
19 abruption is. So if you could give us that data, that
20 would be very useful.

21 DR. PETITTI: I think we've clarified, and
22 after lunch we will have a chance to go back to this topic.

23 Are there other questions by the committee to
24 our presenter or that you feel are burning questions that
25 have to be asked right now? Comments?

1 (No response.)

2 DR. PETITTI: If not, I have 5 of 12:00. We'll
3 have 1 hour for lunch. We'll return here to public
4 comments and the remainder of the FDA presentation. I'd
5 like people to be on time.

6 (Whereupon, at 11:55 a.m., the meeting was
7 recessed for lunch, to reconvene at 1:00 p.m.)

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AFTERNOON SESSION

(1:00 p.m.)

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DR. PETITTI: We have some committee business to attend to, so I'll start with that. First of all, for the benefit of members of the committee whose terms end June 30th, the June meeting has now officially been canceled, so you can free up those dates on your calendar. There will be a meeting of this advisory committee in September; however, there will be three new members of the committee, and, therefore, there will be a poll for available dates rather than announcing the dates of that meeting right now.

The other piece of announcements and committee business is to give the retiring members of this committee their plaque and their handshake, and Dr. Rarick will be doing that.

DR. RARICK: Thanks, Dr. Petitti.

As Diana mentioned, there are three new members to join us after June, and that means three of our current members will be rotating off. For those of you who follow the work of this committee, you'll know that there was an incredible influx and a lot of work in 1996, a meeting in June, July, and November, and that's been the last time that this committee has met. But today they're meeting again, and we really very, very much appreciate the service of the three folks that are rotating off.

1 The folks that will be leaving will be
2 receiving a plaque from the Center for Drug Evaluation in
3 recognition of their distinguished service, a certificate
4 from Dr. Freedman, the acting lead deputy commissioner, and
5 also a letter from Dr. Woodcock in appreciation. So I'm
6 going to just hand these to these three folks and shake
7 their hand.

8 Let's start with Vivian Lewis and give her a
9 round of applause.

10 (Appause.)

11 DR. RARICK: And Deborah Narrigan. Where is
12 Deborah?

13 DR. PETITTI: I think she's having dessert.

14 (Laughter.)

15 DR. RARICK: I'll put it at her table.

16 And then a special thanks to somebody who's
17 been both a member and the chair of the committee, and
18 that's Dr. Diana Petitti.

19 (Appause.)

20 DR. PETITTI: We'll now go on to the portion of
21 the meeting which is the open public hearing speakers, and
22 I will call people in order.

23 The first person I have on my list is Helayne
24 Silver. Please identify yourself, and please attend to the
25 issue of potential conflicts and announce whether or not

1 you might or might not have a potential conflict.

2 MS. SILVER: Hi. My name is Helayne Silver.
3 I'm a maternal-fetal medicine specialist at Brown
4 University, and I am one of the Antocin investigators.
5 I've been an investigator in the Antocin trial since the
6 first Phase II studies. Overwhelmingly, the striking
7 difference between Antocin and other commonly used
8 tocolytic agents, such as beta-mimetics and magnesium
9 sulfate, is the paucity of maternal side effects.

10 Tocolytic agent use is widespread in the United
11 States and will likely continue to be so. While long-term
12 outcomes have never been shown to be influenced by the use
13 of tocolytic agents, they have proven to be effective in
14 achieving the 48 hours critical for maximum steroid
15 effectiveness for the fetus and for safe maternal transport
16 to a tertiary care center. Antocin has been shown to have
17 equal efficacy to ritodrine and superior efficacy to
18 placebo in achieving this goal.

19 Why I believe Antocin approval is so important
20 is because I have had the opportunity to take care of many
21 patients receiving tocolytic agents. While we frequently
22 quantify and consider the serious adverse events occurring
23 with the agents in common use, we put less emphasis on
24 routine side effects which have profound effects on the
25 individual patient. The tocolytic agent most commonly used

1 in the United States is magnesium sulfate. This is an
2 extremely unpleasant drug for the patient.

3 Just last week I was speaking with a former
4 preterm labor patient, who happens to be my dental
5 hygienist. I was sitting in the chair, and I happened to
6 mention to her that I would be attending this meeting this
7 week, and she spoke of her experience with tocolytic
8 agents. She conceived her pregnancy by in vitro
9 fertilization and would have done anything for the benefit
10 of her baby. However, after two episodes of preterm labor
11 treated with magnesium sulfate therapy, she declined a
12 third treatment with magnesium sulfate when she had another
13 episode of preterm labor. She was happy to hear of an
14 alternative and was enrolled in the Antocin trial.

15 She likens magnesium sulfate to what she
16 imagines chemotherapy would be like. She had no strength.
17 She could not even get up to go to her bathroom without
18 assistance. She alternated between episodes of clear
19 mentation and feeling totally foggy. With Antocin therapy,
20 she felt normal. She felt like herself.

21 She pointed out to me how distressing it was to
22 an expectant mother to put herself at odds with her fetus,
23 but she just couldn't bear another course of magnesium
24 therapy, and these sentiments were frequently expressed in
25 the support groups she attended while she was in the hospital.

1 As a clinician working at a tertiary hospital
2 that delivers 9,000 babies a year, I can tell you that this
3 story and these sentiments are not uncommon. The
4 possibility of a safe, well-tolerated alternative such as
5 Antocin is long overdue. Please keep future preterm labor
6 patients, not just statistics, in mind when you consider
7 this proposal.

8 Thank you.

9 DR. PETITTI: Thank you very much.

10 We'll move on now to our second public speaker,
11 and I am going to need some help on the pronunciation.
12 Sherokee Ilse.

13 MS. ILSE: You said that perfectly. My name is
14 Sherokee Ilse. I paid my own way to this meeting, and I
15 have no affiliation with the company that has anything to
16 do with Antocin. I am an international author and speaker
17 on pregnancy and infant loss. Some of you may be familiar
18 with the best noted of my books, "Empty Arms: Coping with
19 Miscarriage, Stillbirth, and Infant Death." Sadly, I know
20 too well the heartache of pregnancy and infant loss, having
21 suffered several. I am fortunate, despite this, to have
22 two healthy sons.

23 I currently serve as chairperson for the High-
24 Risk Pregnancy Task Force of the Coalition for Positive
25 Outcomes in Pregnancy, and I am also the volunteer national

1 spokesperson for this coalition's Best for Baby Campaign,
2 launched in a nationwide effort to safeguard and advance
3 treatment options available to women with high-risk
4 pregnancies.

5 I am here today to urge the panel to expedite
6 review and approval, as appropriate, of Antocin. I do so
7 at the request of three national non-profit women's support
8 organizations, collectively representing nearly 100,000
9 women: the Triple Connection and Mothers of Super Twins,
10 supporting families of higher multiples, and Sidelines
11 National Support Network, winner of a Points of Light
12 citation from President Clinton for its work serving women
13 with complicated pregnancies.

14 I am involved because babies' lives are at
15 stake here. According to the March of Dimes and the
16 National Center for Health Statistics, a premature low-
17 birth-weight baby is born every 2 minutes. That's two to
18 three babies by the end of my testimony. This year alone
19 more than 300,000 American babies will be delivered
20 prematurely and at low birth weight.

21 As you undoubtedly know, preterm birth is a
22 major cause of infant mortality for babies 22 to 37 weeks
23 of gestation. Beyond the shattered dreams of infant loss
24 looms a lifetime of catastrophic consequences associated
25 with babies born too soon, neurodevelopmental disabilities,

1 cerebral palsy, seizure disorders, blindness, and mental
2 retardation, to name but a few.

3 Due to the tremendous advancements in
4 reproductive medicine, multiple birth and pregnancies among
5 older women have dramatically risen, driving up the
6 incidence of high-risk pregnancy. In triplet pregnancies,
7 63 percent of women experience preterm labor. Preterm
8 labor is also associated with more than 98 percent of
9 higher multiple pregnancies. High-risk pregnancy is a
10 national crisis of epic proportion, yet it seems so little
11 is being done about it.

12 There are a limited number of tools available
13 to combat preterm labor, and the few that exist are in
14 jeopardy. As an example, the FDA's November 13, 1997,
15 warning on terbutaline could potentially eliminate one of
16 the few tools currently available to clinicians for
17 prolonging pregnancy. The FDA's surprise reversal of their
18 previous positive stance on terbutaline has given insurers
19 a reason to refuse reimbursement for this effective
20 therapy, and it has also caused profound concern for
21 physicians and their patients for whom this critical
22 treatment option may no longer be available.

23 Our coalition is currently petitioning the FDA
24 to preserve this important high-risk pregnancy treatment
25 option. At the same time, we are equally committed to

1 expanding the arsenal of tools available to physicians who
2 treat women with high-risk pregnancies, and, therefore, we
3 are simultaneously encouraging the FDA to approve new
4 therapies, which we hope will include Antocin.

5 Access to FDA-approved medicines which can help
6 to prolong a pregnancy by several hours, several days, or
7 even several weeks can make a difference with respect to
8 newborn survival and overall health status. We believe
9 that the FDA should be doing everything in its power to
10 encourage and expedite the review of new drugs and
11 technologies for managing high-risk pregnancies. There is
12 a clear need for more and even better tocolytic medications
13 that are FDA approved for the treatment of preterm labor.

14 We respectfully request that the FDA conduct a
15 full, fair, and timely assessment in the interest of
16 helping mothers and their physicians to deliver what's best
17 for baby.

18 Thank you.

19 DR. PETITTI: Thank you very much.

20 Our third speaker this afternoon is Dr. Michael
21 J. Paul.

22 DR. PAUL: Good afternoon. I also am one of
23 the clinical investigators in the atosiban study, and I am
24 the director of the Washington University Center for
25 Multiple Births, in St. Louis, Missouri. I appreciate the

1 opportunity to address the committee in regard to the
2 approval of the new drug atosiban. I'm hopeful that the
3 advisory committee will recognize the benefits of the new
4 tocolytic agents.

5 When I discovered that this meeting was being
6 convened, I recognized that input from clinicians in the
7 practice of maternal-fetal medicine would be important. As
8 atosiban represents one of a very small number of agents
9 tested in the treatment of preterm labor in multiple
10 gestations, it is important to support its approval by the
11 FDA. The incidence of multiple births has increased
12 steadily in the last two decades. Multiple births range
13 from 1.2 percent to now over 2.5 percent of all births in
14 the United States. This increase in the United States has
15 included a 30 percent increase in the number of twin
16 births.

17 More alarmingly, the incidence of triplets and
18 other higher-order births has increased by nearly 250
19 percent. The recent birth of septuplets here in the United
20 States has raised the expectation of the American public to
21 heights that obstetricians cannot regularly achieve with
22 the limited tools available to treat preterm labor.

23 With approximately 100,000 multiple births
24 annually, the United States is experiencing an epidemic
25 that is unlikely to end soon. The etiology of this

1 epidemic is multi-factorial. The biggest contribution to
2 this epidemic is the advent of assisted reproductive
3 technologies to improve fertility. Techniques such as IVF,
4 GIFT, ZIF, cryopreservation, IXY, and ovum donation have
5 resulted in the most dramatic multiple births. These
6 assisted reproductive technologies have become possible
7 through the use of recently approved drugs, including
8 Clomaphine, Seraphine, Perganol, and Metradin.

9 Other new drugs promote patients' ability to
10 conceive, often with disastrous consequences. One
11 consequence is the development of selective fetal reduction
12 to prevent the known complications of multi-fetal
13 pregnancies. This procedure directly forces newly fertile
14 couples to choose between life and death for their babies.

15 The most common complication of multi-fetal
16 pregnancies is preterm labor. As a contributing factor for
17 preterm labor, there's no greater cause. More than half of
18 all twin pregnancies develop preterm labor, and in higher-
19 order multi-fetal gestations, preterm labor is a certainty.
20 The chief consequence of preterm labor is preterm birth at
21 gestational ages ranging from 28 to 36 weeks.

22 The prevention of preterm birth has included
23 surgical, psychological, social, and medical therapies.
24 The medical management remains the primary management
25 technique, but it's been limited by the availability of

1 approved drug therapies. Ritodrine remains the only
2 approved agent to treat preterm labor. The use of other
3 agents such as terbutaline to treat preterm labor
4 continues, despite explicit warnings that terbutaline
5 should not be used for tocolysis.

6 Atosiban represents a new class of agents
7 specifically developed to be used in pregnant women to
8 treat preterm labor. The safety and efficacy data
9 presented today warrants the approval of this new agent.
10 Preterm labor is a multi-factorial process, and atosiban is
11 not likely to be effective in every clinical situation
12 where preterm labor occurs. It would be inappropriate to
13 expect any agent to be a magic bullet.

14 New antibiotic agents are constantly being
15 approved for limited applicability, and it would be
16 unthinkable to limit their use. Atosiban represents a
17 breakthrough new drug for a targeted pregnancy condition.
18 It is both safe and effective for the treatment of preterm
19 labor. If approved for use, a message of support for
20 pregnant women in America will be sent and received. For
21 the 300,000 women and children annually affected by the
22 multiple birth epidemic in the United States, approval may
23 mean the difference between life and death.

24 I thank you for this opportunity to address the
25 committee and look forward to the outcome of your

1 deliberations.

2 DR. PETITTI: Thank you very much.

3 Our next speaker is Cindy Pearson.

4 MS. PEARSON: Thank you. I'm Cindy Pearson.
5 I'm the director of the National Women's Health Network.
6 As most of the committee members know, the network is a
7 non-profit science-based women's health advocacy group. We
8 do not accept financial support from pharmaceutical or
9 medical device companies, and have no financial ties to any
10 company or health care provider involved in pregnancy
11 services.

12 Because we had to prepare our remarks in
13 advance of hearing the data presented this morning, we
14 decided it would be useful for the committee to understand
15 the network's position in general on labor-suppressing
16 drugs and the context within which we developed our
17 position. I'm going to read most of those prepared
18 remarks, but I'm also going to weave in some reactions from
19 our consumer and science-based perspective to what we've
20 heard so far today, which is very much a story interrupted
21 at an exciting point.

22 I'd also like to share with the committee a
23 little bit of our specific work on reproductive health
24 drugs and devices used to intervene to try to prevent or
25 treat preterm labor. We've testified before this

1 committee, for those who have been around long enough to
2 remember the ritodrine and terbutaline hearings, as well as
3 before the OB-GYN devices committees about home uterine
4 activity monitors, always emphasizing how much data exists
5 to show benefit. Are the data really there to show
6 benefit, or are we talking about something that has a
7 statistically significant effect that isn't necessarily
8 related to better outcomes for the babies?

9 As part of that emphasis, we are the group
10 responsible for the FDA's notice last fall and again the
11 first of this year in JAMA about the inadvisability of the
12 continued use of terbutaline long-term through subcutaneous
13 infusion pumps because of the lack of evidence for benefit
14 from that use and the potential for problems.

15 So given our emphasis on and our attention to
16 the issue that everything being commonly used in preterm
17 labor has very good evidence of its benefit to the babies,
18 and our concern about potential harm with these uses, we
19 came today with cautious optimism, very excited about the
20 first new drug in several years, very excited about the
21 prospect of a drug that could potentially be more specific
22 in its effects than the other drugs that are commonly used.

23 First, we come from a place of supporting
24 preterm labor interventions as long as they're effective
25 and safe, but we do believe and feel that it needs to be

1 expressed that this need that is perceived by all of us in
2 the room shouldn't drive us to use treatments just because
3 they're needed if they have not been shown to be safe and
4 effective, and I only need mention DES, which obviously is
5 not completely the same here. I don't think anyone expects
6 20-year-later cancer cases to be showing up in Antocin-
7 treated babies, but it is important to remember that a
8 generation of obstetricians driven by the need to prevent
9 miscarriage ignored the results of a randomized trial which
10 showed that intervention to be ineffective and unknowingly
11 put women and their children at risk.

12 That evidence that we're saying that we need of
13 the effectiveness and not just the need ideally should come
14 from randomized, controlled trials, and it's great that
15 we're here today looking at not just one, but several
16 randomized, controlled trials, because as we know
17 particularly with terbutaline and the long-term use of
18 terbutaline through subcutaneous infusion pumps, if
19 something is used and its results are reported without a
20 comparison group, not only the women who have used that
21 technology, but many of their doctors, unfortunately,
22 believe that that use caused that result when really
23 there's no evidence.

24 So it's great that we're looking at randomized
25 trials here, and our belief is that when we look at these

1 randomized trials, we need to look first at the safety
2 results. The safety of the intervention comes first, and
3 the reason why we believe that is preterm labor and preterm
4 labor interventions are usually addressed to healthy
5 mothers and babies. Now, the baby's health is certainly at
6 risk in the future, although exactly how much risk is not
7 certain, because preterm labor results on its own so much
8 of the time. But because we're starting with a mother and
9 baby that are healthy, we need to keep reminding ourselves
10 that there's really no reason to consider an intervention
11 which might harm babies.

12 Drugs given to the women are given to the
13 babies, and babies are more sensitive than adults, and
14 premature babies are more sensitive than term babies, and
15 I'll just comment on the recent study on the need to change
16 the dose of AZT prevention when it's being given to preterm
17 babies as compared to full-term babies.

18 We believe that it's vital that any drug given
19 to a woman during pregnancy or labor not compromise blood
20 flow to the baby, not compromise the respiratory system or
21 compromise any other organ, and here I'll reflect on what
22 we heard about animals, given, I know, that it's animals
23 and not the babies, but those issues about the kidney and
24 the renal system. And just to make the point, keeping the
25 baby inside a uterus is only a benefit as long as the

1 uterus and placenta are providing a supportive habitat.
2 Extending the baby's stay in a poisoned or oxygen-deprived
3 environment is not really winning.

4 Now, likewise, our concern about safety also
5 applies to the pregnant woman, and as we all know and heard
6 earlier in this section, most pregnant women are willing to
7 accept significant risks to themselves in order to have a
8 healthy baby, but their safety needs to be kept in mind.

9 And then a point that has been discussed so
10 much this morning about wanting to use babies' outcomes as
11 the measure of effectiveness from these wonderful
12 randomized trials that we've asked for. The endpoint needs
13 to be clinically meaningful, and we've heard this 15-year
14 history of how hopes were highest at the beginning and
15 haven't really panned out, and we've gotten down to now a
16 general acceptance and recommendation that if we can extend
17 the pregnancy or if an intervention can extend a pregnancy
18 for 48 hours and if other things take place, babies will be
19 better.

20 So I think we're at the point now of using a
21 two-point consideration of the results of these trials:
22 Was there any delay at all, and did the babies do better?
23 And I'm not sure, sitting and looking at what we've seen so
24 far this morning, that we have seen that. We've certainly
25 seen that Antocin-treated women were more likely to not

1 have delivered or needed other drugs by 48 hours, but it's
2 not clear that those babies did any better, even though in
3 theory they should have.

4 And just to sort of completely deviate from the
5 prepared remarks and really start to respond to what we saw
6 this morning, it seemed that the sponsor had three sort of
7 simple points to make: this is effective if you define
8 effectiveness as 48-hour delay; babies are as well off as
9 babies treated with mimetics; and the moms are better off,
10 and moms are important. Now, I think we have to go back
11 and question whether the conclusion that the sponsor's
12 making that the babies are as well off as babies treated
13 with mimetics and, therefore, we see a benefit of Antocin
14 for the babies -- whether one follows from the other.

15 First, it appears that the studies in which
16 babies treated with Antocin were compared to babies treated
17 with beta-mimetics may not have been designed in a way to
18 really conclusively determine from the studies that they
19 were equivalent, and, second, I think we have to go back
20 and put together two separate things we heard this morning
21 of the meta-analysis and the Canadian study, which were
22 done in the early 1990s, threw doubt on that basic
23 conclusion that beta-mimetics giving babies 48 hours extra
24 made a difference in their outcome.

25 So if we don't have much evidence of outcome

1 benefit for babies, then we sort of can't even get to the
2 point where we look at the benefit to the mother in terms
3 of safety, and we're sort of driven back to safety for the
4 baby questions.

5 And I'll just mention what I was struck by when
6 Dr. Creasy made his summation remarks. He compared
7 efficacy as defined by 48-hour delay, comparing Antocin to
8 placebo to beta-mimetics; maternal safety, Antocin to
9 placebo and beta-mimetics; and infant safety, Antocin
10 compared to beta-mimetics, and these are just my notes from
11 one of the slides he had up there in summary. As a
12 consumer activist, I was struck by the fact that in his
13 summary he didn't want to recap that Antocin to placebo
14 safety comparison, because it seems to be very, very
15 troubling, and I look forward, as I'm sure all of you do,
16 to the rest of the discussion this afternoon.

17 I wish I were making our group's remarks after
18 that discussion so we could say something stronger, but at
19 this time I think we're sitting and watching this with
20 grave doubts about whether babies will benefit if this drug
21 were approved.

22 So I end on that note.

23 DR. PETITTI: Thank you very much.

24 The final speaker of the open public hearing
25 session will be Doris Hare.

1 MS. HARE: Good afternoon. I, too, have had to
2 make a lot of revisions on my talk, because I'm very
3 heartened by the questions that have been posed this
4 morning.

5 I am a former president of the International
6 Childbirth Education Association, and one of the 15 members
7 who organized the first meeting of the National Women's
8 Health Network in Washington over 20 years ago. I chaired
9 the network during its early formation, and subsequently
10 chaired the network's Committee on Health Law and
11 Regulation, and then the Committee on Maternal and Child
12 Health. It was an invaluable experience for me, for it
13 taught me that the FDA will continue to rely too heavily on
14 animal data to assure the safety and effectiveness of
15 obstetric-related drugs unless the agency poses questions
16 that will evoke more information on human data regarding
17 the delayed long-term effects of the drug on the child.
18 The mere survival of an infant does not represent an
19 acceptable infant outcome. A satisfactory neurologic test
20 at the age of 2 does not assure us that the child's
21 intellectual capabilities are intact.

22 I think that most women in the United States
23 would be absolutely appalled to learn that the FDA has not
24 updated in a quarter century its general considerations for
25 the clinical evaluation of drugs in infants and children.

1 It was written in 1974 and published in 1977. The FDA even
2 declined to publish the updated version of the general
3 considerations when it was prepared and offered by the
4 American Academy of Pediatrics Committee on Drugs more than
5 10 years ago.

6 I'm here today to represent the American
7 Foundation and the Alliance for the Improvement of
8 Maternity Services, an international coalition of women's
9 groups concerned with the safety of obstetric drugs and
10 procedures for the baby as well as the mother. The women's
11 groups making up the alliance are adamant that only
12 randomized, controlled trials or trials using undrugged
13 controls can determine whether a drug is safe and effective
14 for both mothers and babies. But even if a drug were
15 proven safe for the mother, there is no guarantee that her
16 fetus would not be permanently harmed by the drug.

17 Altering the fetal environment by administering
18 atosiban to halt the mother's labor could have long-term
19 consequences for the offspring that far outweigh the short-
20 term benefits of the drug. We realize that the FDA is
21 under pressure from Congress to speed up the approval of
22 drugs, but unless a follow-up is carried out in the exposed
23 offspring around the age of 7 or so and determines that the
24 children's intrauterine exposure to the drug does not
25 correlate with an increase in the rate of cognitive

1 dysfunction or other neurologic problems, the FDA should
2 not approve atosiban as safe for use in pregnancy.

3 Both Rosenblatt and Sepkowski and their
4 respective colleagues have documented that a drug approved
5 by the FDA for use in obstetric care can have adverse
6 effects on the infant for several weeks after birth, with
7 no proof that the adverse effects disappear with time.
8 Research on animals by Mallard and colleagues has shown
9 that intrauterine insult can result in significant damage
10 to the hippocampal region of the newborn animal's brain,
11 yet the pH and other parameters of normalcy will be intact
12 at birth. If atosiban injection is approved by the FDA for
13 use as a tocolytic agent and the drug is subsequently found
14 to be harmful to the fetus, thousands of babies may be
15 permanently damaged before the problem is called to the
16 FDA's attention.

17 The seriousness of the underreporting by
18 physicians of adverse drug effects was brought home this
19 past week in a paper by Pomerantz in the April 15th issue
20 of JAMA. The earlier Harvard Medical Practice Study left
21 no doubt that many physicians are reluctant to report an
22 adverse drug reaction, even when that adverse drug reaction
23 is serious or fatal.

24 Because atosiban is likely to be administered
25 for longer than the proposed 48 hours, we are concerned

1 with the inadequacy of information regarding the immediate
2 and long-term infant outcome among those infants exposed to
3 atosiban in utero. The obstetric community seems intent on
4 adjusting the standards of normalcy downward to accommodate
5 the infant outcome of current practice patterns. The 1-
6 minute APGAR score is being abandoned by physicians working
7 in obstetric care in favor of the 5-minute APGAR score, no
8 doubt because many newborn infants today are more likely to
9 be breathing on their own at 5 minutes than at 1 minute. I
10 was stunned to hear at a recent national meeting on
11 obstetric anesthesia that the bottom limit of a normal
12 fetal rate is now considered to be 110 beats per minute.

13 There is no scientific documentation that a
14 fetal heart rate of even 120 beats per minute or an infant
15 born with a pH of 7.2 or an APGAR score of 7 after birth is
16 an optimal condition. These are arbitrary numbers that
17 have no solid scientific basis. Even a good outcome on the
18 Brazelton assessment scale, the gold standard of newborn
19 assessment scales, is no guarantee that the infant is free
20 of intrauterine insult, but its use is a step in the right
21 direction.

22 In this age where the mastery of technology is
23 crucial to a successful career, it is not enough to have a
24 baby that merely survives the birth process. Through the
25 years, the FDA has failed to pose questions to the

1 reproductive health advisory committees which would evoke a
2 scientific response as to whether a drug under
3 consideration may or can alter brain chemistry in the fetus
4 and newborn, and whether these alterations will later alter
5 behavior or cognitive development in the offspring.

6 We urge both the FDA and the Reproductive
7 Health Drugs Committee to withhold their approval of
8 atosiban until the manufacturer conducts randomized,
9 controlled trials which will provide at a minimum answers
10 to the following questions, and I've prepared some
11 questions that I hope will go into the FDA files:

12 When atosiban is administered to a pregnant
13 woman, does the drug alter the woman's cardiovascular,
14 respiratory, and thermoregulatory mechanisms? If yes, how
15 do these alterations affect the physiology of the fetus and
16 newborn? Does atosiban, when administered to the mother,
17 lower maternal oxygenation and metabolism? Does the drug
18 alter brain chemistry in a pregnant or parturient woman?
19 If yes, how long do these alterations persist? Does
20 atosiban increase the parturient's need for uterine
21 stimulants, analgesics, or regional anesthetics during
22 parturition? Does the drug interfere with the maternal/
23 infant attachment, and if yes, how? Does the drug
24 interfere with the initiation or longevity of breast-
25 feeding?

1 And in regard to the exposed infant, does
2 atosiban, when administered to the mother, alter the fetal
3 environment? If yes, how is it altered? Does the drug
4 alter the temperature of the fetal environment? If yes, in
5 what way? Does the drug accumulate in fetal tissues? Does
6 the drug accumulate behind the infant's blood/brain
7 barrier, and if yes, how long before the drug and its
8 metabolites pass out of the blood/brain barrier completely?
9 Does the drug alter the brain chemistry of the fetus and
10 newborn infant? If yes, how long do the alterations
11 persist? If no, what scientifically controlled study has
12 been carried out that shows that such alterations in fetal
13 and newborn brain chemistry do not occur?

14 Does the drug affect neuronal maturation, cell
15 migration, dendritic arborization, or cell differentiation?
16 Does the drug alter the infant's cardiac contractility rate
17 or rhythm? Does the drug increase the incidence of central
18 nervous system depression, seizures, or unexpected
19 excitations? Does the drug interfere with the infant's
20 circulatory adjustment to extrauterine environment? Does
21 the drug impair the closure of the ductus arteriosus? Does
22 the drug lower fetal oxygen saturation, and if so, how long
23 after the drug has been administered?

24 Does the drug increase the need for artificial
25 rupture of membranes at the time of delivery? Does the

1 drug increase the incidence of resuscitation of the
2 newborn? Does it impair the newborn infant's cortical
3 control of respiration? Does the drug increase the
4 incidence of jaundice in the newborn?

5 Or, to put our concerns in reverse, what
6 evidence is there that the drug-induced alterations
7 questioned above are not permanent? Have the researchers
8 scientifically documented that atosiban does not alter the
9 fetal heart rate, fetal breathing movements, or fetal pH?
10 And have they documented that atosiban does not increase
11 the need for uterine stimulants or other obstetric
12 interventions at the time of delivery?

13 I ask these questions, and I hope that the FDA
14 will take them to heart, because neonatologist Jack Scanlon
15 here in Washington taught us long ago that if you don't
16 look, you won't find.

17 Thank you.

18 DR. PETITTI: Thank you.

19 There was one other speaker who had been put on
20 the list, and I want to see if Dr. Murphy Goodwin is in the
21 audience and is going to speak today. There was some
22 uncertainty about whether he would be here today.

23 (No response.)

24 DR. PETITTI: If not, then I'd like to move on
25 to the formal completion of the presentation by the FDA.

1 We will come back to give the sponsor an opportunity to
2 present the specific information that was requested by Dr.
3 Lockwood this morning, if they can come up with those
4 slides or that information.

5 Moving on to the FDA presentation, Joy Mele.

6 MS. MELE: I would like to begin by just
7 thanking the company. Roseanne Lane was very helpful
8 during my review process, and I just wanted to thank her in
9 front of everybody and say thanks for responding very
10 quickly to all my requests.

11 This is a list of the five trials submitted as
12 part of the application for atosiban. The first three
13 studies listed, 096, 098, and the ritodrine study, were
14 submitted with the original NDA, and the last two CAP
15 studies were submitted about 10 months later.

16 During the review process, 096 received the
17 most attention because it was the largest study, twice the
18 size of the ritodrine study. Also, it was placebo-control,
19 and treatment included both acute and maintenance
20 treatment. 098 was considered less important, since it was
21 designed to examine the effectiveness of maintenance
22 therapy in a responder population. Of the CAP studies, the
23 ritodrine study is the most important, since ritodrine is a
24 product which was approved based on placebo-control trials.

25 This slide shows you an outline of what I plan

1 to cover in my presentation of 096. First I'll talk about
2 the baseline comparisons that impact the efficacy results.
3 Then I'll present the primary efficacy results and the
4 components that make up this variable, time to alternate
5 tocolytic use and time to delivery. I will also present
6 the 48-hour outcome results and show the first events
7 driving these results. And, finally, I will talk about the
8 infant outcome results, with an emphasis on the incidence
9 of RDS and infant death.

10 In 096, about 250 patients were randomized and
11 received treatment in each arm. Fifty-four percent of the
12 placebo patients and 69 percent of the atosiban patients
13 achieved uterine quiescence after acute treatment and went
14 on to receive maintenance therapy. Most of those patients
15 did not have another preterm labor episode and, therefore,
16 did not require subsequent I.V. therapy.

17 This bar graph shows the percentage of patients
18 in four gestational age groups, where gestational age is
19 age at admission measured in weeks. These gestational age
20 groups were defined by FDA at a pre-NDA meeting. We were
21 particularly interested in seeing what was happening in the
22 patients receiving treatment at gestational ages under 28
23 weeks. Only about 20 percent of the patients fall into
24 that age group, shown here as the lower two strata. So
25 more than 80 percent of the patients in 096 entered the

1 trial with a gestational age of 28 or greater, and in fact
2 the overall mean age in each treatment group was about 31
3 weeks.

4 In the lower gestational age group, the less
5 than 26 weeks -- that's this group here -- there is a clear
6 imbalance between the treatment groups, with more atosiban
7 patients than placebo patients. The treatment group means
8 in this subgroup are significantly different, about 25 for
9 placebo versus 23 for atosiban. Now, as the sponsor
10 mentioned earlier, the treatment groups were imbalanced for
11 effacement and dilation at admission within the less-than-
12 28-week gestational age subgroup.

13 Here I am presenting the means and medians for
14 each measure in each subgroup. If we look first at the 28-
15 week-or-greater gestational age group, and that's the lower
16 two lines -- and I'll just point out, on your handout it's
17 mislabeled -- the treatment groups are clearly comparable
18 in that subgroup. In the less-than-28-week age subgroup,
19 differences between the treatment groups are evident, with
20 larger mean values in the atosiban group; however, these
21 differences are not statistically significantly different.

22 Now I will talk about the primary efficacy
23 variable results. This is a Kaplan-Meier curve of time to
24 delivery or therapeutic failure. Red is atosiban, and blue
25 is placebo. A shift to the right of the curve indicates

1 prolonged time to the event. Just from looking at the
2 graph, it is clear that atosiban does not beat placebo. An
3 analysis censoring only the three patients lost to follow-
4 up and adjusting for either center or gestational age group
5 yields a P value greater than .5. These results are
6 consistent with results from additional analyses presented
7 by the sponsor, where patients taking alternate tocolytics
8 for reasons other than failure are censored. If we do a
9 statistical test which gives more weight to the early
10 differences we see here, then we get a P value of .36.

11 We looked at these results by those gestational
12 age groups that I just mentioned earlier, and I'll show you
13 those results now. This is a graph of the primary efficacy
14 results by the four gestational age groups, and the only
15 place we see some evidence of efficacy is for patients with
16 a gestational age of greater than or equal to 32 weeks, and
17 that's this graph right here.

18 Because of the small sample size in the lower
19 two subgroups, and because the sponsor has proposed
20 labeling to focus on patients with gestational age of 28 or
21 greater, I looked at the results by less than 28 versus
22 greater than or equal to 28. The results of patients under
23 28 favor placebo, while no treatment difference is evident
24 in the upper strata. Recall for the group of patients
25 under 28 weeks, the treatment groups differed in two ways,

1 gestational age at admission and baseline labor parameters.
2 Adjusting for either of those measures in a proportional
3 hazards model resulted in a larger P value of .7 as opposed
4 to .2. So the difference in favor of placebo that you see
5 here is diminished, but the results still do not favor
6 atosiban.

7 Even though the results of this combined
8 endpoint did not favor atosiban, I was interested in
9 examining the components of this endpoint -- the alternate
10 tocolytic use and the delivery times -- to see how each
11 impacted the results, and in particular I was looking for
12 an explanation for the separation of the curves during the
13 first few days post-initiation of treatment that you see in
14 the greater-than-28 subgroup.

15 First, let's look at the use of alternate
16 tocolytics in this trial. Fifty-one percent of the placebo
17 patients and 42 percent of the atosiban patients were given
18 an alternate tocolytic sometime during the trial. This
19 difference of 9 percent is statistically significant. For
20 the next two bullets, I have broken down use by reason for
21 use and then by timing of the use. In the placebo group,
22 progression of labor as defined by the protocol was the
23 major reason for using an alternate tocolytic, and most
24 switching took place during the initial I.V. treatment
25 phase of this trial. In the atosiban group, the same was

1 true, but to a lesser degree.

2 Notice that about the same percentage of
3 patients in each group, about 20 percent, were given
4 alternate tocolytics at the discretion of the treating
5 physician. For 57 percent of those placebo patients and 50
6 percent of the atosiban patients, the reason given for
7 discontinuation by the physician was progression of labor.

8 On this slide and the next, I will show you the
9 time-to-event data for alternate tocolytic use and then the
10 time-to-event data for delivery. This slide shows you the
11 time to alternate tocolytic use by the gestational age
12 groups. Within the less-than-28-week subgroup, the
13 treatment groups are not different, while the treatment
14 groups are significantly different, with a P value of .02,
15 in the older subgroup. And if I were to combine these
16 subgroups, the P value again is about .02. Now, notice
17 that both groups show more alternate tocolytic use in the
18 placebo group versus the atosiban group within the first
19 week of treatment.

20 Here are the results for time to delivery, the
21 measure we are most interested in impacting. These results
22 look similar to the results I showed you for the combined
23 endpoint, with the results in the less-than-28-week
24 subgroup favoring placebo and no difference evident in the
25 older subgroup. Here notice that there is no difference

1 between the groups evident during the first few days of
2 treatment. Again, the imbalances in the labor parameters
3 in the less-than-28-week subgroup impact the delivery
4 results such that adjustments for those parameters increase
5 the P value and make the results look less favorable to
6 placebo, but that are still not positive for atosiban.

7 So, overall, no significant treatment effect
8 was seen in 096 for time to delivery or therapeutic
9 failure, the primary efficacy measure, and adjustments for
10 imbalances in the less-than-28-week gestational age group
11 do not alter this result. It was evident from examining
12 the components of the combined endpoint that the separation
13 of the Kaplan-Meier curves in the 28-week-or-greater
14 gestational age subgroup is due to placebo patients
15 switching to an alternate tocolytic.

16 Now, this is a list of the seven secondary
17 variables defined in the protocol. The first one listed
18 here is time to delivery. I have shown you that there is
19 no difference between the groups on this measure.

20 The second one is time to delivery or alternate
21 tocolytic use for any reason. The results for this
22 variable are favorable to atosiban if we do an analysis
23 that weights early differences more heavily than later
24 differences. That was an analysis that was not proposed or
25 performed by the sponsor.

1 The next variable listed is percentage of
2 patients undelivered or not therapeutic failures at 24
3 hours, 48 hours, and 7 days, and I will just present the
4 48-hour results on the next slide. For the remaining four
5 variables listed on this slide, no differences between
6 placebo and atosiban were observed.

7 This slide shows the results for the 48-hour
8 outcome computed in two ways. I would like to point out
9 that no analysis plan was proposed in the protocol for this
10 variable. The numbers on the right are the results for the
11 protocol-defined variable I just showed you on the previous
12 slide. For this 48-hour outcome variable, only therapeutic
13 failures or deliveries are counted as failures, and all
14 patients are included in this analysis. Therapeutic
15 failure is defined as for the primary efficacy variable --
16 that is, progression of labor, which was well defined in
17 the protocol, and it was progression of labor that led to
18 alternate tocolytic use.

19 The P values for this variable, you can see,
20 are all greater than .05. An alternate analysis presented
21 by the sponsor in this submission discarded from the
22 denominator patients who received an alternate tocolytic
23 for reasons other than therapeutic failure, and that
24 analysis yielded a P value of .065.

25 Now, on the left are the results for variation

1 in the protocol-defined variable. These results were
2 presented in the sponsor's submission, as well as in their
3 presentation today. For this variable, all patients given
4 an alternate tocolytic for any reason are counted as
5 treatment failures. The inconsistencies between these two
6 analyses rests on how one treats the patients, giving
7 alternate tocolytics for reasons other than protocol-
8 defined treatment failure. If they are treated as
9 failures, you get the results on the left. If they are
10 treated as discontinuations from treatment, you get the
11 results on the right.

12 In my review, I further focused on the results
13 on the left, since these are the only positive results in
14 the study, and I was interested in knowing what events were
15 driving the differences. This table shows the first events
16 for the 48-hour outcome variable that counts alternate
17 tocolytic use for any reason as a failure event. So that
18 was the variable that was on your left in the previous
19 slide. So these are the events that occurred during the 48
20 hours after initiation of therapy, by gestational age
21 group.

22 The biggest difference can be noted on the
23 first line, with more alternate tocolytic use seen in the
24 placebo group than in the atosiban group. This is what we
25 would expect, given what we have already seen for the

1 primary efficacy measure. Note that the delivery rates are
2 higher in the atosiban group, and this is disconcerting,
3 since we are most interested in impacting time to delivery.

4 I looked then at the delivery rates over the
5 first 7 days following initiation of therapy. These
6 results are for both gestational ages combined. The Y axis
7 is the percentage of patients delivering, so a higher line
8 indicates a higher percentage of deliveries. These results
9 clearly do not favor atosiban. If I were to show you these
10 results by gestational age subgroup, you would see no
11 difference between the two groups on the first day, as you
12 see here, and the results from Day 2 on favor placebo in
13 the less-than-28-week subgroup and look comparable in the
14 older subgroup.

15 Interpretation of these results is clouded by
16 the use of alternate tocolytics. Nevertheless, the results
17 are not favorable in this small window of time.

18 So for the secondary variables in 096, a
19 significant treatment effect was seen on one derived
20 secondary variable. We consider this comparison to be
21 nominally significant at the .05 level, since we have made
22 no adjustments for multiple comparisons based on the number
23 of outcome variables and number of subgroups. In addition,
24 the lack of significance on the primary outcome variable
25 generally precludes looking at secondary outcomes. The

1 treatment differences for the 48-hour outcome variable may
2 be ascribed to a difference in alternate tocolytic use for
3 any reason, not a difference in proportion of patients
4 delivering. No significant treatment effects were observed
5 in the less-than-28-week gestational age subgroup.

6 Now I'm going to present some infant outcome
7 results. Infant outcome data was collected at delivery, in
8 hospital, and 6, 12, and 24 months after delivery, and I'm
9 just focusing on the delivery and in-hospital results.
10 Ultrasounds were performed on all the infants. The
11 treatment groups were comparable regarding the number of
12 multiples, treatment exposure, and they both had similar
13 gestational ages at delivery at about 35 weeks.

14 This is a list of the infant outcome variables
15 that we consider to be the most important variables. I
16 will be showing results for the first five variables, since
17 those five are variables traditionally focused on:
18 percentage of infants spending time in the ICU, days in the
19 ICU, deaths, weight at delivery, and incidence of RDS. For
20 the last three variables, there were some treatment
21 differences worth noting. There was a higher percentage of
22 abnormal ultrasounds in atosiban patients under 28 weeks
23 compared to placebo, 32 percent versus 18 percent, and
24 that's a difference of eight patients. Intraventricular
25 hemorrhage data was comparable for the two groups. More

1 delivery room resuscitation was seen in the greater-than-
2 28-week atosiban group than the placebo group, and that was
3 18 percent versus 9 percent.

4 On this slide and the next two slides, I
5 summarize results for these four outcome measures: percent
6 of infants spending time in the ICU, deaths, mean weight at
7 delivery, and incidence of RDS. These results for all
8 patients do not trend in favor of atosiban, but clearly the
9 differences are not significant. The differences in the
10 less-than-28-week subgroup are more striking, even
11 considering the imbalances at base line in this stratum.
12 Ten percent more infants in the atosiban group than the
13 placebo group spent time in the ICU, 20 percent more
14 infants died, mean weight was less by about 500 grams, and
15 13 percent more RDS was recorded.

16 Now let's look at the greater-than-or-equal-to-
17 28-week group. Here the results look comparable. These
18 infant outcome results do not suggest a benefit for
19 atosiban-treated patients, which is not surprising, given
20 the time-to-delivery data. The infant outcome data in the
21 less-than-28-week group, though, concerned us, a
22 gestational age group where we thought it was important to
23 show benefit to babies. So I examined the RDS data and the
24 mortality data further in the next few slides.

25 On this slide and the next few slides, OR

1 stands for odds ratio, and an odds ratio of greater than 1
2 indicates an increased risk in the atosiban group. The
3 incidence of RDS was higher for atosiban compared to
4 placebo in both subgroups, so the odds ratio is greater
5 than 1, 1.3. This odds ratio does not suggest that
6 atosiban is a significant risk factor for RDS. Adjusting
7 for gestational age at admission increases the odds ratio
8 in the less-than-28-week group to 1.7, but, again, a value
9 that does not suggest that atosiban is a statistically
10 significant risk factor. It should be pointed out, on the
11 other hand, though, that these results are clearly not
12 favorable to atosiban.

13 Now, after showing you the RDS data, I would
14 like to say a few words about steroid use in this trial.
15 Overall, the treatment groups were comparable for steroid
16 use. By subgroup, there was a difference. There was
17 greater use in the atosiban group than the placebo group
18 for patients in the less-than-28-week subgroup, with
19 placebo use at 34 percent and atosiban use at 55 percent.
20 Steroid use varied greatly among the centers, going
21 anywhere from 0 percent to 100 percent. Approximately 49
22 percent of the placebo patients and 35 percent of the
23 atosiban patients were given steroids within 48 hours of
24 initiation of treatment.

25 Within the less-than-28-week group, there was a

1 paradoxical relationship between the steroid use and RDS,
2 with more RDS in steroid users in the atosiban group. This
3 finding concerned us, but we felt the interpretation of the
4 steroid data was very complex, given that factors such as
5 timing of use, variability of care among the clinics, and
6 lack of a consistent definition of RDS could influence
7 these results.

8 This table shows you the infant and fetal
9 deaths broken down by gestational age group. From these
10 numbers, it is clear that the risk for infant death is
11 highest for atosiban-treated patients, with gestational age
12 at entry of under 28 weeks. The odds ratio for this
13 comparison is 9.2, and it is statistically significant.
14 All the deaths in that subgroup occurred for patients
15 entering with gestational ages of 24 weeks or less. For
16 seven of the patients, delivery occurred within 7 days of
17 admission, and for six of the patients, the deaths occurred
18 within 3 days of delivery. One of the atosiban deaths
19 occurred after discharge.

20 So gestational age at admission is clearly a
21 factor related to death. Adjusting for gestational age at
22 admission results in an odds ratio of 3.8, as opposed to
23 the unadjusted odds ratio of 9.2. So with adjustment, the
24 risk in the less-than-28-week subgroup remains notable, but
25 not statistically significant. In the older subgroup, the

1 estimate favors atosiban. So the data suggest a lack of
2 benefit for atosiban patients regarding infant mortality,
3 either due to a lack of efficacy or due to possible toxic
4 effects of the drug, but there are too few placebo patients
5 in the less-than-26-week subgroup to draw definitive
6 comparative conclusions.

7 This is a pretty busy slide, and I'll try to
8 walk you through it. During my review, I was interested in
9 understanding the relationship between the efficacy data,
10 particularly the 48-hour outcome and the infant data, since
11 the sponsor had argued in their submission that if atosiban
12 could give the mothers 48 hours, we will be helping the
13 babies. So the point of this table is to see how infants
14 are doing when patients are able to complete 48 hours
15 without delivery or alternate tocolytic use for any reason
16 compared to the non-completers. The first two columns are
17 the 48-hour completers, and the last two the non-
18 completers. Each row is an infant outcome, and the data is
19 shown by subgroup.

20 To orient you to this table, let's just pick a
21 row, the weight row in the less-than-28-week subgroup.
22 That's this row here. So for the patients who did not
23 deliver or receive an alternate tocolytic for 48 hours, the
24 mean weight for the placebo patients was about 2,800 grams,
25 and for the atosiban patients about 2,200 grams. For the

1 patients that discontinued treatment for any reason, the
2 mean weight for the placebo infants at delivery was about
3 1,700 grams, compared to about 1,000 grams for the atosiban
4 infants.

5 Now, if we compare the first two columns, the
6 completers, to the non-completers, the last two columns, it
7 is clear that the babies of patients who do not deliver or
8 use alternate tocolytics for 48 hours do appreciably better
9 than the babies of patients discontinuing treatment. Now,
10 if we compare the treatment groups, remembering, however,
11 that these are non-randomized groups defined by outcome, so
12 we wouldn't perform any statistical comparison, we don't
13 see the atosiban babies faring better, and in fact they
14 look appreciably worse among the discontinued patients.
15 For example, look at the greater-than-28-week subgroup, and
16 remember in this subgroup we had no imbalances. We see on
17 each measure that babies appear to be doing worse. I also
18 looked at the data this way for the 24-hour and 7-day
19 outcomes and consistently saw in these measures that the
20 magnitude of the responses rarely favored atosiban.

21 So for study 096, we saw that there was no
22 significant treatment effect on the primary efficacy
23 variable. The results for the 48-hour outcome variable are
24 only significant if we consider patients who received
25 alternate tocolytics for reasons other than protocol-

1 defined therapeutic failure as failures in that analysis,
2 an analysis not proposed in the protocol. The infant
3 outcome data does not favor atosiban, which is not
4 surprising, given that we saw no impact on time to
5 delivery. However, we were concerned that we saw in the
6 less-than-28-week subgroup results that favored placebo.

7 In addition, one should recognize there are
8 problems with interpretation of significant P values in a
9 secondary endpoint when no statistically significant
10 treatment effect was observed for the primary efficacy
11 variable, which in this case was a related variable.
12 Interpretation is also difficult in this study due to the
13 number of secondary variables and the subgroups.

14 The sponsor has given you a rather thorough
15 look at 098, but I will just remind you of some of the
16 features of this trial and make a few comments. Recall
17 that this study was designed to show the effectiveness and
18 safety of maintenance therapy, not acute therapy. About
19 two-thirds of the patients treated open-label with atosiban
20 in the less-than-28-week subgroup achieved uterine
21 quiescence. The percentage was higher in the greater-than-
22 or-equal-to-28 group, at 82 percent. Two hundred and
23 sixty-one patients were randomized to atosiban and 251 to
24 placebo for maintenance therapy.

25 The mean gestational age of the randomized

1 patients was 31 weeks, like in 096. So most of the
2 patients receiving maintenance therapy were in the older
3 gestational age group, but, interestingly enough, primary
4 efficacy results by subgroup are more favorable in the
5 less-than-28-week group, with a P value of .09 versus a P
6 value of .19 in the gestational age group greater than 28.
7 The overall results were statistically significant, with a
8 P equal to .02.

9 No other efficacy measures in this trial showed
10 a statistically significant difference between the
11 randomized treatment groups, although the results favored
12 atosiban for this responder population.

13 This slide shows you how all the patients did
14 during the open-label treatment period. It is interesting
15 to contrast these results to the atosiban results of 096.
16 In 096, 26 percent of the patients received an alternate
17 tocolytic and 7 percent delivered. Also recall that 69
18 percent of the atosiban patients in 096 achieved uterine
19 quiescence and went on to receive maintenance therapy,
20 compared to 77 percent here.

21 The sponsor has already shown you the infant
22 outcomes for the responder population, and recall that the
23 infant outcomes were comparable for the randomized groups.
24 On this slide, I'm showing you how the infants of patients
25 who were not successfully treated did. So these are the

1 patients who were only given I.V. treatment. The first
2 column is a summary of the infant outcomes for those 098
3 patients, and the last two columns contain data for the
4 discontinued patients in 096, and this is the same data
5 that I showed you earlier.

6 Note that the infant outcomes in 098 are very
7 similar to the discontinued atosiban patients in 096. Now,
8 we would not make a direct comparison between these groups
9 from different studies; however, these results do show
10 consistency of responses across studies.

11 I just want to make one more comment about the
12 mortality rate of 39 percent in the less-than-28-week
13 subgroup. This rate comes from 15 deaths out of 38 I.V.-
14 only patients. Of those 15 deaths, 13 entered the study at
15 a gestational age of 24 weeks or less.

16 Now I'm going on to the CAP studies. Recall
17 that these three studies were all active-control studies
18 designed to study acute therapy, and that a different beta-
19 mimetic served as a control in each. All the studies were
20 initiated in 1994. The ritodrine study was completed first
21 and submitted as part of the original NDA. The other two
22 studies were submitted about 10 months later.

23 Comparability to ritodrine, a product approved
24 based on placebo-controlled trials, would be acceptable if
25 a definition of equivalence was presented in the protocol,

1 effacement and contraction rates. Mean dilation was about
2 1.3 centimeters. Remember that in 096, it was about 2
3 centimeters. The mean contraction rate of 8 per 30 minutes
4 is comparable to what was observed at baseline in the study
5 096. From the data I was provided with, it appears that
6 about 60 percent of the patients in these studies would not
7 fulfill the entry criteria of 096 and 098, which required
8 greater than 75 percent effacement, with dilation under 3
9 centimeters.

10 This slide shows the percentage of alternate
11 tocolytic use in each of the CAP studies, and I'll just
12 point out what shorthand I've used here: 001R for
13 ritodrine; 001S for salbutamol; 001T for terbutaline. The
14 overall data for each study is on the first three lines,
15 followed by the subgroup data. The patients in these
16 studies could be switched to an alternate tocolytic at any
17 time during treatment at the discretion of the physician.
18 Generally, alternate tocolytic use was higher in the
19 control group than the atosiban group. But notice that
20 there is a great amount of variability across the studies.

21 For example, in the salbutamol study, and we'll
22 just look at the patients combined, about 60 percent of the
23 patients were given an alternate tocolytic, while in the
24 ritodrine study the rate was about half that. The
25 ritodrine numbers are more in line with what we might

1 expect in an active-control trial. That is, we might
2 expect less switching than in a placebo-controlled trial
3 where the physician is aware that their patient may be on
4 placebo. So the 60 percent use in the salbutamol study is
5 surprising.

6 There were two primary efficacy variables in
7 the CAP studies: percentage of patients who remained
8 undelivered or did not receive an alternate tocolytic after
9 7 days after initiation of therapy, and that's the results
10 that the sponsor showed you earlier; and time to alternate
11 tocolytic use or delivery. For my analysis of these
12 variables, I included all patients as randomized, in
13 contrast to the sponsor's analysis of evaluable patients.

14 These graphs show the point estimate and the 95
15 percent confidence interval for the treatment difference
16 for the 7-day outcome. Results for the less-than-28
17 gestational age group are on the left, and the greater-
18 than-or-equal-to-28 gestational age group are on the right.
19 Data to the right of the line, at zero -- I hope you can
20 all see the lines right here -- indicates favorable results
21 for atosiban, while data to the left indicates results
22 favorable to control. In addition to the results for each
23 CAP study -- and the order here is terbutaline, salbutamol,
24 and then ritodrine -- I've included the combined treatment
25 effect and the results from the placebo-controlled trial

1 096.

2 The magnitude of the responses in the three CAP
3 studies are favorable to atosiban, particularly in the 28-
4 week-or-greater gestational age subgroup. Analyses with
5 the subgroups combined in each study produced P values less
6 than 0.1. For the salbutamol study, the results were
7 statistically significant.

8 I did not show you the 7-day results previously
9 for 096, so I wanted you to notice them here. You can see
10 here with the bottom symbols that the treatment groups are
11 significantly different on the right, in the greater-than-
12 or-equal-to-28-week group, but not on the left.

13 As for 096, I looked at the percentage of
14 patients delivering within 7 days to see the impact on
15 delivery apart from alternate tocolytic use. In two of the
16 three studies, ritodrine and salbutamol, the proportions
17 delivering is slightly higher in the atosiban group, while
18 the reverse is true in the terbutaline study. These
19 patterns held true when we broke these down by gestational
20 age group.

21 The other primary efficacy variable in the CAP
22 studies was time to delivery or alternate tocolytic use.
23 In the sponsor's analyses -- actually, they didn't present
24 this to you, but I'll just mention that they had done an
25 analysis where they censored patients at a gestational age

1 of 34 weeks. When the ritodrine study was submitted to the
2 FDA, the data was analyzed using the same approach used in
3 096 and 098, and that is that all the patients were
4 followed to use of alternate tocolytics or delivery, and
5 that's the approach I've taken here.

6 In all three studies, analyses for this
7 variable yielded P values greater than 0.2 with the
8 subgroups combined, and greater than 0.1 by subgroup. Here
9 I am only presenting the ritodrine results. With the
10 subgroups combined, the P value is about 0.4. By subgroup,
11 the results in the greater-than-or-equal-to-28-week group
12 are more favorable to atosiban than the results in the
13 younger subgroup, as you can tell from the graphs.

14 As for 096, I was interested again in seeing if
15 delivery was impacted. Here are the time to delivery
16 curves. Only in the terbutaline study did the results look
17 more favorable to atosiban, and there the P value is 0.48.

18 This is a list of the 11 secondary variables
19 named in the final CAP protocol. Six of the 11 variables
20 are infant outcome variables, and they are listed here as
21 the last six variables. I'm going to show you the results
22 of four of the variables listed here. The first two listed
23 are treatment success and the 48-hour outcome variable, the
24 former because it was well-defined in the protocol, and the
25 latter for comparison to 096. In addition, I will present

1 the RDS and infant mortality data.

2 Two of the three criteria listed here were
3 required to consider a patient a treatment failure:
4 contraction rate of 4 per hour or greater, an increase in
5 dilation of 1 or greater, an increase in effacement of 25
6 percent or greater. It was not necessary in these trials
7 for progression of labor to be followed by use of an
8 alternate tocolytic to be considered a treatment failure,
9 as in the 096 trial. In all studies, the success rates are
10 slightly higher for the beta-mimetic, but none of the
11 treatment differences are statistically significant.

12 Here is the 48-hour outcome data. This data is
13 clearly not as convincing as the 7-day data. With the
14 less-than-28-week group, we see a great deal of
15 variability. Notice that the X axis runs to 70 percent, so
16 large differences in either direction are plausible given
17 this data. In the greater-than-28-week group, the results
18 look more favorable to atosiban, but clearly in the CAP
19 studies, even with them combined, we see no significant
20 difference between the beta-mimetics and atosiban.

21 Now I'm going to show the RDS data and the
22 infant mortality data. This first slide is the RDS data.
23 You will notice that out of the 10 symbols shown here,
24 seven are on the left side of the graph, favoring control.
25 Nevertheless, all confidence intervals overlap zero, so

1 there appears to be no significant risk for RDS in the
2 atosiban group or with the beta-mimetics.

3 The ritodrine study results, however, appear to
4 favor ritodrine over atosiban, particularly in the less-
5 than-28-week subgroup, and that's the green symbol here.
6 This trend in favor of ritodrine was also evident for
7 percentage of infants spending time in the intensive care
8 unit and mean weight at delivery.

9 Now, a definition for comparability is really
10 needed here to interpret this data for the ritodrine study,
11 and we don't have a definition.

12 Let me first point out on this slide that the
13 scales for the two graphs are different. The graph on the
14 left, the less-than-28-week subgroup, goes from minus 40
15 percent to plus 40 percent, and the one on the right goes
16 from minus 20 percent to plus 20 percent. Let's first look
17 at the 28-week-or-greater subgroup. There were no deaths
18 in this subgroup in the ritodrine study, and very few in
19 the other studies. In the salbutamol study and in the
20 terbutaline study, there was one death in each treatment
21 group.

22 For the less-than-28-week subgroup in the three
23 CAP studies, there were a total of 16 deaths in the
24 subgroup. In the ritodrine study, there were two atosiban
25 deaths and one ritodrine death. In the salbutamol study,

1 there were no atosiban deaths and three salbutamol deaths,
2 all at the gestational age at admission of 24 weeks or
3 less.

4 In the terbutaline study, there were two
5 atosiban deaths and six terbutaline deaths. Only one of
6 the terbutaline patients entered with a gestational age
7 under 24 weeks.

8 When I began our presentation of the CAP
9 studies, I mentioned that ritodrine is the only approved
10 tocolytic. So to establish the efficacy of atosiban, we
11 would expect atosiban to be superior to terbutaline and
12 salbutamol, and comparable to ritodrine. All three trials
13 were designed as superiority trials, so no criteria for
14 comparability were established at the protocol stage, which
15 presents difficulties in interpreting some of the ritodrine
16 study data, and in particular the infant outcome data.

17 There were two primary efficacy variables, and
18 only one of them, the 7-day outcome variable, showed
19 results that were favorable to atosiban. Only in the
20 salbutamol study were the results significantly in favor of
21 atosiban. However, the P values in the other two CAP
22 studies were under 0.1. The treatment differences for the
23 7-day outcome variable appear to be associated with
24 switching to alternate tocolytics, since no appreciable
25 differences in delivery rates in favor of atosiban were

1 observed.

2 There was no documentation regarding the
3 reasons for switching to an alternate tocolytic, so it is
4 not clear from our patients on the beta-mimetics for
5 switching due to lack of efficacy or due to adverse events,
6 or for reasons even unrelated to treatment. It is
7 therefore difficult to attribute the treatment differences
8 to a difference in effectiveness as a tocolytic.

9 Neither the RDS data nor the mortality data
10 produced results definitively in favor of or against
11 atosiban. There were very few deaths in the greater-than-
12 or-equal-to-28-week subgroup. Deaths in the less-than-28-
13 week group were primarily in the terbutaline study, and all
14 were at a gestational age less than 26 weeks. As we saw in
15 the results for study 096, the risk for RDS for atosiban is
16 not significant over control in the CAP studies. However,
17 the uncertainty of the results in both subgroups suggests
18 that important differences cannot be ruled out.

19 On the next few slides I will summarize what
20 I've shown you, but first I will make a few comments about
21 the difficulties of interpreting data from these trials.
22 Combined endpoints in any setting can be problematic,
23 particularly when one component of the endpoint is of more
24 interest than the other, which is the case here. We are
25 more interested in impacting delivery, but for ethical

1 reasons, and to incorporate the standard of clinical care,
2 alternate tocolytic use was allowed and was defined also as
3 an endpoint.

4 So the interpretation of the time to delivery
5 data, and other data as well, was confounded by the use of
6 alternate tocolytics. Furthermore, interpretation of
7 alternate use was complicated by a lack of stringency
8 regarding criteria for switching. The protocols for these
9 trials did not define how steroids should be used, so there
10 was a great deal of variation in use among the clinics, and
11 this led to difficulties in interpreting some of the RDS
12 data. The lack of stratification on gestational age in the
13 096 study presented significant problems for the
14 interpretation of the infant outcome data. And there were
15 several multiplicity problems. Should we be making
16 adjustments to P values based on subgroups? Multiple
17 endpoints? Multiple analyses? We haven't done so, but we
18 think this issue should be considered when interpreting the
19 P values.

20 Lastly, as I've already mentioned, it is
21 difficult to interpret the ritodrine data without a
22 definition of equivalence, especially for the infant
23 outcome data.

24 On this slide I have a few closing comments
25 about the studies in this submission. Study 096 was the

1 largest study in the NDA database, and it was placebo-
2 controlled. For those two reasons alone, it is considered
3 the most important study in the submission. In addition,
4 the study was well-designed with carefully defined
5 endpoints. The only positive results in 096 were nominally
6 significant results on a secondary endpoint. Results for
7 both efficacy and safety in patients entering the trial at
8 a gestational age under 28 weeks, a subgroup we hoped to
9 impact, did not favor atosiban over placebo.

10 Now, as Dr. Kweder has already suggested,
11 without a strong demonstration of efficacy in a major
12 placebo-controlled trial such as 096, active-control
13 studies are difficult to interpret. The CAP studies were
14 particularly troublesome because two of the three controls
15 are unapproved products. The effectiveness of these two
16 drugs, salbutamol and terbutaline, has not been shown, so
17 showing comparability is not sufficient for establishing
18 the efficacy of atosiban. Superiority would be required,
19 and this was not shown.

20 For the ritodrine study, comparability would be
21 acceptable if we knew the definition of comparability
22 before we started the trial, which was not the case here.

23 This is my last slide. Overall, no effect on
24 prolongation of time to delivery was shown. The infant
25 data does not assure the safety of infants exposed to

1 atosiban. There was no evidence of efficacy in a subgroup
2 we feel could derive the most benefit from tocolysis; that
3 is, the patients submitted at gestational ages under 28
4 weeks. And even in the older subgroup, efficacy was
5 limited. Lastly, as I've already mentioned several times,
6 there are numerous problems with interpretation of the data
7 that make it difficult to draw definitive conclusions.

8 Thank you.

9 DR. PETITTI: Thank you very much.

10 We now move on to -- Dr. Kweder, are you going
11 to make your comments now? Five minutes of comments.

12 DR. KWEDER: My purpose in these final FDA
13 comments -- and these are the final formal FDA comments --
14 is really to take what you've heard from the regulatory
15 history, Dr. McNerney's presentation, and Dr. Mele's, and
16 try to help to take a step back now, now that we've been
17 immersed in data, and think of some of the broad issues
18 that you're going to need to be covering in your answers to
19 the specific questions proposed.

20 So what I have here is I have a set of five or
21 six background issues. Background issue number one is
22 really that the pathophysiology of preterm labor is
23 essentially unknown. It is, in reality, a multifactorial
24 condition that most likely comes to attention, as we heard
25 from the presentations this morning, well after the process

1 itself is underway. The diagnosis itself is challenging
2 and did differ in this NDA from one trial to the next, as
3 Dr. Mele pointed out, the differences in the CAP studies
4 and the 096 and 098.

5 Because of these things, it is important that
6 we consider most heavily trials that employ very rigorous
7 entry and endpoint criteria when we're looking at new
8 tocolytic agents.

9 Background issue number two is that the
10 clinical management of preterm labor varies greatly, and we
11 saw that illustrated just in the differential use by
12 centers of antenatal steroids, for example. There are
13 numerous possible interventions, such as antenatal
14 steroids, alternate tocolytics, and antibiotics, and in
15 particular, the early gestational age patients, the ones
16 that are presenting the most thorny issues for
17 consideration today, are the most challenging clinically as
18 well.

19 Background issue number three is that, in
20 addition, we have this multifactorial nature of neonatal
21 morbidity and mortality, and gestational age remains the
22 major predictor of that. Dr. Mele didn't show you this
23 data, but she did some additional analyses trying to look
24 at predictors of outcome, and gestational age repeatedly
25 came out in her analyses as the strongest predictor. But

1 we also know that antenatal interventions affect outcome,
2 such as antenatal steroid use. That wasn't controlled for
3 in the data we have. We also know that neonatal
4 interventions affect outcome, and obviously in obstetric
5 trials, these are often not controlled for, such as the use
6 of neonatal surfactant.

7 Finally, no tocolytic, either in published data
8 or data that's been presented to the FDA, has ever
9 consistently shown neonatal benefit in controlled trials.
10 Whether that is simply because the efficacy in terms of
11 obstetric endpoints in actually delaying delivery and
12 having an impact on gestational age isn't there, or it has
13 to do with study planning. We really don't know, and it's
14 really a matter of speculation and best judgment.

15 Background issue number four really gets a
16 little bit more to the heart of the matter, and that is,
17 what are reasonable efficacy endpoints for tocolytic trials
18 and not just these that we've seen today? I think a sub-
19 question of that is, when we have measure of benefit, how
20 robust must that benefit be? How many ways do we need to
21 be able to look at the data and see that it's all going in
22 the same direction, or is it enough to just look at it in
23 one piece of multiple analyses? In particular, if the
24 duration of benefit to the mother is brief, the obstetric
25 benefit, then how do we weigh and consider the balance of

1 infant data that come out at the same time?

2 I think it's realistic to ask, can neonatal
3 benefit be realistically demonstrated in the absence of a
4 dramatic impact on obstetric endpoints?

5 On the other hand, I think that there's a
6 difference between demonstrating neonatal benefit, or the
7 absence of establishing benefit, and when data raise the
8 question of harm.

9 So issue number five really brings us to this
10 NDA. In the obstetric data, as Dr. Mele has presented,
11 this was the major control trial of this study. What we
12 have is we have a 48-hour benefit on one analysis. If you
13 move the data around or you censor patients a little bit
14 differently, the statistical benefit doesn't hold up,
15 unfortunately. We have a maintenance study of 098 that is
16 most helpful probably as an extension of and as a general
17 comparison for trends with 096, and we have the active
18 control CAP trials that are challenging, as Dr. Mele
19 presented, in light of the limited efficacy that we've seen
20 now in the placebo-controlled trials.

21 As far as the maternal safety data, Joy didn't
22 really present that to any great degree because we agree,
23 absolutely, that atosiban clearly is much better tolerated
24 by mothers than the beta-mimetics in the comparison trials,
25 and was very well tolerated in the placebo-controlled

1 studies. We've looked at that data very carefully and
2 we're satisfied that that's the case.

3 But that brings us to the infant outcomes,
4 which are really part of both safety and efficacy. We do
5 have this nagging question of whether or not there is harm,
6 particularly in the youngest babies in the 096 study, and
7 for the patients who only received intravenous therapy in
8 the 098 study, who are the most similar probably to the
9 096. Unfortunately for us, that's one of the reasons that
10 you're all here today. These data raised more questions
11 than they answered. The first question is -- and much of
12 the questions from the panel this morning focused on the
13 randomization. It is a pretty weird looking randomization
14 balance.

15 Was it just bad luck in that the scheme wasn't
16 stratified by gestational age, or was there indeed a flawed
17 execution of that randomization which we have not been able
18 to find any evidence of? An alternative question that has
19 to be addressed is, do the preclinical data and potentially
20 the vasosuppression activity of this drug put these young
21 babies in particular at a disadvantage? Is it that these
22 young babies can't respond appropriately to the stresses
23 that we know preemies undergo -- infections, breathing
24 problems, all of the endpoints that we've heard discussed
25 today -- enough so that we see most of the detriment in

1 that highest-risk group?

2 Finally, one of the questions that I think
3 could be addressed -- one of the differences that hasn't
4 been highlighted greatly is that there was a little bit of
5 difference in the dosing of atosiban in the CAP studies.
6 It was a less dose-intense regimen. Patients received
7 intravenous therapy for a shorter period of time than in
8 the others, and one question that I think is reasonable and
9 I don't think we can necessarily answer from these data is,
10 did that differential in dose intensity have some bearing
11 on why we saw less toxicity in those trials?

12 Finally, I think one of the most important
13 issues here today is how can we address all of these issues
14 for this NDA and for future drugs -- because some of the
15 questions that you have before you are more generic --
16 without discouraging clinical development of tocolytic
17 agents in the future? This is the first advisory committee
18 meeting on a new tocolytic in many years, and we'd like to
19 see more.

20 I'm going to close there. Thank you.

21 DR. PETITTI: Thank you very much.

22 I'd like to remind all of us where we're going
23 with this discussion this afternoon so we use our time as
24 wisely as possible. The first thing is we will return to
25 committee questions for Dr. Mele, and I'd like perhaps for

1 Dr. Mele to come to the podium so you can answer questions
2 as they come up from the committee.

3 If you recall, I promised this morning that we
4 would give the sponsor a chance to present the specific
5 data addressing the specific question asked by Dr. Lockwood
6 this morning related to abruption of placenta, if those
7 data are available immediately.

8 Then our committee will return to a more
9 general discussion which will address specifically the
10 questions on page 2 of your handout, which are the
11 questions that were posed ahead of time related to the NDA.

12 The first order of business, then, is to
13 address questions to Dr. Mele related to her presentation.

14 Dr. Azziz?

15 DR. AZZIZ: Dr. Mele, in your analysis of 48-
16 hour outcome of study 096, in which you have taken figures
17 for undelivered or no alternative tocolytic for any reason,
18 which is what the sponsor had presented, versus your
19 reanalysis looking at undelivered versus no alternative
20 tocolytic or therapeutic failure as protocol-defined, could
21 you give us some idea of the numbers of individuals in that
22 analysis? We have percentages here, and then, of course,
23 the P value was non-significant. But again, that depends
24 on the numbers. I can't give you a slide number, but it's
25 on page 3 of your handout.

1 DR. MELE: It would take a little looking to
2 give you the exact numbers, but I can give you a rough
3 idea. Remember that there are about 250 patients in each
4 treatment group, and the placebo and atosiban group, and
5 then when you break it down by subgroup, we called that
6 about 80 percent of the patients were greater than 28
7 weeks. So that should give you an idea of how many
8 patients we're talking about.

9 DR. AZZIZ: You did delete some patients from
10 your analysis when you considered only those undelivered or
11 on no alternative, or you simply shifted them in group.
12 How was that reanalysis done?

13 DR. MELE: No, I didn't delete any patients.

14 DR. AZZIZ: Okay. You simply shifted them.

15 DR. MELE: Right. They're no longer called
16 failures, so they remain in the denominator. So it's the
17 complete data set. What I did mention was that there was
18 another analysis proposed by the sponsor in their
19 submission where they excluded from the denominator
20 patients who had taken alternate tocolytics. So that's
21 where the exclusions came from.

22 DR. AZZIZ: The second question is, in your
23 alternate tocolytic use from your study 096 on the previous
24 page, page 2, where you note the percentages of patients
25 progressing in labor -- and this is "Reasons for Use" --

1 DR. MELE: Yes, I see it.

2 DR. AZZIZ: You have 32 percent for placebo
3 versus 22 percent for atosiban. Is this an indication --
4 and again, I'm having a hard time interpreting that because
5 it seems to be repeated in another analysis. Is this an
6 indication that perhaps less individuals taking the drug
7 complained of progression of labor versus those taking
8 placebo, or we cannot interpret that?

9 DR. MELE: There was a specific definition of
10 progression of labor, and it's in my review. I can tell
11 you where it is. So that's a very specific definition
12 based on changes in effacement and dilation and contraction
13 rate. So it wasn't based on the patient thinking that
14 they're progressing in labor or the physician deciding
15 that. It was a specific definition of progression of
16 labor.

17 DR. AZZIZ: So one interpretation of this data
18 is that less of the treated patients have progression of
19 labor versus placebo, yes?

20 DR. MELE: Right.

21 DR. PETITTI: I have a follow-up question on
22 exactly the same slide. The data on time of use have a
23 line, "Initial I.V. Treatment." Could you describe that?
24 Is that I.V. treatment after the first hour but during the
25 first episode of I.V. treatment?

1 DR. MELE: That would be during the entire
2 episode of I.V. treatment, which could last for 48 hours.

3 DR. PETITTI: Fine. Thank you very much.

4 DR. OH: I have a related question on the 48
5 hours prolongation, not so much for Dr. Mele but for the
6 sponsors. I was just wondering if you can provide a
7 rationale, either statistical or clinical, for using your
8 methodology in making your analysis.

9 DR. CREASY: Which methodology are you
10 referring to?

11 DR. OH: Your 48 hours. The one defined by the
12 FDA is the protocol-defined parameters.

13 DR. PETITTI: Excuse me. Could we wait and
14 finish our questions to Dr. Mele? Then we'll come back
15 specifically to that question. We'll still come back to
16 that.

17 Dr. D'Agostino?

18 DR. D'AGOSTINO: I have just a couple of
19 questions. The comment you made about the combined
20 endpoint, I wasn't clear as you were saying it if we're
21 supposed to think it's a good thing to do or not a good
22 thing to do. I mean, I would have responded that the time
23 to delivery or failure was a reasonable thing to do given
24 that you probably weren't going to get enough cases with
25 delivery or failure as particular endpoints. Could you

1 comment on that? I'm trying to think of where we're going
2 to go with some of the questions you're asking. Could you
3 comment on the reasonableness of this combined endpoint?

4 DR. MELE: I wasn't involved with the protocol
5 development of this study, but the combined endpoint is
6 very reasonable given that alternate tocolytic use is the
7 ethical approach to take. So I'm not at odds with that.
8 What I was referring to was the difficulty in trying to
9 determine the effectiveness of the drug given that you have
10 a combined endpoint and you're not sure what's really
11 driving the results of it.

12 DR. D'AGOSTINO: One other question. I'm
13 sitting here thinking that someone is going to ask me later
14 on to explain it, and I'd prefer you to explain it.

15 (Laughter.)

16 DR. D'AGOSTINO: Would you say a few more words
17 about what your concern is about the lack of definition of
18 equivalence in the positive control trials?

19 DR. MELE: Well, what's difficult there -- and
20 particularly I pointed out the problem in the ritodrine
21 study with the infant outcomes, and in particular the RDS
22 data. Since the confidence intervals have a certain width
23 to them, how wide would we let it be before we were
24 concerned that ritodrine could be that much better than
25 atosiban? So that was the point there, that we don't know

1 how much worse we would accept a difference to be to accept
2 that atosiban was equivalent.

3 DR. D'AGOSTINO: So switching from statistical
4 significance, that somehow or other we don't have a
5 clinical significance to fall back on.

6 DR. MELE: Right.

7 DR. PETITTI: Other questions for Dr. Mele?

8 (No response.)

9 DR. PETITTI: Could we then go back? There
10 were two specific issues that have been addressed to the
11 sponsor. The first relates to the question this morning by
12 Dr. Lockwood, and then Dr. Oh had a question, which I
13 believe was, could the justification for using the
14 secondary versus the protocol-defined primary endpoint be
15 clarified more directly?

16 DR. CREASY: Dr. Petitti, is it fair for me to
17 have a question for the statistician regarding one of the
18 views of the data?

19 DR. PETITTI: I'd like you to address our
20 questions first.

21 DR. CREASY: Okay. May I have slide 542,
22 please? I believe the question this morning had to do with
23 the definition of the reproductive disorders that were
24 given in the background booklet. First let me say that the
25 reason that the background disorders appeared in the text

1 for the atosiban paragraph is because there weren't a whole
2 lot of cardiovascular disorders of higher frequency to sort
3 of bump it down the list. The paragraphs were describing
4 the most frequent adverse events, and so the cardiovascular
5 events came to the top of the list in the paragraph for the
6 beta-mimetic comparitor, and other events which were
7 occurring at much lower rates came into the paragraph for
8 atosiban.

9 What you see here is basically comparable
10 rates. This is the pooled data for atosiban versus all of
11 the beta-mimetic agents. It was easier to pull together on
12 one slide to make the point that I think you were looking
13 for. Placental disorders, uterine disorders were mainly
14 rupture of membranes. Vaginitis was on the list. Uterine
15 hemorrhage is here, 2 percent for atosiban, 4 percent for
16 the beta-mimetic. Infectious complications, that should be
17 endometritis actually, 1 percent and 2 percent. Uterine
18 atony, 1 percent and 2 percent. It's very comparable, and
19 it didn't appear to us as we had reviewed this data
20 initially that there was any complication or problem being
21 induced by the use of atosiban on these disorders.

22 Can I have slide 243? To look at the rate of
23 chorioamnionitis and abruption in the PTL-096 study, the
24 rate on atosiban for chorioamnionitis was 6 percent, 4
25 percent for placebo. Abruption was equal between atosiban-

1 initiated care, if you will, and placebo-initiated care.

2 Slide 544. Also from the PTL-096 study, we had
3 specific data on postpartum hemorrhage, which was no
4 different, and on hypotonic uterine dysfunction, really no
5 difference.

6 We were able to also extract, although I don't
7 have it on this slide, from the CAP-01 trials the
8 occurrence of polyhydramnios that you had asked about.
9 There was a single case on both treatments, less than 1
10 percent on atosiban and less than 1 percent for the beta-
11 mimetic.

12 With regard to maternal white counts and
13 lymphocytes, there were no differences. I don't have that
14 on a slide to show you, but there weren't any.

15 Was there an interest in the 1-minute APGAR?
16 Because I have that on slide 325.

17 DR. PETITTI: No, we weren't interested in
18 that.

19 DR. CREASY: Okay.

20 DR. PETITTI: There was one other specific
21 question about a brief description of the justification for
22 the use of the secondary endpoint of 48 hours versus the
23 protocol-defined primary endpoint.

24 DR. CREASY: I'll ask Ms. Lane to address this,
25 but I believe this had to do with censoring and the reasons

1 the patients were censored.

2 MS. LANE: That's correct. I'm Roseanne Lane,
3 biostatistics. In the 096 trial, there were approximately
4 17 patients at the 48-hour endpoint on atosiban who
5 received alternate tocolytics for reasons other than
6 progression of labor, the protocol-defined definition, and
7 33 subjects on placebo. In the analysis defined in the
8 protocol, we excluded those patients from the analysis. We
9 just didn't count those data because they received the
10 alternate tocolytics for reasons other than progression of
11 labor.

12 When we took a look at the reasons why they
13 received those alternate tocolytics, most subjects received
14 them for reasons related to efficacy. It was clear from
15 the description that they had labor progressing, but they
16 didn't actually meet the protocol definition. So we
17 thought that we should include that data. Instead of
18 excluding those patients, we included them in more of an
19 intent-to-treat approach.

20 DR. PETITTI: Thank you.

21 Does that answer your question? Okay.

22 I am going to not allow questions to the FDA
23 statistician from the sponsor but move right along to the
24 discussion among the committee members about the general
25 issues raised in the questions here.

1 However, Dr. Azziz has asked if we can have
2 questions for the sponsor and further questions for the FDA
3 members from the committee, and the answer to that is yes.
4 If committee members have further questions for the sponsor
5 and/or to our FDA presenters in this more general
6 discussion, that would be acceptable.

7 I should also say that I am trying to move us
8 through this without taking a break, although I'm generally
9 a person who believes in breaks, who sometimes even needs
10 to have a break.

11 (Laughter.)

12 DR. PETITTI: Because there are a number of
13 people in the room who might leave before we have time to
14 fully address these issues, and I'd like to have as
15 complete a discussion with all members of the committee who
16 are both voting members of the committee and invited guests
17 as is reasonable.

18 I just want to review these questions and then
19 we will have a general discussion before we attempt to
20 address each question individually, or, as most of you know
21 who have been on FDA committees before, we don't have to
22 have these questions. We can have new questions, we can
23 decide not to answer questions, or we can pretty much do
24 whatever we want as a committee.

25 (Laughter.)

1 DR. PETITTI: Except leave --

2 (Laughter.)

3 DR. PETITTI: -- until we give some advice to
4 the FDA.

5 The questions that were posed ahead of time to
6 the committee were: Do the data presented today support
7 the effectiveness of atosiban for preterm labor? Do the
8 data presented today support the safety of atosiban as a
9 treatment for preterm labor? Taking into consideration the
10 overall benefits and risks of atosiban, do you recommend
11 that this drug be approved as a treatment for preterm
12 labor? Should additional studies of atosiban be conducted?
13 If so, what specific types, and in what population? Then
14 the fifth question is, what are reasonable and appropriate
15 endpoints to require for approval of studies of new
16 tocolytic agents?

17 I believe these were some of the issues that
18 Dr. Kweder talked about at great length. We could probably
19 have a whole day on that topic specifically.

20 However, before we move on to specifically each
21 question, I'd like to have some general discussion of the
22 committee. This is the appropriate time to have that
23 general discussion.

24 Dr. Azziz?

25 DR. AZZIZ: I have a question for the sponsor.

1 This may sound like a semantic question, but it isn't.
2 There is a lot of difficulty interpreting the data as far
3 as fetal outcome because there is no -- at least the
4 protocol did not call for a use of steroid and it was left
5 up to the physician. Any rationale for that that you could
6 enlighten us?

7 DR. CREASY: Well, these protocols were
8 initiated at the end of 1993, and our investigator meeting
9 took place at the end of 1993. The consensus conference on
10 steroids occurred in November of 1994, and the publication
11 of those results didn't come until our trials were nearly
12 over. So it's not like some of those data weren't in the
13 public domain, but when we had our investigator meeting,
14 there was absolutely no agreement to put that into the
15 protocol. So it was left up to the discretion of the
16 practicing physicians who were participating in these
17 trials.

18 DR. PETITTI: I'd like to make a comment in
19 general about the issue raised by Dr. Kweder on her last
20 slide related to the placebo-controlled component of this
21 project. I have to say ahead of time -- and this is to the
22 other members of the committee -- that I find these data
23 incredibly bewildering on some level because I come to
24 believe either that there's a true interaction where this
25 drug might have an adverse effect on the fetus at low

1 gestational ages and no effect on the fetus at higher
2 gestational ages, which is, from what I've heard,
3 physiologically plausible; or that the difference in fetal
4 outcomes in the lower gestational ages might be due to an
5 imbalance in the percentage of high-risk infants who
6 entered the atosiban-controlled arm.

7 I find that difficult to understand absent some
8 sort of concern about the randomization, and it was my
9 reason for asking for clarification about some of the exact
10 procedures for randomization.

11 If, in fact, there had been some concern or
12 proof that the randomization might not have gone quite as
13 well in that age group or that high-risk group because of
14 investigator concern communicated indirectly to the
15 pharmacist who was not blind to treatment, that very high-
16 risk infants were being put on placebo, then the whole
17 story would fall into place. I only mention that because,
18 again, I would be almost happier to learn that there was
19 this explanation for the anomaly in the data in the very
20 high-risk infants than that there was some way in which
21 atosiban caused low birth weight, actually very low birth
22 weight, without it in fact having much of an effect on
23 decreasing gestational age. It's sort of bewildering to
24 me, and I wanted to put that on the table.

25 DR. LEWIS: Kind of as a follow-up to that,

1 were the under-28-week infants distributed equally among
2 centers? They were? Okay.

3 DR. HAMMOND: Along the same lines, I have a
4 question about the 096 study that perhaps I just don't
5 understand. I feel like the patients have a wide range of
6 cumulative doses, that some of these people may have had an
7 hour of the drug and others may have had days of the drug.
8 Is there any way that we can look at that in terms of fetal
9 safety data, the cumulative dose received by the fetus?

10 DR. CREASY: I have slides of the cumulative
11 exposure and of some of the infant outcomes. It's easy to
12 summarize, that the longer the infants were exposed to the
13 drug, the better their outcomes are. The deaths below 24
14 weeks, many of them, I think it was already pointed out,
15 had very brief exposures to the drug, and the infants who
16 had cumulative exposures over 32 continuous days had the
17 highest weights and the lowest stays in a NICU.

18 DR. HAMMOND: So it wouldn't seem to fit that
19 there was a drug toxicity. It would seem to be that that
20 would be dose dependent. At least that's the way I would
21 see it.

22 DR. CREASY: That's our position.

23 DR. PETITTI: Dr. Van Marter.

24 DR. VAN MARTER: I have to ask if those results
25 were adjusted for the gestational age of the infants as

1 well.

2 DR. CREASY: In the analyses, was gestational
3 age taken in as a covariate? Yes. Well, Dr. Mele can --

4 DR. MELE: I did do an analysis like that where
5 I used treatment exposure as a covariate, and I also looked
6 at it by gestational age group. I found essentially what
7 Dr. Creasy just explained to you.

8 DR. PETITTI: Dr. Van Marter.

9 DR. VAN MARTER: I had two questions. One
10 relates to the whole biologic plausibility question, and I
11 was wondering if you could amplify the issue of, for
12 example, oxytocin receptor development in gestation and
13 whether that provides an explanation, a biologic
14 plausibility for why this drug might be more effective in
15 more advanced gestations.

16 The other question I had related to the
17 neonatal outcomes protocol. Specifically with regard to
18 that, whether infants were subjected to examinations for
19 head ultrasounds and ophthalmologic examinations, what
20 proportion of infants got those and whether that was
21 automatically included in your study protocol.

22 DR. CREASY: The head ultrasound was included.
23 I don't think we specifically had ophthalmologic
24 evaluations, but there were head ultrasounds to be
25 performed on all of the infants.

1 I'd like to ask Dr. Romero to address the issue
2 of the oxytocin receptors.

3 DR. ROMERO: The question that you ask is
4 biological plausibility and the mechanism of action that
5 justifies the observation of effectiveness related to
6 gestational ages. There are three lines of evidence. The
7 first is that oxytocin is less effective to stimulate
8 uterine contractility at early gestational ages of delayed
9 pregnancy. Hence, in clinical medicine we use oxytocin to
10 induce labor at term, but never to induce termination of
11 pregnancy in early gestation.

12 Second, if we measure oxytocin receptors in
13 myometrial decidua at the functional gestational age, the
14 earlier the gestational age, the lower the concentration of
15 receptors. So that is consistent with the observation that
16 at later gestational ages, there is an effect.

17 The third line of evidence comes from studies
18 that were conducted by Garcia in Uruguay a number of years
19 ago in which an in-dwelling catheter was placed in the
20 uterus, and then the oxytocin sensitivity that was required
21 to induce uterine contractions determined during pregnancy.
22 To no surprise, the later in gestation, the greater the
23 sensitivity of the uterus to oxytocin compared to early
24 gestation.

25 DR. DATTEL: Isn't it true also that receptors

1 in the uterus are actually related whether or not labor is
2 present? So at least in myometrial strips that I've
3 personally studied, if preterm labor was present and you
4 looked at receptor concentration in the uterus that was
5 already contracting, then actually the number was up. So,
6 in fact, gestational age is important, but that kind of
7 puts holes in your theory, because if these patients
8 actually truly had preterm labor, the receptors would be
9 more responsive and the number would be increased as well.

10 DR. PETITTI: Dr. D'Agostino.

11 DR. D'AGOSTINO: I guess in this time we can
12 make some general comments, and looking at the data that we
13 had presented to us today in trying to sort out the
14 different issues, I think that -- and I'd just like to
15 throw out some general comments. I think that the study
16 096 is truly the important study in terms of the
17 effectiveness. In terms of viewing the study, they had a
18 primary endpoint which didn't show very much, and then they
19 went to a secondary endpoint which sort of starts causing
20 you some interpretation problems, and then to a subset
21 which adds to the problems. When you focus on this
22 secondary endpoint, which may be a good endpoint, and this
23 subset, you start seeing some support of the data.

24 But I think in clinical trials, you'd sort of
25 like it the other way around. You'd like to have the right

1 endpoint as the primary endpoint and see significance
2 there, and then try to look at the subsets to try to
3 understand that.

4 I'm concerned with the term "support support."
5 As we go to support support, I don't want to get trapped
6 into saying, yes, we see support, but we don't think the
7 trials make it. I mean, I think that it would be nice to
8 approach this with a global anticipation of what we mean by
9 pivotal trials and what it means to ultimately have a
10 recommendation for drug approval.

11 The other thing I want to raise -- and we've
12 raised it before, but I really think I need to say it again
13 for my comfort -- is this endpoint. It's very much a
14 surrogate endpoint. You've got 48-hour activity in which
15 you can do something, but it's a surrogate endpoint, and
16 I'm looking to see something that happens later on and is
17 it safe even in maternal, which is very comforting. But
18 when you don't see any impact on the delivery time, and
19 it's not clear if you see something positive or negative on
20 the infants, I think that even if we buy into the 48 hours,
21 we have some serious considerations and problems of what
22 we've bought into and what the interpretation of that is
23 and the comfort that that variable leads to later
24 inferences.

25 Those are the sort of global comments I'd like

1 to make.

2 DR. PETITTI: Dr. Azziz.

3 DR. AZZIZ: I just have something in the
4 comments arena. When we find something that may be
5 targeted for a small population, whether it's OB or
6 otherwise, you'd like to see some robust changes, something
7 that would stand up to the reanalysis one way or another,
8 and that is one of the biggest concerns that I have here.
9 This is not very robust here. I mean, you change a few
10 patients and out goes significance.

11 One of the questions I have in that regard is
12 that partly it may be due to design. I mean, 55 percent of
13 patients treated with placebo alone did quite well
14 according to the secondary endpoint, meaning they were
15 undelivered or no alternative tocolytic was used. That
16 seems a bit high for a true disease process. So the
17 question is, is there perhaps some problem in the patients
18 selected initially which has created a number of patients
19 that may not have to be treated or may not have needed to
20 be treated in the beginning? Fifty-five percent of
21 patients who do well on placebo alone is pretty high.

22 DR. GREENE: As an obstetrician, I'll just
23 respond that I'm not troubled by that. Identifying these
24 patients reliably is very, very difficult. So that doesn't
25 trouble me.

1 In terms of global comments, if I may, about
2 everything I've heard today and the data that I've reviewed
3 so far, I guess my first global comment is that I found the
4 reports of the studies that we were provided prior to the
5 meeting, the way the data was reported made each one of the
6 studies uninterpretable and unevaluatable for me, on the
7 basis of the data in this book. I could not come to
8 conclusions about each one of the studies from the data
9 provided. That's my first sort of global observation.

10 The other global observations are that I'm
11 troubled whenever the results of a large study result in an
12 insignificant finding but a subgroup analysis is able to
13 tease out a marginally significant difference or something
14 to find efficacy of treatment. I think the sponsor has
15 already acknowledged that the efficacy after 28 weeks was
16 not an a priori hypothesis but was derived upon review and
17 analysis of the data. If it was an a priori hypothesis, it
18 seems that it would have saved a lot of anxiety in
19 explaining after the fact if patients less than 28 weeks
20 had been excluded from the study. It seems to me you'd
21 have a lot less explaining to do here today about those
22 poor outcomes at less than 28 weeks.

23 The proposal, then, is to propose the drug for
24 use after 28 weeks, and specifically for the goal of
25 prolonging labor for 48 hours for two purposes. One is to

1 administer steroids, and two is to make possible transfer
2 to a high-risk center for a patient who is discovered in a
3 community hospital, let's say, to be in premature labor. I
4 am concerned now that if we propose that therefore a study
5 be done to evaluate those endpoints to say that, okay, then
6 let's do a study in patients in community hospitals to see
7 if it actually facilitates transfer, the sponsors may
8 rightfully say it's impossible to do such a study, you
9 can't organize those kinds of things in a community
10 hospital.

11 Alternatively, if we propose that a study be
12 conducted that proves efficacy in reducing perinatal
13 mortality or some other endpoints that we consider more
14 meaningful, the sponsor will again cry that the numbers
15 prohibit us from doing such a study, as Dr. Sibai correctly
16 pointed out with respect to the endpoint of intracranial
17 hemorrhage. To do such a study would require what I
18 sometimes term an intergalactic collaborative trial. It
19 just wouldn't be done.

20 So I wonder if we're not setting up a situation
21 where we have concerns about the efficacy of the drug given
22 the endpoints that we've been given, but that the proper
23 endpoints would require studies that can't be done.

24 DR. PETITTI: I think those are excellent
25 points.

1 Dr. Harris had some comments.

2 DR. HARRIS: It's more a question than a
3 comment for clarification to Dr. Mele. Is it a matter of
4 statistical opinion or a question about methodology, this
5 inclusion and exclusion, or censoring that gives us such a
6 difference in outcomes? I think it's shown on the 48-hour
7 outcome slide on page 3 of your presentation and one of the
8 central questions that we're having in trying to decide
9 whether in fact the drug is effective or not.

10 DR. MELE: I just want to point out that in
11 both of those analyses, all the patients are included. So
12 there's no one excluded. It's just the numerator that
13 changes, okay? The numerator changes because in one
14 analysis --

15 DR. HARRIS: The numerator or denominator?

16 DR. MELE: The numerator. The denominators are
17 the same because all patients are included in both
18 analyses, okay? And the difference is that in one
19 analysis, only the therapeutic failures are counted as
20 failures and not patients who took alternate tocolytics for
21 other reasons. Those patients are considered continued
22 patients in the analysis for the therapeutic failures only,
23 okay? Does that help to clarify it?

24 DR. HARRIS: It does, but my question is, is
25 that just a matter of statistical analysis opinion where

1 you put them, or is it a real methodological issue in
2 analyzing where the effectiveness is of the data?

3 DR. MELE: I think it's more of a
4 methodological issue, because I think that you have to
5 decide whether those patients who took alternate tocolytics
6 for other reasons should be counted as failures, or should
7 they be just treated as any other discontinued patient. I
8 had mentioned earlier that about 50 percent of the patients
9 in each of the groups were given the alternate tocolytics
10 for reasons other than protocol-defined failure for
11 progression of labor.

12 DR. CREASY: Dr. Petitti, could our
13 statistician comment on that question?

14 DR. PETITTI: I'd like Dr. Harris to make sure
15 that that answered your question.

16 DR. HARRIS: I think that clarified it.

17 DR. TITI: Jim Titi from PRI. Actually, I
18 would like to comment on the previous question regarding
19 the subpopulation greater than 28 weeks and less than 28
20 weeks. We did look at the overall population results for
21 the 48-hour endpoint, and that was significant. I think
22 keeping in usual practice, we did look then for treatment
23 by gestational age interaction to see if there was a
24 differential effect. As you would if one were to find an
25 interaction with any factor, say with investigator, you

1 would pull out the investigators that would cause an
2 interaction and look at the subset where that interaction
3 did not occur.

4 That's why we looked at the greater than 28
5 weeks as a particular subgroup when we did some modeling,
6 to see what was causing the interaction and where this
7 interaction was occurring. Again, the treatment by
8 gestational age interaction relative to response, it was at
9 28 weeks when that occurred. So there was an analytical
10 explanation for why we looked at that particular group. I
11 think, as Dr. Romero also referred to this morning, in that
12 less than 28 population, there are a lot of other factors
13 that I think affect the interpretation of the results which
14 cloud the issue.

15 So, again, I think there were important reasons
16 for why we would want to focus on the population greater
17 than 28 weeks where, again, 85 percent of the patients were
18 enrolled.

19 DR. PETITTI: Dr. Van Marter, then Dr.
20 Lockwood, then Dr. Oh.

21 DR. VAN MARTER: I'd just like to speak as an
22 advocate, that the neonatal and fetal effects are very
23 important considerations here, and I'd like to make a
24 couple of points in that regard.

25 The first is, as a number of people have noted,

1 the numbers were quite small in the group of babies that we
2 consider the most vulnerable, the babies less than 28 weeks
3 gestation. If atosiban is approved for use greater than 28
4 weeks, I think we all know that practice creep is a real
5 phenomenon and babies in this lower gestational age group
6 will be exposed to the medication, almost certainly. So
7 I'd like to speak as their advocates, that we not abandon
8 consideration of this group in considering the approval of
9 the drug.

10 Likewise, in looking at the group of babies at
11 or above 28 weeks gestation, if we consider the fact that
12 the mean birth weight at 28 weeks gestation is something on
13 the order of 1200 to 1300 grams, looking at the birth
14 weights in the treatment groups in this study, we can see
15 that they're well above 2 kilos. So even the 28-week
16 gestation group is skewed in a direction favoring higher
17 gestational ages. That's important for two reasons.

18 One, to underscore a point made by Dr. Oh this
19 morning, the neonatal morbidities at those upper
20 gestational ages are so small that one would need an
21 extremely large study to demonstrate a statistically
22 significant benefit or increase in risk.

23 The second is that because of the lower
24 prevalence of those disorders at the 33-34 week gestations,
25 the clinicians caring for those babies often don't screen

1 for the disorders of interest here. So I think that the
2 opportunity to make the diagnosis is also limited because
3 of the large size of the babies.

4 Second, in terms of looking at the outcomes, I
5 was surprised that neonatal infection wasn't considered as
6 a principal outcome, and also I think there are a couple of
7 other things including chronic lung disease and
8 periventricular leukomyelasia, the latter being a condition
9 that's been strongly linked with adverse developmental
10 outcomes later, that were not considered as either primary
11 or secondary outcomes.

12 Finally, with regard to the analyses, I would
13 have really liked to have seen a bit more in terms of
14 multivariate modeling that controlled for a number of
15 factors. I thought Dr. Ward did a very nice job of looking
16 in various strata at the antenatal glucocorticoid effects
17 and the effects of extreme prematurity. But other factors
18 that I would like to have seen considered in multivariate
19 analyses of the effects would include surfactant therapy,
20 ethnicity, sex, the specific medical center, multiple
21 gestations, and even looking at birth weight or gestational
22 age within such large gestational age groups.

23 So I think looking at the neonatal data, I'm
24 having trouble certifying that atosiban is a safe drug
25 because I think that there are limitations to the power of

1 the studies that we've seen today to show that these are
2 outcomes that we can really rely on as being equal between
3 the groups.

4 I think that in addition to doing the
5 intergalactic trial, there are other approaches that might
6 be able to answer the question. First, limiting the
7 population to one enriched for the neonatal outcomes we're
8 interested in, the smaller babies, or using a similar
9 approach but randomizing in blocks by gestational age. So
10 those are a couple of suggestions I would have if we were
11 to engage another study.

12 DR. CREASY: Some of the things that you
13 mentioned were included.

14 DR. PETITTI: Excuse me. I'd like to go to
15 members of the committee.

16 Dr. Lockwood?

17 DR. LOCKWOOD: Well, strangely enough, I have
18 exactly the opposite interpretation of the same data. I
19 guess I'm going to make an argument that I've been
20 convinced over the course of the last few days and the last
21 few hours that it's unlikely that, in fact, this drug is
22 particularly dangerous in an unstressed setting. I mean, I
23 think it's very likely that this could be very dangerous if
24 the fetus is anemic or if the fetus is hypoxic or if there
25 are other factors in which vasosuppression is playing a

1 crucial homeostatic role. But I think that in a healthy
2 fetus it's unlikely, very unlikely, and I think that there
3 isn't a shred of data that we've seen that there's an
4 intrinsic risk to this drug.

5 We haven't seen stillbirths, we haven't really
6 even seen this early loss phenomena, except in the 096
7 study. It wasn't present in the other studies, and it
8 looks like it was just bad study design.

9 No offense, guys.

10 But I think that they ended up with a lot of
11 very early fetuses that were in advanced preterm delivery
12 and they weren't going to survive. Twenty-one, 22, 23-
13 weekers aren't going to survive. So I'm not terribly
14 concerned that there is an intrinsic risk to therapy, and I
15 guess I'm now more convinced that there is an extrinsic
16 risk to the therapy. I don't think that this therapy is
17 promoting these real early preterm deliveries. It doesn't
18 seem to be, according to their data, promoting infections,
19 promoting abruptions, promoting other factors. So I'm less
20 concerned, actually, about the earlier gestational ages,
21 although a strong caveat is that it ought to be not used in
22 settings of potential fetal stress or anemia or
23 hypotension. So bleeding, hemolytic anemia, IUGR, maternal
24 preeclampsia or lupus, et cetera.

25 The second thing that is very clear, and I

1 guess I could have predicted it a priori, is that this
2 wasn't going to be a very effective tocolytic. The reason
3 for that is that, first of all, oxytocin hasn't exactly
4 been implicated in any of the various pathogeneses that
5 promote preterm delivery, and I think that it's actually
6 probably much like magnesium or alcohol, which work through
7 oxytocin receptors, or the beta-mimetics. It's sort of
8 paralyzing the uterus for a short period of time until
9 whatever the inciting event is, whether it's hemorrhage or
10 infection or distention or stress or physiologic onset of
11 labor, overwhelms that minor role played by poisoning the
12 oxytocin receptors.

13 That's why it seems to be pretty good at
14 stopping labor for 48 hours, but it doesn't seem to do a
15 damn thing in terms of preventing the really crucial
16 endpoints of preventing preterm deliveries before 32 weeks,
17 33 or 34 weeks.

18 So I'm actually pretty convinced now that it's
19 safe, and I would say that it is as inefficacious as the
20 current repertoire of agents that we use. It's probably
21 comparable to magnesium from a maternal standpoint, but it
22 seems to be safer than the beta-mimetic agents we use.

23 DR. PETITTI: Dr. Oh.

24 DR. OH: Let me first make a general comment,
25 and that is that clinical research is always a very

1 difficult thing to do, and I think that makes the double-
2 blind placebo-control trial so powerful. The important
3 thing is that the study design was such that there was lack
4 of stratification by gestational age. I think that's the
5 major problem with the study design, causing imbalance of
6 the distribution of infants in the lower gestational ages,
7 which I think accounts for the lack of safety, if you will,
8 in terms of higher mortality and morbidity.

9 I think Dr. Ward has made it very clear that if
10 you have 19 out of the 43, as I recall, weeks pre-viable,
11 anything you look at becomes problematic. So that poses
12 the real problem in terms of safety.

13 On the other hand, in the other spectrum, we do
14 a secondary analysis looking at the benefit side of it, the
15 low event rate, as I pointed out earlier, which makes a
16 problem in terms of interpreting whether prolonging 48
17 hours or 72 hours would make an impact on the outcome or
18 not.

19 So I think if you look at it overall, although
20 there is evidence of safety, on the maternal side it's
21 okay. I think that's pretty clear. We attribute the lack
22 of safety on the infant side on the basis of imbalance.
23 I'm still troubled with the fact that we don't have
24 documented benefits for the prolongation of pregnancy. So
25 I still think that there's a need, whether it's an

1 intergalactic trial or not, a need to have a trial that
2 will target the morbidity on the neonatal side that has a
3 higher event rate, which could not only reduce your sample
4 size requirement but also will show the real benefit.

5 That's really where the money is, and that's my
6 conclusion, that given the information so far today, I
7 cannot go along with approval, and I would plead for an
8 attempt, although Dr. Sibai already said that maybe it's
9 unethical, but I don't think it's unethical to do a study
10 if you really don't have benefit demonstrated, particularly
11 on the infant side, for a certain tocolytic agent.

12 DR. PETITTI: I'd like to address this comment
13 to Dr. D'Agostino. You mentioned your concern about
14 focusing on a subgroup analysis as the basis for making a
15 recommendation for approval of the drug as a treatment for
16 preterm labor. Could you make a comment assuming that the
17 imbalance in gestational age and in birth weight
18 particularly, because I think the imbalance in birth weight
19 is actually much worse even than the imbalance in
20 gestational age, birth weight within gestational age as a
21 basis for rejecting any claims to lack of safety for the
22 infant?

23 DR. D'AGOSTINO: Because of the imbalance?

24 DR. PETITTI: Yes.

25 DR. D'AGOSTINO: I think because you have the

1 randomized trial, you're sort of locked into what the
2 randomized trial produces. If you start peeling away and
3 explaining, then you're really making clinical judgments,
4 which may be sensible but they're not based on the
5 statistics of it anymore. I think that some of the
6 analysis we're talking about in terms of the interactions
7 with the gestational week is certainly a good analysis to
8 do, but the primary outcome didn't work, and then you went
9 to a secondary outcome. You have a lot of secondary
10 outcomes. Only one secondary outcome worked, and then you
11 try to understand that one secondary outcome.

12 You may be doing all the right things, but I no
13 longer am of help to you in terms of interpreting it. The
14 statistics is long gone where you can really get valid
15 statistical interpretations. Am I answering what you're
16 asking?

17 DR. PETITTI: Yes, you are.

18 DR. D'AGOSTINO: I just don't think we're at
19 that point where we can do that on any sort of statistical
20 basis. We're really interpreting the data, and that's what
21 cries for another study to straighten it all out.

22 DR. NARRIGAN: I have one question and one
23 comment. I'm very troubled by the interaction of the use
24 of secondary drugs or an alternate tocolytic during the
25 study. I can't sort out for myself where the effect of the

1 study drug is. It's just very hard. I'll just say that.

2 The other thing is that I found the FDA's
3 review, the history of how this committee has operated over
4 the last 20 years very helpful, because I hear us today
5 saying that our concern about neonatal outcomes is primary
6 or one of our deep concerns, whereas prior committees have
7 not focused on that or have not asked the sponsor to show
8 safety to the extent that we're asking today. So I guess
9 historically we're evolving as a professional group and
10 asking for that. It's a break in the history or the
11 evolution. So I would just say that.

12 DR. D'AGOSTINO: I'm not necessarily going to
13 give you an explanation for that, but I think if you look
14 at 10, 15, 20 years ago, you found I think a lot more faith
15 in surrogate endpoints, that if you did something with
16 holding the time to delivery, then it has to have a
17 positive effect on the child and so forth, and we found
18 that you can stop arrhythmias very well but you were
19 killing people. We found over and over again that
20 surrogate endpoints don't necessarily deliver, and I think
21 maybe what we're seeing is some of that reflected in our
22 deliberations.

23 DR. PETITTI: I wanted myself to reemphasize
24 what you said about the difficulty of sorting out what has
25 become almost combined interventions, or lack of

1 interventions. I think one of the problems actually that
2 Dr. Azziz pointed out here is that in some ways the thing
3 that you now know you ought to do to optimize perhaps
4 infant outcome within that 48 hours that you probably may
5 buy in the greater-than-28-week infants was not done in
6 this study, for reasons that I think are very justifiable
7 given the state of opinion about the use of steroids at the
8 time that these studies were conducted.

9 So again, we have complicated combined
10 endpoints, a failure of infant treatment within that 48-
11 hour window to have been optimized, and incredible
12 difficulties in interpreting it in terms of this drug
13 alone.

14 DR. LEWIS: I would echo what you said. It's a
15 very good summary of the whole thing, and I think it would
16 have been far more satisfying if, instead of 098, we'd had
17 a randomized trial limited to people who were over 28
18 weeks, and placebo-controlled.

19 DR. AZZIZ: This issue isn't perhaps a part of
20 what the FDA asked us, but supposing that the drug does not
21 cause any harm to the fetus, and supposing that it doesn't
22 have a lot of effect on preterm labor? Perhaps we're being
23 too demanding on a study of a problem that is clinically
24 very difficult to study. Perhaps we're being overly-
25 demanding and unrealistic. So what is the downfall of

1 approving a drug that is not very effective and perhaps
2 harmful to, say, the younger fetus? Perhaps there's
3 nothing, and maybe we should let it go to market and let
4 the marketplace decide.

5 But the reality is that if it is used in
6 fetuses under 28, or it's used in stress conditions, which
7 I would say plenty of preterm pregnancies are under stress
8 conditions, then perhaps we are killing more babies. So I
9 think it is important that we don't forget that it doesn't
10 suffice to say, well, gee whiz, it isn't really that good
11 but we don't have anything else out there, so why don't we
12 try it? I'm not sure that this is the place to do that.

13 DR. PETITTI: Dr. Dattel?

14 DR. DATTEL: I just had one or two general
15 comments, and maybe I'll be playing devil's advocate. I'm
16 not sure. Maybe I'll just be arguing with myself. I'm not
17 sure about that either.

18 First of all, I also noted in all of my reviews
19 that the placebo worked good about half the time and, as we
20 know, that's generally the way it does. I'd just like to
21 put in a plug that it actually isn't really placebo. It's
22 placebo drug. We're actually treating the mother. We're
23 treating the mother with bed rest and hydration and
24 attention and all sorts of other things that are
25 immeasurable, and the only thing that's placebo is the

1 drug. So mothers are actually getting treatment, and it
2 always bothers me a little bit that we feel like we're not
3 doing anything when we actually are.

4 Early Canadian data said that that's probably
5 good enough for most people, and we've just proven over and
6 over again that it is probably good enough for most people.

7 By the same token, having been in preterm labor
8 and having been on drugs and having treated it for almost
9 20 years, I think it's nice to be able to have an option
10 for women who fail or who cannot tolerate other types of
11 agents, and I guess this is where the devil's advocacy
12 comes in. I'm not convinced that this is a dangerous drug.
13 I'm not convinced that the study was actually carried out
14 very well for patients under 28 weeks either, which I think
15 confounds all of our discussions today. To have cleaner
16 data in that age group, probably excluding multiple
17 gestations, because I think that confounds most of your
18 deaths, which occur in multiple gestations, I think that
19 kind of rear-ends your data under 28 weeks.

20 I'm also not convinced that we should
21 completely say that this drug should go away and never be
22 heard from again, because I do think it offers an
23 alternative, and most of the other alternatives that we
24 have available to women other than the standard tocolytic
25 agents are just beta-mimetics and the off-label use of

1 magnesium sulfate. All are fraught with risks for mother
2 and fetus, including calcium channel blockers and
3 inhibitors, and they all have known adverse effects which
4 are probably worse than any of the ones we're going to see
5 with this drug.

6 Those are my general comments.

7 DR. PETITTI: More comments?

8 (No response.)

9 DR. PETITTI: We are now at the time in this
10 meeting when the chair wishes that the chair could leave.

11 (Laughter.)

12 DR. PETITTI: We have a specific charge, which
13 is to give some specific advice to the FDA, and we have
14 five questions that have been posed to the committee, and I
15 think we all ought to know that we don't have to answer
16 these questions. We can start off by deciding that there
17 was some other set of questions that we would prefer to
18 answer.

19 I think Dr. D'Agostino raised a very important
20 point in the ordering of the questions and asking for sort
21 of a yes/no answer. By the way, these do have to be pretty
22 much yes/no answers about do the data presented support the
23 effectiveness, support the safety, and only then going on
24 to the issue of, taking into account the overall risks and
25 benefits, do we recommend approval. But I would like a

1 sense of the committee if we would like to take these
2 questions as they have been posed, if there are some
3 modifications, and whether or not we are ready to move on
4 to give specific advice to the FDA.

5 DR. NARRIGAN: I think we've done this at other
6 meetings. We tend to try to define such words as
7 "effectiveness." Are we going to do that here?

8 DR. PETITTI: We could amplify on the questions
9 by clarifying what it is that our committee is voting on.
10 Do you have a specific suggestion along that line?

11 DR. NARRIGAN: I think the sponsor is somewhat
12 convincing about effectiveness after 28 weeks, but
13 certainly not before. So this question could be split by
14 gestational age perhaps, or not. I'm looking at the first
15 question. I'm sorry. Do the data presented support the
16 effectiveness of the drug for preterm labor?

17 DR. AZZIZ: Correct. I'm not sure that we can
18 -- whether we recommend approval or disapproval, I don't
19 think we can at this stage tell the sponsor to change their
20 indication. I mean, they've asked for an indication which
21 is verbatim, "Antocin is indicated for the acute treatment
22 of preterm labor for up to 48 hours in patients who are at
23 least 28 weeks gestation to facilitate therapies designed
24 to hasten fetal lung maturation and/or for maternal
25 transfer to the appropriate facilities." That's what

1 they're asking.

2 DR. NARRIGAN: Thanks. So that's all we're
3 voting on, then, is efficacy after 28 weeks? Okay.

4 DR. PETITTI: Yes, specifically in relationship
5 to that.

6 Dr. D'Agostino?

7 DR. D'AGOSTINO: Can I go back, then, to my
8 concern? My concern is that we have the word "support" in
9 this statement. The usual criteria for effectiveness is
10 having a couple of pivotal trials that are confirmatory and
11 not necessarily trials that are subset analyses. I think
12 we have to be very careful of how we interpret this. We
13 may think there's some nice data going on with the first
14 study, the 096, in that greater-than-28-weeks, but we have
15 to look at how they got to that subset in terms of the root
16 of looking at the primary variable, not getting it, going
17 to one secondary variable, getting it, and then sorting it
18 out. So to jump and say it looks like we have positive
19 results there, I think we have to be very careful of saying
20 that.

21 DR. RARICK: The word "support" may not be the
22 best word for that question. If you would like to consider
23 "Do the data presented today establish the effectiveness,"
24 would that be easier for you?

25 DR. D'AGOSTINO: It would be a lot easier for

1 me.

2 DR. RARICK: Thank you. Why don't we do that,
3 then? For both Question 1 and Question 2, change the word
4 "support" to "establish."

5 DR. LOCKWOOD: The only problem here is -- the
6 fundamental problem -- and this is good that we're sitting
7 next to each other -- is the difference between biology and
8 statistics, and the fact of the matter is that this is an
9 unbelievably complicated system with heterogeneous
10 etiologies that have distinct biochemical pathways, some
11 which may respond to oxytocin antagonists, some that don't,
12 and we're trying to interpret -- I'm very bad with
13 metaphors, but we're trying to interpret whether or not
14 some painting hanging in the Louvre is beautiful or not
15 using some kind of statistical approach.

16 The fact of the matter is that in this
17 particular condition, where the biology is just now being
18 better understood, I don't think that a larger study, a
19 more rigorous study is going to produce results that are
20 going to be any more palatable than what we find right here
21 today. They may improve the safety issues, but unless you
22 establish your endpoints crystal clear, I don't think we're
23 going to get there.

24 DR. VAN MARTER: Dr. Lockwood, I think the
25 issues you raise are important. I think all of us are keen

1 to have the best possible tocolytic we can have available
2 to prevent preterm birth. I think that the safety issues
3 are really important, and I do think that there are
4 methodologic modifications that could impact on providing a
5 clearer answer to the safety questions.

6 DR. LOCKWOOD: Agreed about safety.

7 DR. PETITTI: Dr. Azziz had a comment.

8 DR. AZZIZ: Dr. Lockwood, you're absolutely
9 correct. This is an incredibly complex system which none
10 of us really understand very well, what's going on in
11 preterm labor, period. But we're trying to address, I
12 think, a clinical question. When this is approved or
13 disapproved, whatever it is, it is for a clinical question,
14 where the physician makes a judgment. The clinician
15 doesn't think, "Is this prostaglandin or is this oxytocin
16 or does this resist infection?" It's a clinical question.

17 So the clinical question in my mind has to show
18 -- there has to be a demonstrated effectiveness for the
19 clinical question under consideration. Otherwise, we'll
20 sit here until Doomsday trying to figure out if we're
21 actually treating oxytocin-related preterm labor versus
22 infection-related preterm labor. We'll never resolve that
23 question.

24 So I think it's a clinical question. I don't
25 think we're disagreeing. I'm just simply pointing out that

1 it's a clinical question.

2 DR. LOCKWOOD: I hope you're wrong about
3 specific therapies. Otherwise, Roberto and I and a lot of
4 other people are wasting our time.

5 DR. PETITTI: Dr. Harris, and then Dr.
6 D'Agostino.

7 DR. HARRIS: Let me just chime in again. This
8 is why I raised the question with Dr. Mele about whether
9 exclusion or inclusion and the fact that it changed the
10 outcome of what was significant at 48 hours was really a
11 statistical opinion versus a methodological issue, because,
12 if I understand this correctly, her interpretation of the
13 data would suggest little or no benefit at 48 hours. Am I
14 misunderstanding that?

15 DR. MELE: That's not my interpretation of the
16 data. The one variable that showed no difference between
17 the groups was the one that was defined in the protocol,
18 the therapeutic failures.

19 DR. PETITTI: Could you say that again? The
20 variable in the protocol showed no difference? Is that
21 correct?

22 DR. MELE: That's right. But then if you
23 included -- and the sponsor talked about why they included
24 the other users of alternate tocolytics as failures. If
25 you include them as failures, then you find a significant

1 difference between the groups.

2 DR. D'AGOSTINO: I think we have to be very
3 careful of what the use of statistics is. Statistics isn't
4 coming in to change the clinical decisions and the clinical
5 interpretations. Statistics is coming in to say do you
6 have enough data so that you can get on to the clinical
7 arguments. When you have a study put together where a
8 major endpoint didn't show differences and you had to go to
9 a subset of the data on a secondary endpoint to find
10 something, you have to really sit back and say, "Did you
11 really find that? Is it really established?" There are
12 lots of studies where confirmation doesn't come.

13 I mean, we're seeing this before us because
14 they got a positive result in this subset, which we haven't
15 even talked about what level of confidence we can attach to
16 it, but it's very much an exploratory search that has
17 pulled this out. It's not a confirmatory study by any
18 stretch of the imagination.

19 DR. DATTEL: I guess I was just going to say
20 that we're not necessarily here to say that this is better
21 than something else, but that it is effective. That's my
22 understanding. We're not saying this is better or that
23 it's going to replace anything else, but that it's
24 effective at what it says it's going to do, and does it
25 cause harm. That's how I'm trying to answer these

1 questions.

2 DR. PETITTI: I think the way we have re-worded
3 the question, "Do the data presented today establish the
4 effectiveness of atosiban for preterm labor?" is the
5 question that we are addressing here.

6 DR. LOCKWOOD: What does that mean? "Do the
7 data presented today establish the effectiveness of
8 atosiban for preterm labor?" For what?

9 DR. PETITTI: I personally would follow up on
10 Dr. D'Agostino's comments, which are do the data presented
11 here show what the sponsor set out to show in terms of
12 establishing the effectiveness for preterm labor.

13 DR. LOCKWOOD: Prevention, delay, delay for 48
14 hours.

15 DR. PETITTI: Well, I believe the primary
16 endpoint in this trial was the one that was described by
17 the statistician, and it was a study that was done
18 including infants that were less than 28 weeks of
19 gestation, and I have my own concerns about the subgroup
20 analysis and the use of seven secondary endpoints, only one
21 of which met a statistical criterion for effectiveness.

22 DR. LOCKWOOD: But did you read this question?

23 DR. PETITTI: "Do the data presented today
24 establish the effectiveness of atosiban for preterm labor?"
25 It should be treatment.

1 DR. NARRIGAN: I can't find the sponsor's
2 statement of the purpose.

3 DR. AZZIZ: It's on Slide 10.

4 DR. RARICK: The purpose of the study, or the
5 indications?

6 DR. NARRIGAN: The application.

7 DR. RARICK: The original objective of the
8 study?

9 DR. NARRIGAN: Actually, that helps us
10 understand the first question.

11 DR. PETITTI: I'd like to clarify this with Dr.
12 Rarick. Are we to consider today this question in
13 relationship to the stated indication, or are we to make
14 our own interpretation of this question? Because the
15 stated indication has changed to --

16 DR. RARICK: Yes, the stated indication has
17 changed, as you all know. I think you received it -- I
18 received it Tuesday. Of course, we did our review based on
19 the original NDA statement. I think that you will need to
20 decide how you want to answer this question. If you want
21 to add a caveat as the sponsor has newly stated the
22 indication, then I'd ask -- I wrote that in after Dr.
23 Azziz' comment that he was assuming that you were answering
24 it according to the new indication, but I would then ask
25 you to follow up. Depending on how your answers go, you

1 may need to follow up with us with some labeling questions.

2 DR. NARRIGAN: If we take Slide 10 as the
3 stated purpose, that's a secondary outcome. So that's a
4 big shift.

5 DR. AZZIZ: Can I ask Dr. D'Agostino a question
6 about study design? I think maybe it's just a rhetorical
7 question.

8 Usually when we do experiments where we do
9 either large population studies or even laboratory studies,
10 and we find a trend or we find a secondary analysis to
11 indicate that all of a sudden our obese PCOS patients are
12 the ones who really benefit and not the thin ones, that
13 simply, as you said earlier, supports the idea, and then
14 you have to do a study to confirm your idea. So would not
15 this fall into that category, where the study supports this
16 possibility and then you have to confirm it?

17 DR. D'AGOSTINO: Well, this is the way I
18 interpret it, that you have a study that had Objective A,
19 that objective didn't work out, Objective B looks pretty
20 good, and that gives you some sense that maybe you do, in
21 fact, have something going on, and now you want a
22 confirmatory study. This is why I was objecting or I was
23 raising questions with the word "support." I mean, it does
24 give you a good feeling that something is going on there,
25 but it hasn't established that the results you're seeing

1 are really going to be confirmed and duplicated and
2 replicated in another study.

3 DR. PETITTI: Are we very clear now? I'm
4 sorry, Dr. Bilstad from the FDA.

5 DR. BILSTAD: I just wanted to say from the FDA
6 standpoint that while the issue of efficacy may hinge upon
7 the current indication that the sponsor is seeking, at the
8 same time, inherent in our question of efficacy is that
9 this is based on a study design as done and the analyses as
10 done. So the question is, is it justified to move from the
11 original study design and the analyses to the conclusion
12 that supports the sponsor's indication?

13 DR. PETITTI: Thank you for that clarification.
14 I think that's very important.

15 DR. VAN MARTER: I may be mistaken, but I
16 thought I read somewhere in the materials provided to us
17 that the sponsor had originally proposed the 48-hour
18 outcome as a principal outcome measure, and then that was
19 subsequently renegotiated.

20 DR. PETITTI: I wasn't there. Can we have some
21 clarification?

22 DR. RARICK: I think Dr. Kweder presented in
23 her discussion of the drug development for atosiban that
24 the original proposal was for a study that looked at the
25 48-hour endpoint as the pivotal endpoint, and although I

1 think I heard Deborah mention that she thought that the
2 committee was evolving to change the neonatal outcome
3 benefits, you'll remember that with ritodrine, although it
4 was shown to have the 48-hour indication, I don't know if
5 you remember from Dr. Kweder's presentation, but their
6 whole point was that it was also the higher birth weight
7 babies, greater gestations, the assumption that there was a
8 neonatal benefit.

9 I think the sponsor initially came in with the
10 48-hour endpoint as their requested indication in terms of
11 their protocol, but that protocol was then redesigned and
12 powered and sample-sized for the objective that was stated.

13 DR. D'AGOSTINO: I did see that also, and it's
14 a sign of sadness, I suppose, that they may have been on to
15 something that didn't materialize. I just don't know how
16 to go back and look at a study that was designed to do
17 something else now for a discussion that they had. There's
18 also the gestational age which wasn't clear in what they
19 were originally bringing forth to the FDA. But I feel that
20 we have to look at the study that was performed with the
21 objectives of the study that was performed.

22 DR. PETITTI: Dr. Azziz, you had a comment.

23 DR. AZZIZ: Just to remind us, the original
24 ritodrine approval was actually only approved after there
25 was the indication of long-term benefits to the fetus. The

1 fact that later on in the marketplace further studies
2 indicated that that wasn't so doesn't necessarily negate
3 the reasoning of the committee at that time. Am I correct?
4 It seems all of a sudden that we're starting to say that 48
5 hours was the gold standard, when in fact I don't think, at
6 least for ritodrine, that wasn't the case.

7 DR. RARICK: Correct. The original assumption
8 at the 48 hours, that improvement was going to make a
9 neonatal benefit. The agency went back to review the
10 neonatal outcome information to make sure of at least a
11 sign and trend of neonatal improvement. It is true that
12 subsequently studies have been published that don't show
13 that, and maybe we should bring that back to the committee.

14 (Laughter.)

15 DR. PETITTI: Yes, Dr. Lockwood.

16 DR. LOCKWOOD: Can I maybe move this along,
17 because my bladder is very full.

18 (Laughter.)

19 DR. LOCKWOOD: May I propose a question to vote
20 on, and then we can use the criteria of Dr. D'Agostino's
21 from a statistical standpoint, and those of us who are more
22 biologically oriented from a biological standpoint to
23 answer it. But the question would then be, "Do the data
24 establish the effectiveness of atosiban for the acute
25 treatment of preterm labor for up to 48 hours in patients

1 greater than 28 weeks gestation?" Would that work?

2 DR. PETITTI: I think it then dictates the
3 answer.

4 DR. LOCKWOOD: That's the point.

5 DR. AZZIZ: Wait a minute. I'm not sure that
6 it dictates the answer necessarily, but why can't we just
7 do two questions? One is the preterm labor, and the other
8 one is as requested by the sponsor.

9 DR. PETITTI: I think we're also looking to the
10 third question. Taking into consideration the overall
11 risks and benefits, do we recommend the drug be approved
12 for treatment for preterm labor? So I could live with this
13 reformulation of the first question into two sub-parts
14 being, do the data presented today establish the
15 effectiveness of atosiban for preterm labor, for acute
16 treatment of preterm labor in -- what did you say?
17 Gestation of 28 weeks --

18 DR. LOCKWOOD: Do the data establish the
19 effectiveness of atosiban for the acute treatment of
20 preterm labor for up to 48 hours -- taken right out of
21 their indication -- in patients greater than 28 weeks
22 gestation?

23 DR. PETITTI: And could we have a parallel
24 question? Do the data establish the effectiveness of
25 atosiban for the same thing in patients less than 28 weeks

1 gestation?

2 DR. AZZIZ: How about just overall?

3 DR. PETITTI: No. I would prefer to actually
4 not have the overall, because the overall is driven by the
5 numbers in the larger group.

6 DR. LOCKWOOD: Okay. Same question, less than
7 28 weeks, or in preterm patients.

8 DR. AZZIZ: I think it's getting almost as
9 confusing as the data presented by the sponsor.

10 (Laughter.)

11 DR. AZZIZ: What is useful here? First we have
12 to vote on the indication requested by the sponsor. Then
13 we can do lots of things.

14 DR. PETITTI: Dr. Bilstad, can you clarify
15 this?

16 DR. BILSTAD: Again, I want to emphasize that
17 if you separate out and vote on the 28-week greater than or
18 less than, you've got to keep in mind that the design of
19 the studies and the analyses that were done to get to the
20 evidence that supports the greater-than-28-week gestational
21 period efficacy, that's a very key factor and I don't want
22 you to lose that perspective when you separate out and just
23 look at the 28 weeks. You need to take into consideration
24 the studies that were done, the study design, and the
25 analyses that were necessary to get to the point of

1 supporting or whatever you choose, demonstrating
2 effectiveness for that subgroup.

3 DR. LOCKWOOD: We can vote no for this
4 question. I'm not wording the question for --

5 DR. PETITTI: Dr. D'Agostino, do you have one
6 final comment?

7 DR. D'AGOSTINO: It's exactly the comment that
8 was just made, that whatever we vote for, we have to
9 remember how the data gets us there.

10 DR. PETITTI: And that a vote for no could even
11 be because you don't like the way we got there or because
12 you don't believe the data provides support.

13 With that clarification, the final reading of
14 the question is -- it's a two-part question. Do the data
15 presented today establish the effectiveness of atosiban for
16 the acute treatment of preterm labor for up to 48 hours in
17 patients who are at least 28 weeks gestation? And the
18 second question is exactly the same question except it
19 would be for up to 48 hours in patients who are less than
20 28 weeks gestation.

21 Now, I want to clarify again that, taking into
22 account the FDA and Dr. D'Agostino's comments, a no vote on
23 either question could be either because it's no to the data
24 or no to the way in which these data are used to attempt to
25 establish this issue.

1 Are we ready to vote? I would like to clarify
2 that the voting members of the committee are Dr. Hammond,
3 Dr. Lewis, Dr. Greene, Dr. Azziz, myself, Dr. D'Agostino,
4 Dr. Lockwood, Dr. Narrigan, and Dr. Harris. And Dr. Scott.
5 I just skipped over this -- Julia Scott, right.

6 How many vote yes? Do the data presented today
7 establish the effectiveness of atosiban for the acute
8 treatment for up to 48 hours in patients who are at least
9 28 weeks gestation?

10 Yes votes?

11 (Show of hands.)

12 DR. PETITTI: One yes vote, two yes votes.

13 Please hold your hands high.

14 No?

15 (Show of hands.)

16 DR. PETITTI: No abstentions?

17 (No response.)

18 DR. PETITTI: For the second question, do the
19 data presented --

20 DR. D'AGOSTINO: Could you say what the vote
21 was?

22 DR. PETITTI: The vote was 10 to 3.

23 MS. TOPPER: Two yes, 10 no -- 9 no.

24 DR. PETITTI: Two yes and 9 no. Thank you.

25 DR. D'AGOSTINO: Thank you.

1 DR. PETITTI: For the second question: Do the
2 data presented today establish the effectiveness of
3 atosiban in infants with a gestational age less than 28
4 weeks?

5 Yes votes, same question, less than 28 weeks.

6 (No response.)

7 DR. PETITTI: No yes votes.

8 No votes?

9 (Show of hands.)

10 DR. PETITTI: So the committee is unanimous.

11 No votes are 11.

12 Question 2. Do the data presented today
13 establish the safety of atosiban for treatment for preterm
14 labor? I would like to suggest here that there are two
15 safety issues. There's a maternal safety issue and a fetal
16 safety issue. Would we agree for the mother? That would
17 be the first sub-question.

18 DR. NARRIGAN: Are you combining fetus-neonate?

19 DR. PETITTI: Fetus-neonate.

20 DR. GREENE: Are you doing the mother first?

21 DR. PETITTI: Mother first. Are we ready to
22 vote on that question?

23 DR. NARRIGAN: What about by gestational age?
24 Are you going to break that down?

25 DR. PETITTI: For the mother I think we don't

1 need to break -- I mean, I would say that most people would
2 probably agree we don't need to break that down for the
3 mother.

4 Do the data establish the safety of atosiban as
5 a treatment for preterm -- safety for the mother as a
6 treatment for preterm labor? This is for all gestational
7 ages.

8 Ready for a vote? Hands held high, yes votes.
9 (Show of hands.)

10 DR. PETITTI: Eleven. The vote again is
11 unanimous, 11 votes yes.

12 Now, the second question relates to safety for
13 the fetus. Do the data presented today establish the
14 safety for the fetus as a treatment for preterm labor for
15 fetuses 28 weeks or more gestation? Fetus and neonate.
16 I'm sorry.

17 Are we ready to vote, or is there more comment
18 on this?

19 Votes yes, establish the safety for at least 28
20 weeks for the fetus and neonate. Hold your hands high.

21 (Show of hands.)

22 DR. PETITTI: Four.

23 No?

24 (Show of hands.)

25 DR. PETITTI: Five. Dr. Harris is going to

1 vote no, and there is one abstention. That final vote was
2 4 yes, 6 no, 1 abstention.

3 Less than 28 weeks, do the data presented today
4 establish the safety of atosiban for the fetus as a
5 treatment for preterm labor? Fetus and neonate at
6 gestations less than 28 weeks.

7 How many yes votes? This is for safety to the
8 fetus at less than 28 weeks. How many yes votes?

9 (No response.)

10 DR. PETITTI: Zero.

11 How many no votes?

12 (Show of hands.)

13 DR. PETITTI: Eleven, a unanimous no.

14 The third question. Taking into consideration
15 the overall benefits and risks of atosiban, do you
16 recommend that this drug be approved as a treatment for
17 preterm labor?

18 DR. AZZIZ: As requested?

19 DR. PETITTI: I actually am not sure we need to
20 break it down.

21 Lisa, you had a comment?

22 DR. RARICK: It can be as proposed.

23 DR. PETITTI: As proposed. Are we ready to
24 vote?

25 DR. NARRIGAN: As proposed by whom?

1 DR. PETITTI: As proposed by the sponsor most
2 recently, 48 hours, at least 28 weeks.

3 Yes?

4 (Show of hands.)

5 DR. PETITTI: One vote.

6 No?

7 (Show of hands.)

8 DR. PETITTI: Ten. The vote is 10 to 1, 1 yes,
9 10 no.

10 Oh, you didn't vote? That's an abstention.

11 Question 4. Should additional studies of
12 atosiban be conducted? If so, what specific types and in
13 what population?

14 First of all, should additional studies of
15 atosiban be conducted?

16 DR. AZZIZ: I think that's a decision of the
17 sponsor.

18 DR. PETITTI: Well, we're making a
19 recommendation from this advisory committee. We have to
20 take a vote.

21 Yes? Raise your hands.

22 (Show of hands.)

23 DR. PETITTI: I think this is a very promising
24 drug, and I think that personally, speaking with the
25 chair's prerogative since I don't have to do this anymore,

1 that it would be a shame if this were abandoned because of
2 discouragement about this particular set of data in this
3 study.

4 If so, what kinds of studies? What specific
5 types, and in what populations?

6 DR. GREENE: I would just like to request a
7 study be done that specifically looks at their proposed
8 indication as their primary study, look at it in babies
9 greater than 28 weeks to see if it does improve the
10 outcome, improve the percentage of babies that receive
11 steroids, improve the number of babies that get to tertiary
12 care facilities, just strictly address their own requested
13 indication for use.

14 DR. LOCKWOOD: But that's not their indication.
15 It's just that it will prolong gestation for more than 48
16 hours. That's it.

17 DR. GREENE: But they say in order to receive
18 steroids, and it would be nice if there was some reduction
19 of respiratory distress syndrome. You don't need enormous
20 numbers to do that. It's not like intracranial hemorrhage.

21 DR. AZZIZ: Certainly I think we request that
22 they do a study targeted for their indication, and that
23 they routinely use corticosteroids in their treatment as
24 part of protocol since that is the reason for this 48-hour
25 window, and that they monitor fetal outcome much more

1 carefully in terms of neonatal use of surfactant and so on
2 and so forth. So obviously targeted to the questions we
3 want answered.

4 DR. PETITTI: Dr. Dattel, then Dr. Harris, then
5 Dr. D'Agostino.

6 DR. DATTEL: I think, of course, that this
7 needs to be studied further in the greater-than-28 group,
8 and I would be certain that there are adequate controls and
9 stratification for gestational age and not just randomizing
10 people so that we don't have the same problem occur again.
11 And I would even do a separate study for multiple
12 gestation, which is something that appears to be one of the
13 indications for use, and leave that out of the main study
14 or control for that in a different way.

15 I'd also re-explore the issue of safety and
16 efficacy in under 28 weeks because, as Dr. Van Marter
17 stated, once it's approved, it will be used for that
18 gestational age, and it's better to know the problems so
19 that there's informed consent of consumers with that.

20 DR. PETITTI: Dr. Harris.

21 DR. HARRIS: I think there were questions about
22 the uniformity of the diagnosis of preterm labor, and they
23 may want to revisit that, with perhaps an emphasis on
24 cervical change and the frequency of contractions in any
25 given interval.

1 DR. PETITTI: Thank you.

2 Dr. D'Agostino?

3 DR. D'AGOSTINO: I'm not clear in the way we're
4 making the recommendations. There is an indication and
5 they have a study which is sort of supportive, and now
6 we're asking them to confirm it. What I'm not clear on is
7 what are the implications for the child. I mean, we've had
8 a lot of discussion about how important it was to see some
9 outcome on the child, and now are we only saying that
10 that's somehow or another a safety tally that we do, or are
11 we saying it's part of the study?

12 DR. PETITTI: Well, I think if you look at our
13 very last question, it's perhaps one of the most important
14 questions of this advisory group in terms of giving advice
15 to the FDA, which is, what should be the endpoint in any
16 further study that was done of this topic, and I think this
17 goes beyond this particular drug and new tocolytics but to
18 other devices and procedures that are used to intervene for
19 preterm labor.

20 Having said that, Dr. Azziz?

21 DR. AZZIZ: I just wanted to repeat. There is
22 some fetal sheep data that is in process that will help
23 interpret some of the safety data. Clearly, that should be
24 completed.

25 DR. PETITTI: This is back to the Question 4.

1 Are there other comments, or can we move on to
2 this very critical discussion question, which is advice
3 from this committee about having looked at these data and
4 other data about what are the reasonable and appropriate
5 endpoints, and I guess appropriate endpoints is really the
6 key here, for approval of studies of new tocolytic agents?
7 This is, I guess, an open discussion, with Kim taking some
8 fairly good notes.

9 DR. HAMMOND: Well, I have a question. Not
10 being a maternal-fetal specialist, have maternal-fetal
11 specialists given up on the concept of curing premature
12 labor? It's not likely. In other words, are we looking
13 for a cure, or are we looking for just a delay? I think
14 that's the first question.

15 DR. PETITTI: Does anyone around the table want
16 to comment?

17 I have a question which is a related question,
18 which is, is it really possible to study an unbundled
19 intervention? In other words, as I see it, we're studying
20 almost -- it's almost getting closer to an effectiveness
21 kind of approach than an efficacy approach, where you're
22 looking at the combination of an intervention to delay
23 birth combined with a set of interventions which are meant
24 to promote optimized fetal outcome. I would wonder if you
25 could ever say that the drug per se did anything if you

1 have a combination of the drug plus optimal fetal outcome.

2 Dr. Azziz?

3 DR. AZZIZ: I think that comes up to the
4 question of endpoints. If the treatment is optimum and the
5 only difference between one treatment and another is the
6 lack of or the addition of drug, then obviously you still
7 can, even in a complex situation where multiple things are
8 being done to the patient, you still can determine whether
9 the addition of that drug improves significantly, and
10 clinically significantly, the outcome. So that comes back
11 to the issue of is just a surrogate endpoint of 48 hours
12 improvement enough to say that this drug is good?

13 Of course, we're all reminded of DES, we're
14 reminded of the fluoride story where bone mass got better
15 but fractures did not. My feeling, and I'd like to see if
16 the committee goes along with this, is that I still think
17 we should recommend to manufacturers that they do prove
18 some improvement in fetal outcome. If there isn't some
19 improvement, some decrease in RDS or decrease in deaths or
20 IVHs, then the drug only prolongs something theoretically
21 but doesn't have any benefit, and that is a major issue
22 today, both economically and otherwise.

23 So I'm making that recommendation, that that
24 endpoint be included. Otherwise, we're simply approving
25 drugs that are toys.

1 DR. LOCKWOOD: The problem with that is that
2 those criteria are so stringent. Now, there may be a day
3 when we have very specific agents that really do make a
4 difference. But, first of all, many of these fetuses are
5 stressed or are infected, are having abruptions, and may be
6 better off being delivered. I don't think that that's an
7 endpoint that is fair to ask any manufacturer to be held
8 to. Number one, it will stop all research in this country
9 on tocolytics. We're lucky enough to get this company to
10 have spent the amount of money they've spent to do what
11 they've done. If we hold them to a standard that can't
12 possibly be reached, certainly in the next 25 years, then
13 we'll have absolutely no research being done by U.S.
14 companies in this area.

15 I think that it is reasonable and fair to ask
16 them to demonstrate vis-a-vis the currently used tocolytic
17 therapies, primarily magnesium sulfate and/or beta-
18 mimetics, that they have comparable or better efficacy in
19 delaying deliveries for 48 hours. Stick to their
20 indication. But the minute you begin to go down the
21 slippery slope of tying this to outcome -- first of all, we
22 need to define outcome. Is a retinopathy? Is cerebral
23 palsy? Is bronchopulmonary dysplasia? It ain't gonna be
24 perinatal mortality because you'd need 30,000 patients in
25 each group.

1 I think it becomes just inexorably complex to
2 do. I think that a reasonable criteria -- and this is
3 obviously my opinion -- is to hold them to current
4 standards, which is prolonging pregnancy for 48 hours to
5 allow the administration of glucocorticoid therapy, and it
6 should obviously be proven to be more efficacious than the
7 drugs we're using currently, mag sulfate or beta-mimetics.

8 DR. AZZIZ: I hate to disagree, but the
9 slippery slope is that of the approval of drugs that have
10 now been on the market for 25 years that are worth mare's
11 urine. I have no product in mind, by the way.

12 (Laughter.)

13 DR. AZZIZ: But truly, we have products out
14 there that have never been tested rigorously, and we are
15 allowing them. Then it's a slippery slope, so I disagree.
16 If we are going to use corticosteroids and we are going to
17 use a drug that works, we should have some improvement in
18 outcome. Now, I am certainly not going to recommend what
19 outcome in fetal improvement will be tested, but you have
20 to have some benefit, because otherwise what you're not
21 testing for is a drug which is actually detrimental.

22 So if you use steroids and they improve fetal
23 outcome, and then the drug that you're testing worsens
24 fetal outcome, and then it's a wash in the end and you have
25 basically the same kind of outcome, that is not helpful.

1 So I don't agree that we should allow ourselves to be lax
2 and say, well, nobody is going to invest money into this,
3 because it doesn't take that much to demonstrate some
4 improvement and benefit. We're not saying mortality here.
5 We're saying some improvement in RDS incidence, whatever
6 you want to call it.

7 DR. LOCKWOOD: I disagree.

8 DR. PETITTI: Dr. Harris?

9 DR. HARRIS: I think Dr. Petitti asked a
10 different question, really, which is the treatment or the
11 diagnosis of preterm labor. Since we've acknowledged that
12 it is multifactorial, that's where the real issue is in
13 deciding how to target it. We've made the assumption that
14 there's some common pathway for all of these factors that
15 either mag sulfate or atosiban or a beta-mimetic responds
16 to, and what we're finding is that's not the case. So
17 before we start talking about outcomes, we need to talk
18 about mechanisms and get some more of the basic work, like
19 Peter Nathaniels and some others have been doing, to try to
20 answer this question, what is it that triggers this whole
21 process. It's really a reproductive endocrine question,
22 not a maternal-fetal question.

23 DR. PETITTI: I have the sense that we're not
24 going to come up with the exact answer, and that there is
25 some amount, obviously, of controversy among committee

1 members. I think that ideally, if money were no object and
2 one could do a study that would definitively evaluate hard
3 fetal outcomes, and I would consider RDS a hard fetal
4 outcome, it would be hard to argue against a study that
5 would look at fetal outcomes. Then I think the question
6 becomes almost what other outcomes might be acceptable
7 outcomes if, in fact, the definitive study that everyone
8 would love to see, the intergalactic study with the
9 outcome, can't be done for reasons either of practicality
10 or cost.

11 But again, I think that the sense of the
12 committee is that this is a discussion which maybe hasn't
13 occurred at the FDA previous to this and that it is a
14 legitimate question and one where we would like to see
15 further discussion and I think come into the 20th Century
16 -- the 21st Century. I'm going backwards.

17 (Laughter.)

18 DR. PETITTI: Lisa, does that help? Is there
19 something more that we can do?

20 DR. RARICK: Is that your answer to the
21 question?

22 DR. PETITTI: What are the appropriate
23 endpoints?

24 DR. RARICK: Yes. Are you saying you're
25 putting it back in our laps to work with sponsors as to

1 what are the appropriate endpoints?

2 DR. AZZIZ: I would like to propose that the
3 endpoint still be some improvement in fetal outcome, and we
4 can decide later what improved fetal outcome is, but some
5 improvement. I'd like to see if any other committee
6 members are in agreement or disagreement with that.

7 DR. PETITTI: Lisa, what I would question is,
8 could anyone disagree that mortality is an appropriate
9 outcome? That RDS is an appropriate outcome? So the
10 question is, are outcomes more upstream from those outcomes
11 appropriate outcomes?

12 DR. RARICK: Correct, and if there's a
13 surrogate that can be used to declare those outcomes. We
14 believe there is such a thing.

15 DR. PETITTI: Right. Would anyone disagree
16 that, let's say, mortality and RDS are appropriate
17 outcomes, fetal outcomes? If somebody came in with that,
18 would you argue with it? I mean, could anyone argue with
19 that as an outcome?

20 DR. LOCKWOOD: We'd love them, but they might
21 not do the study for fear of wasting \$8 million.

22 DR. AZZIZ: How about RDS? Let me just ask a
23 question. Is the prevalence of RDS in those infants enough
24 to allow us to create a study with sufficient power within
25 a reasonable amount of time? RDS, not mortality.

1 DR. DATTEL: What about severity of RDS?

2 DR. AZZIZ: Or severity of RDS.

3 DR. DATTEL: There are some problems with the
4 diagnosis in that you're more likely to look at something
5 like neonatal length of stay as a marker, a surrogate
6 marker for how severe the neonatal course was, because
7 there's an issue of is this streptococcal pneumonia, is
8 this RDS -- I don't know. You guys are the neonatologists.
9 But to me, whenever I'm looking at those things, neonatal
10 length of stay as a surrogate marker -- in fact, that's
11 brought out in some of the information and data in here in
12 terms of it being a difficult diagnosis to be uniform on
13 for the neonatologists, just like preterm labor is a very
14 difficult diagnosis for perinatologists to agree on. Am I
15 wrong on this?

16 DR. PETITTI: Dr. Greene, you had a comment and
17 you haven't spoken.

18 DR. GREENE: I don't think anyone wants to
19 raise the bar beyond which anyone could reasonably be
20 expected to jump. That's not in anybody's best interest.
21 I'm also sensitive and feel badly that I wouldn't want, in
22 this particular case, the sponsor to feel as though the
23 goal posts are being moved in the middle of the game, and I
24 feel badly about that as well.

25 However, we do have some history that we can't

1 ignore which is very relevant in the area of perinatal
2 medicine. As I was discussing with you at the break a
3 little earlier, some months ago I was involved in a
4 discussion with some other members of the FDA, and a group
5 of maternal-fetal medicine physicians were castigating
6 these FDA representatives who were from the devices
7 division for the original home uterine activity monitoring
8 as the result of the ultimate thing that didn't seem to be
9 very helpful or improve perinatal outcome.

10 The representatives of the FDA turned it back
11 to the maternal-fetal medicine people in the crowd and said
12 that they only followed the advice they were given by their
13 consultants. If we felt as though they were given bad
14 advice by their consultants, we ought to look in the
15 mirror.

16 So, given that as being our history, here's our
17 chance to give some advice to the FDA as to what we think
18 are appropriate endpoints, and as Dr. D'Agostino said quite
19 rightfully, there was some greater faith 10 or 20 years ago
20 in surrogate endpoints. I think as surrogate endpoints
21 have failed us ultimately in improving perinatal outcome,
22 we're somewhat more hard-nosed about wanting to see real
23 outcome data rather than surrogates.

24 I think that perinatal mortality is an
25 unrealistic bar given the incidence of perinatal mortality

1 in 1998, and I certainly would not ask for that level of
2 proof. But I do not think it's unreasonable to ask for
3 some evidence of improved perinatal outcome.

4 DR. PETITTI: Do we agree on that point?

5 PARTICIPANT: Yes.

6 PARTICIPANT: Yes.

7 DR. PETITTI: Is there anything more that we
8 need to say on this issue?

9 DR. NARRIGAN: I would like to suggest that
10 hopefully in the next few weeks there would be some way of
11 understanding better fetal tolerance for the actual drug
12 that's being given to it. I don't know what I mean by
13 that, but what effect is it actually having on fetal
14 physiology? Maybe that will become something that is
15 studyable, or it's becoming more possible to study it.

16 Also, we haven't really talked about long-term
17 effects on the infant exposed to this drug. I don't
18 understand its biology very well. Its half-life is short,
19 I assume, and maybe there aren't any, but I would suggest
20 that that would be something clearly that would be
21 reasonable to look at.

22 DR. PETITTI: One final comment.

23 Dr. Van Marter?

24 DR. VAN MARTER: I just wanted to say as a
25 neonatologist, my earlier concerns were raised mostly out

1 of interest in establishing safety for the newborn apart
2 from the efficacy question in terms of demonstrating a
3 definite neonatal or fetal benefit. I wanted to raise the
4 possibility that we think along the lines of not raising
5 the bar too high, as Dr. Greene mentioned. Maybe we could
6 think creatively about a composite outcome, and especially
7 about establishing comparability between groups, which I
8 think would be accomplished much better with a logged
9 randomization strategy or really careful thought about how
10 we're enrolling patients in the study.

11 DR. PETITTI: I would like to thank all the
12 members of the committee. I'd like to thank the sponsor
13 for their excellent presentation. I know there is
14 disappointment that the committee came up perhaps with a no
15 answer, and I hope that this does not discourage work on
16 what is obviously a very promising drug in an important
17 area.

18 I'm saying goodbye to everybody.

19 DR. RARICK: Thank you, Dr. Petitti.

20 (Applause.)

21 DR. DUNTON: Dr. Petitti, on behalf of the
22 sponsor, I would just like to thank you, and the committee
23 as well, for your deliberations. I know they were
24 difficult discussions, so thank you very much.

25 DR. RARICK: And thank you all very much,

1 of interest in establishing safety for the newborn apart
2 from the efficacy question in terms of demonstrating a
3 definite neonatal or fetal benefit. I wanted to raise the
4 possibility that we think along the lines of not raising
5 the bar too high, as Dr. Greene mentioned. Maybe we could
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15 answer, and I hope that this does not discourage work on
16 what is obviously a very promising drug in an important
17 area.

18 I'm saying goodbye to everybody.

19 DR. RARICK: Thank you, Dr. Petitti.

20 (Applause.)

21 DR. DUNTON: Dr. Petitti, on behalf of the
22 sponsor, I would just like to thank you, and the committee
23 as well, for your deliberations. I know they were
24 difficult discussions, so thank you very much.

25 DR. RARICK: And thank you all very much,

1 committee members.

2 (Whereupon, at 4:20 p.m., the meeting was
3 adjourned.)

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