

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF
THE PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

8:02 a.m.

Monday, December 15, 1997

Embassy Ballroom
Ramada Inn
8400 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

NDA 20-793, Cafcit (caffeine citrate injection)
for Intravenous or Oral Use in the Treatment of
Apnea of Prematurity

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DR. LI: Good morning, ladies and gentlemen. My name is James Li. I'm the Chair of today's Pulmonary Allergy Drug Advisory Committee, and welcome to everybody here. Thank you for coming.

I would like to start by having the panelists and the committee members introduce themselves. I'm an allergist at the Mayo Clinic. I've been on the committee for about three or four years.

Perhaps we could go around the table and have each individual just introduce themselves and where they are from, perhaps what their specialty is.

DR. GOLDSMITH: I'm Jay Goldsmith from the Ochsner Clinic in New Orleans. I'm a neonatologist.

MS. CONNER: Good morning. I'm Brenda Conner. I'm a nurse with 20 years pediatric asthma and allergy experience. I'm from Atlanta, Georgia. I'm the consumer representative to the committee.

DR. SESSLER: Good morning, I'm Curt Sessler. I'm an adult pulmonary and critical care specialist at the Medical College of Virginia, at Virginia Commonwealth University in Richmond.

DR. CROSS: I'm Carroll Cross, University of California, Davis, adult pulmonologist-intensivist.

1 DR. SZEFLER: I'm Stan Szeffler from Denver,
2 Colorado, Director of Clinical Pharmacology at the National
3 Jewish Medical and Research Center.

4 DR. CHINCHILLI: Vern Chinchilli,
5 biostatistics, Penn State, Hershey Medical Center.

6 DR. ROTHSTEIN: Peter Rothstein, Columbia
7 Presbyterian Medical Center, Babies and Children's
8 Hospital. I'm a pediatric anesthesiologist and was a
9 neonatologist in my previous life.

10 MR. MADOO: Leander Madoo, FDA, by way of Yale
11 University.

12 DR. OSBORNE: Molly Osborne, pulmonary and
13 critical care, Oregon Health Sciences University, in
14 Portland.

15 DR. JENNE: John Jenne, adult pulmonary
16 medicine, formerly Hines VA in Loyola, Chicago.

17 DR. JOBE: Alan Jobe. I'm a neonatologist and
18 I'm from Cincinnati Children's Hospital.

19 DR. KELLY: Bill Kelly from the University of
20 New Mexico Health Sciences Center. I'm pediatric pulmonary
21 and critical care.

22 DR. HENDELES: Leslie Hendeles, University of
23 Florida. I'm a clinical pharmacist in the pediatric
24 pulmonary division.

1 DR. HIMMEL: Marty Himmel. I'm Deputy Division
2 Director of the Division of Pulmonary Drugs.

3 DR. PINA: Miriam Pina, medical reviewer,
4 Division of Pulmonary Drug Products.

5 DR. JENKINS: I'm John Jenkins. I'm the
6 Director of the Division of Pulmonary Drug Products, FDA.

7 DR. BILSTAD: Jim Bilstad, Office of Drug
8 Evaluation II.

9 DR. LI: Thank you. Dr. Jenkins, would you or
10 any of the members of the FDA like to make some
11 introductory comments?

12 DR. JENKINS: Thank you, Dr. Li. I'd first
13 like to just start by thanking the members of the advisory
14 committee, the sponsor, my FDA colleagues, and the members
15 of the audience for attending today's meeting, which should
16 be very interesting.

17 First I'd like to make several acknowledgments
18 for members of the panel, to make it known what their new
19 positions may be or to acknowledge their presence.

20 First I'd like to thank you, Dr. Li, for
21 agreeing to serve as chair of the advisory committee for
22 the remainder of your term. We look forward to working
23 with you on the issues that come to the committee over the
24 next six to seven months.

1 We also have a couple of members joining us
2 today as consultants who will be official committee members
3 as soon as the paperwork is finalized. First is Brenda
4 Conner. She's is currently the acting consumer
5 representative, but will be in that position permanently
6 soon, we hope. Also Dr. Bill Kelly from University of New
7 Mexico will be joining us on the committee as well. We
8 look forward to working with you over the next several
9 years as you continue your service on the committee.

10 Finally, given the nature of today's topic, we
11 have asked several consultants to join the committee to
12 bring their unique expertise to this issue. First, Dr.
13 Jobe, who is a former member of our advisory committee who
14 is joining us, as well as Dr. Goldsmith and Dr. Rothstein.
15 We appreciate your willingness to review the materials and
16 join us today in our discussion. And also Dr. Les
17 Hendeles, who is also a former member of our advisory
18 committee. Thanks, Les, for agreeing to attend today also.

19 I think today's meeting will be very
20 interesting. It is an indication for which this committee,
21 to my knowledge, has never had an advisory committee
22 discussion, that being apnea of prematurity. It is also a
23 unique situation for our committee because I don't recall
24 in the last several years a situation where the drug

1 product being brought before the committee was one for
2 which we have essentially one adequate and well-controlled
3 study prepared by the sponsor, as well as numerous reports
4 from the literature, and the widespread common use of ad
5 hoc compounded versions of caffeine citrate for this
6 indication.

7 So, we look forward to the committee's
8 discussion of this new indication and also this new type of
9 data set. Thanks.

10 DR. LI: Thanks, John. Next Mr. Madoo will
11 read the conflict of interest statement.

12 MR. MADOO: Yes, and I also have some general
13 announcements. The committee will see in front of them
14 desk copies of today's slide presentations. The black
15 folder pertains to the sponsor, Roxane's presentation.
16 Feel free to take any notation you require on these. Then
17 we have FDA's slide presentation, Dr. Pina's presentation,
18 and that's clipped here.

19 Also I would like to reiterate that Brenda
20 Conner and Dr. Kelly will shortly be on board. In fact, I
21 think their formal appointment is in fact signed off and it
22 is just a formality and they will be with us very shortly
23 as full-fledged members.

24 I'd also like to note that all of our invited

1 consultants have been granted, from Dr. Woodcock, voting
2 status at this meeting, so everyone around the table will
3 be in a voting mode.

4 Let me proceed on to the conflict of interest
5 statement.

6 The following announcement addresses the
7 conflict of interest with regard to this meeting and is
8 made part of the record to preclude even the appearance of
9 such at this meeting.

10 Based on the submitted agenda and the
11 information provided by the participants, the agency has
12 determined that all reported interests in firms regulated
13 by the Center for Drug Evaluation and Research present no
14 potential for a conflict of interest at this meeting.

15 In the event the discussions involve any other
16 products or firms not already on the agenda for which an
17 FDA participant has a financial interest, the participants
18 are aware of the need to exclude themselves from such
19 involvement, and their exclusion will be noted for the
20 record.

21 With respect to all other participants, we ask
22 in the interest of fairness that they address any current
23 or previous financial involvements with any firms whose
24 products they may wish to comment upon.

1 Thank you.

2 Dr. Li?

3 DR. LI: Thank you, Mr. Madoo. We will move on
4 to the open public hearing phase of today's meeting. My
5 understanding, Mr. Madoo, is that we have not heard from
6 anyone who requested time to speak to us this morning.

7 MR. MADOO: That is correct, Dr. Li. No one
8 has contacted us prior to the meeting. Of course, anyone
9 in the audience who has comments germane to the issue at
10 hand can feel free to approach the mike in the audience
11 area.

12 DR. LI: Is there anyone in the audience who
13 would like to address the committee?

14 Hearing none, we will proceed to the sponsor's
15 presentation from Roxane Laboratories, and we look forward
16 to hearing the sponsor's presentation. I would ask the
17 speakers to help us keep on schedule.

18 MR. READE: Good morning. Welcome to O.P.R.
19 Development's presentation of Cafcit for the treatment of
20 apnea of prematurity to the Pulmonary Allergy Drug Products
21 advisory committee meeting. My name is Sean Alan Reade.
22 I'm Director of Regulatory Affairs and I will introduce
23 this session and tell you a little bit about the chronology
24 of how we got here.

1 I will be followed by five speakers on this
2 morning's program. Dr. Kirk Shepard will present the
3 history of caffeine development. Dr. Allen Erenberg will
4 talk about apnea of prematurity. Dr. Kristen Mosdell will
5 present an overview of literature base for caffeine's
6 efficacy and safety. Dr. Beverly Wynne, assisted by Dr.
7 Dennis Haack, will present the clinical data for Cafcit.

8 On September 20th, 1988, Pediatric
9 Pharmaceuticals, Inc. was granted orphan drug designation
10 for caffeine citrate for the treatment of apnea of
11 prematurity.

12 On 3 December 1991, the ownership of the
13 product and the IND was transferred to Oread Laboratories.

14 On the 23rd of February, 1993, the ownership
15 and the IND was transferred once again to O.P.R.
16 Development, L.P. This partnership includes Pediatric
17 Pharmaceuticals, NAIAD for Oread Holding, and Roxitrate for
18 Roxane Laboratories. From this you can see how the acronym
19 O.P.R. was derived.

20 On 28 December, 1996, Roxane Laboratories was
21 appointed as the U.S. agent for Cafcit by O.P.R.
22 Development.

23 We pre-submitted the CMC section of the NDA 6
24 January of this year. We submitted the NDA 22 August. It

1 was logged in on 25 August, and after accelerated review we
2 are here today, 15 December, for the PADAC meeting.

3 The next speaker will be Kirk Shepard. He'll
4 will present the history of caffeine development. Dr.
5 Shepard is Senior Vice President of Medical Affairs,
6 Marketing and Product Development for Roxane Laboratories.
7 He is an integral piece of our active R&D program at
8 Roxane. He is also an assistant clinical professor of
9 medicine at the Ohio State University Comprehensive Cancer
10 Center, where he is a board certified hematologist and
11 oncologist. Dr. Shepard?

12 DR. SHEPARD: Thank you, Sean. Good morning.

13 Regarding the history, in 1985 the FDA
14 contracted the University of Iowa to perform a literature
15 search and review and provide a summary of published data
16 concerning the use of selected drugs used to treat
17 newborns. Caffeine was one of the seven drugs selected for
18 review.

19 The completed FDA contract report was submitted
20 to the agency in April of 1986 and indicated that caffeine
21 was being used to treat apnea of prematurity and concluded
22 that the literature provided persuasive evidence of
23 caffeine's effectiveness.

24 The report also cited that theophylline was

1 used and was useful for treating apnea of prematurity, but
2 indicated that caffeine was the drug of choice to treat
3 apnea of prematurity, based on the following features of
4 the drug: caffeine's larger therapeutic index, once-daily
5 administration, smaller fluctuations in plasma concentrates
6 due to a longer half-life, penetration into the cerebral-
7 spinal fluid, more potent central respiratory effect, and
8 fewer adverse effects.

9 The FDA contract report concluded that it would
10 be in the interest of public health to encourage an NDA for
11 caffeine for the treatment of apnea of prematurity in that
12 there was no approved indication for the use of caffeine or
13 other drugs for apnea of prematurity. There was no
14 commercially available caffeine for this indication, but
15 caffeine preparations were, and still are, prepared
16 individually by hospital pharmacies for use in the neonatal
17 intensive care units. And, three, although a volume of
18 literature exists in the use of caffeine treatment through
19 the 1970's and 1980's, there had never been a placebo-
20 controlled, double-blind clinical study completed and
21 published on the use of caffeine in apnea of prematurity.

22 Subsequent to the completion of the FDA
23 contract report, caffeine was designated as an orphan drug
24 for the treatment of apnea of prematurity. Development of

1 caffeine citrate injection was initiated and formulated by
2 Roxane Laboratories as a standardized product. A solution
3 of 10 milligrams of caffeine base per milliliter with all
4 the associated quality attributes that come only with a
5 commercially manufactured product, including sterility
6 assurance, pyrogen free and particle free control for
7 materials, with tightly controlled impurity profiles.

8 Following discussions with the FDA, a
9 double-blind, placebo-controlled study was planned,
10 supported by an extensive literature report.

11 Now I'd like to introduce Dr. Alan Erenberg,
12 who will discuss the clinical aspects of apnea of
13 prematurity. Dr. Erenberg has been Director of Neonatology
14 at the University of Iowa and Chair of Pediatrics at the
15 University of Kansas, and currently Medical Director at
16 Kern Medical Center in California.

17 DR. ERENBURG: Thank you, Kirk.

18 Apnea of prematurity is one of the most common
19 problems that is identified in the neonatal intensive care
20 unit. Apnea is defined as respiratory pauses varying
21 between 10 and 20 seconds in duration and associated with
22 bradycardia, which is defined as a heart rate of less than
23 80 beats per minute.

24 Short respiratory pauses are often associated

1 with startles, movement, defecation, or swallowing during
2 feeding in these preterm infants, but are self-limiting and
3 not associated with bradycardia.

4 Apnea of prematurity must be distinguished from
5 periodic breathing. There are three types of apnea
6 described: central, obstructive, and mixed, which has a
7 component of both central and obstructive causes. The
8 literature has noted that the more preterm the infant, the
9 greater its frequency and its occurrence.

10 The major concern as a physiologic consequence
11 of apnea is hypoxemia. Often reflux effects of these
12 apneic episodes may include hypotension, bradycardia, and
13 change in cerebral perfusion. The literature has stated
14 that apnea of prematurity will most frequently occur during
15 REM sleep. Preterm infants will spend 80 percent of their
16 day in a sleep state, of which 50 percent of that is in an
17 active state.

18 The proposed actions of methylxanthines include
19 a decreased frequency or elimination of the episodes of
20 apnea, normalization of respiratory patterns, or an altered
21 sensitivity of the medullary respiratory center to carbon
22 dioxide.

23 Apnea of prematurity is a rule-out diagnosis,
24 which requires a detailed history, a complete physical

1 examination, and laboratory tests if indicated. Once these
2 are done, the diagnosis can be made.

3 If one consults standard textbooks, one will
4 find there are various modalities advocated for treatment
5 of apnea of prematurity, including continuous positive
6 airway pressure, tactile stimulation, and although there
7 are no approved indications, pharmacologic simulations with
8 either caffeine or theophylline or aminophylline.

9 Now I would like to introduce Dr. Kristen
10 Mosdell, who was formerly the Clinical Research Manager at
11 Roxane Laboratories and now is a consultant to the company.

12 DR. MOSDELL: Good morning. The following is a
13 review of efficacy and safety data from the published
14 literature describing the use of caffeine citrate for the
15 treatment of apnea of prematurity. Studies included in
16 this review were identified through a comprehensive
17 literature search which included databases such as Medline,
18 Toxline, Excerptamedica, Biosis, and International
19 Pharmaceutical Abstracts.

20 You will see that there is a large body of
21 literature to support the efficacy and safety of caffeine
22 for the treatment of apnea of prematurity. This is
23 noteworthy, considering the fact that neither caffeine nor
24 theophylline are currently indicated for this use.

1 The literature search which we conducted
2 identified over 1,000 articles on the use of caffeine.
3 From this database we identified 22 studies which described
4 the efficacy of caffeine for the treatment of apnea of
5 prematurity. An additional five studies were submitted to
6 the FDA. However, these are not included in this table
7 because they were considered to be review articles in
8 nature.

9 All of these studies used extemporaneously
10 compounded formulations of caffeine. Controlled clinical
11 trials either compared caffeine to theophylline, of which
12 there were seven studies, or used historical or untreated
13 controls, of which there were two studies each. In
14 addition, 11 uncontrolled clinical trials were published.

15 A wide range of infants were studied. Mean
16 gestational age ranged from 24 to 33 weeks and mean birth
17 weight ranged from 0.7 to 1.89 kilograms. The duration of
18 these studies was from 24 hours to over 3 months.

19 This slide summarizes the results of these
20 efficacy studies. It's important to note that numerous
21 endpoints were used in these studies, and not all endpoints
22 were used for all studies. Therefore, it was extremely
23 difficult to identify the primary efficacy variable to use
24 for the double-blind study. Overall, the following can be

1 said about the conclusions from these articles.

2 First, both caffeine and theophylline were
3 equally efficacious in reducing the number or frequency of
4 apnea episodes compared to baseline.

5 In addition, significant decreases in the
6 following parameters were identified. First, a decrease in
7 the total number of apnea attacks. Also, a decrease in
8 apnea density, which is defined as the time spent in apnea
9 per 100 minutes of sleep.

10 Studies also demonstrated a decrease in apnea
11 index, which is defined as the average number of apnea
12 episodes per 100 minutes. Studies also showed a decrease
13 in the number of episodes of bradycardia, a decrease in
14 oxygen desaturation, decrease in pCO₂, and a decrease in
15 periodic breathing and percent periodic breathing.

16 Studies also demonstrated a significant
17 increase in respiratory rate and a normalization of
18 pneumocardiograms.

19 In summary, the following conclusions can be
20 gleaned from efficacy studies.

21 First, both caffeine and theophylline were
22 equally efficacious in reducing the efficacy or frequency
23 of apnea episodes compared to baseline.

24 Second, significant improvement was noted in

1 caffeine-treated infants when compared to untreated or
2 historical controls.

3 And last, reports from uncontrolled trials
4 indicated that caffeine was efficacious according to
5 various parameters.

6 Moving on to the safety data, this chart
7 reviews the safety studies which have been published.
8 These studies were only studies that discussed caffeine.
9 Studies that only discussed theophylline were not included
10 in this review.

11 Overall, there was a total of 41 studies
12 identified, including 887 caffeine-treated infants.
13 Sources of these data included six studies that compared
14 caffeine to theophylline, four studies that used untreated
15 or historical controls, five uncontrolled studies, one
16 clinical pharmacology study, two pharmacokinetic studies,
17 and 23 studies which discussed specific safety parameters
18 concerning the use of caffeine.

19 This next table is a further breakdown of the
20 safety data and it describes the number of subjects that
21 were exposed to caffeine and the number of studies which
22 were published by type of adverse event. It's important to
23 note that the most frequent adverse events involved the
24 central nervous system, the cardiovascular system, and the

1 gastrointestinal system.

2 Beginning with the central nervous system, the
3 most frequently reported adverse event was central nervous
4 system stimulation. This included irritability,
5 restlessness, and jitteriness. Seizures were only reported
6 following overdose, of which there was one case, or
7 following the use of caffeine for the treatment of near
8 sudden infant death syndrome, of which there were two
9 cases.

10 It's interesting to note that although this is
11 a common adverse event, some studies did not report central
12 nervous system adverse events. Data also seem to suggest
13 that tolerance to these adverse events develops over time.

14 Cardiovascular adverse events published in the
15 literature were variable but generally less than those
16 observed with theophylline, particularly tachycardia.
17 Increased left ventricular output and stroke volume was
18 observed with caffeine in some studies. It has been
19 hypothesized that methylxanthines could decrease cerebral
20 blood flow by causing hyperventilation, resulting in
21 decreased carbon dioxide tension and resulting
22 cerebrovascular vasoconstriction.

23 Cerebral blood flow could also decrease through
24 antagonism of adenosine, a compound known to be involved in

1 the regulation of cerebral vascular resistance. Studies,
2 however, have not shown caffeine to adversely affect
3 cerebral blood flow. Theophylline, on the other hand, has
4 been shown to decrease cerebral blood flow.

5 This slide reviews gastrointestinal adverse
6 events which were reported in the literature. Both
7 caffeine and theophylline were shown to increase
8 gastroesophageal reflux in infants at risk for developments
9 of sudden infant death syndrome. Gastrointestinal adverse
10 events, however, were generally less in caffeine-treated
11 compared to theophylline-treated infants. One study
12 demonstrated that mean gastric aspirate was significantly
13 higher with theophylline compared to caffeine in one study.

14 It's important to take a few minutes to discuss
15 the fourth bullet point on this slide, which is necrotizing
16 enterocolitis. Necrotizing enterocolitis is a very common
17 disorder in the preterm infant. Incidence has been
18 estimated to be up to 15 percent. The etiology of
19 necrotizing enterocolitis is currently unknown, and the
20 association of methylxanthines with enterocolitis is
21 unclear.

22 Reviewing the 41 safety studies, we found no
23 direct reports associating necrotizing enterocolitis to
24 caffeine treatment. In some of the studies which compared

1 caffeine to theophylline, necrotizing enterocolitis was
2 identified in theophylline-treated infants. An additional
3 study stated that there was no significant difference
4 between caffeine and theophylline-treated patients in the
5 incidence of necrotizing enterocolitis. However, this
6 study failed to provide the frequency of enterocolitis in
7 each of these groups.

8 Several long-term studies were published which
9 described effects after use of caffeine for the treatment
10 of apnea of prematurity. In these studies caffeine was not
11 shown to adversely affect neurological development or
12 growth parameters.

13 Some additional conclusions can be stated
14 regarding safety data in the literature. First, most of
15 the adverse events that were published were mild to
16 moderate in severity. Of the 41 studies which we reviewed,
17 only one death was reported. This death was due to
18 cytomegalic inclusion disease and occurred 30 days after
19 the last caffeine dose.

20

21

22 As previously stated, there were no long-term
23 sequelae, and caffeine appears to have a very large margin
24 of safety. In cases of overdose, caffeine levels up to 346

1 milligrams per liter have been observed without reports of
2 neurological sequelae or death.

3 Several studies have identified advantages of
4 caffeine versus theophylline for the treatment of apnea of
5 prematurity. One study demonstrated that there was a
6 faster increase in respiratory rates in caffeine-treated
7 versus theophylline-treated infants. Less cardiovascular,
8 central nervous system, and gastrointestinal adverse events
9 have been described with caffeine compared to theophylline.
10 And last, less variability in plasma caffeine
11 concentrations compared to plasma theophylline
12 concentrations have been observed.

13 In conclusion, there is a large body of
14 evidence to support the efficacy and safety of caffeine
15 citrate for the treatment of apnea of prematurity.

16 I would now like to introduce Dr. Beverly
17 Wynne, Medical Director, Medical Affairs Department at
18 Roxane Laboratories, who will discuss the double-blind
19 study OPR-001. Thank you.

20 DR. WYNNE: Thank you, Kristen.

21 Also, Dr. Dennis Haack, our consultant
22 biostatistician, is in the audience and can answer any
23 biostatistical questions.

24 OPR-001 is the one double-blind, randomized

1 placebo-controlled study that was conducted for this
2 application. Patients were randomly assigned to receive
3 caffeine citrate, or placebo, and the investigators had the
4 option of transferring these patients at any time to an
5 open-label caffeine phase.

6 According to the protocol, the efficacy was to
7 be in a 24- to 48-hour period, at least a 50 percent
8 decrease in apnea episodes. I bring that to your attention
9 because it will become very important later on. So, at
10 that point they were able to transfer the patients to open-
11 label caffeine.

12 This was a difficult study to conduct, as you
13 may well know, because caffeine and the other
14 methylxanthines have been used for the treatment of apnea
15 of prematurity for many years. So, some physicians became
16 quite nervous when they did not know whether their patient
17 was receiving caffeine or placebo.

18 The population were preterm infants, age 28 to
19 32 weeks post-conception at the time of study, and had
20 apnea of prematurity.

21 The primary objective was to determine the
22 efficacy of caffeine as compared to placebo, comparing the
23 rates of apnea episodes. Secondary objectives were to
24 determine the safety of caffeine as compared to placebo,

1 and thirdly, to obtain plasma concentrations of caffeine in
2 premature infants treated up to 12 days.

3 I'm just going to quickly review the inclusion
4 and exclusion criteria for you. The inclusion, at least 6
5 episodes of apnea in 24 hours or less, defined as cessation
6 of breathing for greater than 20 seconds, had to be
7 clinically observed and documented in the neonatal
8 intensive care unit. Post-conceptual age was between 28
9 weeks, 0 days, and 32 weeks, 6 days, and the infant had to
10 be greater than 24-hours old. There had to be of course a
11 signed, written informed consent by the parent or the
12 guardian.

13 The exclusion criteria included infants with
14 CNS disorders, primary lung disease, generalized
15 disturbances, metabolic disturbances, cardiovascular
16 abnormalities, abnormal temperature, and obstructive apnea
17 defined as visual observation of chest wall movement, with
18 presence of bradycardia, cyanosis with respiratory effort,
19 and/or airway obstruction.

20 Infants were also excluded if the blood urea
21 nitrogen was greater than 20 grams per deciliter, the serum
22 creatinine was greater than 1.5 milligrams per deciliter,
23 and after the first 48 hours of life, the urine output was
24 less than 1 milliliter per kilogram per hour.

1 Infants were excluded if their AST or ALT was
2 greater than three times the upper limit of normal, or they
3 required mechanically assisted ventilation.

4 Previous treatment with methylxanthines within
5 7 days prior to study enrollment or previous treatment with
6 H2 antagonists were also exclusionary factors.

7 Babies were excluded if they were receiving or
8 experiencing the effects of CNS active medication at the
9 time of enrollment.

10 So, I'm sure you understand with this very
11 strict criteria that we had to actually screen almost 1,000
12 babies before we were able to enroll the study population
13 that I'm going to describe.

14 Also, I would like to note at this time that
15 because this was a placebo-controlled trial, and the
16 methylxanthines have been used for many years, as you well
17 know, some institutions felt it was unethical to conduct
18 this trial. So, we doubt if it could ever be conducted
19 again, but just to give you a feeling for the difficulty.

20 This shows you the loading dose and the
21 maintenance dose, and this was based on what is in the
22 literature. Of course, this is not the only recommendation
23 but we felt it was the most frequently recommended dose.
24 The loading dose was 10 milligrams per kilogram of caffeine

1 base, or 1 milliliter per kilogram of caffeine citrate
2 solution, or placebo. This was administered intravenously
3 over a 30-minute period.

4 The maintenance dose was then followed with 2.5
5 milligrams per kilogram of caffeine base, which is .25
6 milliliters per kilogram of caffeine solution, or babies
7 received placebo. This could be administered intravenously
8 over 10 minutes or administered orally. The maintenance
9 dose was to be administered every 24 hours for the length
10 of the study.

11 For infants that were transferred to open-label
12 caffeine, they received another loading dose, again 10
13 milligrams per kilogram of caffeine base administered
14 intravenously, followed by a maintenance dose not of 2.5,
15 but it was increased to 3 milligrams per kilogram, based on
16 the fact, or the assumption I should say, that these babies
17 had failed in the double-blind phase and some of them were
18 in the caffeine arm. Again, it was administered
19 intravenously or orally every 24 hours.

20 Success for this study really reflected what is
21 primarily seen in the literature, and that is at least a 50
22 percent reduction in the number of apnea episodes from
23 baseline on days 2 through 10. Now, you'll see that
24 actually drug could be administered up to 12 days. This

1 was the fifth amendment, but only 4 patients were enrolled
2 after the fifth amendment that received drug longer than 10
3 days.

4 So, therefore, we could not actually assess
5 these after 10 days because of the small numbers. So, all
6 the data henceforth will be included from 2 to 10 days.

7 We also decided to do another very strict
8 analysis, and that is looking at the elimination of apnea
9 on days 2 through 10.

10 The study population were 87 patients, 46 of
11 whom were randomly assigned to caffeine citrate and 41 to
12 placebo. However, 2 of these 87 patients, both placebo,
13 never received drug. Therefore, our safety database is 85
14 patients, 46 of whom received caffeine citrate and 39 who
15 received placebo.

16 For the efficacy, 3 of these 85 patients were
17 excluded. They were excluded because they had less than 6
18 apnea episodes at baseline. They never should have been
19 enrolled in the study because they didn't qualify and were
20 discontinued when they were identified by this major
21 protocol violation. There was very little data that could
22 not be evaluated.

23 The baseline characteristics, you'll see sex,
24 race, mean gestational age, mean post-conceptual age, mean

1 baseline apnea episodes, and mean baseline weight. You can
2 see the values here. I would just like to draw your
3 attention to the right-hand side of the slide and you will
4 note that there are no significant differences in any of
5 these baseline parameters. So, the two groups were
6 similar. There were no significant differences between
7 caffeine and placebo in the double-blind trial at baseline.

8 We wanted to look at what was the disposition
9 of these patients. It becomes very important because as
10 you'll see, a lot of patients were discontinued from the
11 study or transferred to open-label. I think this really
12 bears special attention.

13 Of the 45 patients that were randomly assigned
14 to caffeine, 20 patients actually completed the double-
15 blind phase. Of the 37 that were assigned to placebo, 11
16 completed the double-blind phase. 14 patients in the
17 caffeine group and 16 in the placebo group were transferred
18 to open-label, and I am going to tell you a little bit more
19 about these patients in a moment.

20 Also, 10 patients and 9 patients, respectively,
21 in the caffeine and the placebo groups were permanently
22 discontinued. 1 patient in caffeine and 1 one patient in
23 the placebo also received 8 and 7 days of therapy. They
24 weren't really, according to the protocol, discontinued

1 prematurely, so we bring those as a little separate
2 category. The caffeine patient actually was transferred to
3 another hospital after 8 days of therapy as a success,
4 elimination of apnea. On the other hand, the placebo
5 patient remained in the study for 7 days and was then
6 transferred, but the patient was a failure at the time of
7 transfer.

8 Now, looking at the reasons for permanently
9 discontinuing therapy on these patients, and this is
10 presented as it was on the case report form. There were 2
11 adverse events in the caffeine, and 1 was dyspnea, the
12 second was sepsis, and 1 in the placebo, and that was
13 necrotizing enterocolitis.

14 Apnea recurrence was given as the reason for
15 permanently discontinuing 5 patients in the caffeine group
16 and 6 in the placebo group, as was investigator discretion
17 for discontinuing 2 in the caffeine group and 2 in the
18 placebo. 1 infant was transferred to a referring hospital.
19 So, there were a total of 10 patients in the caffeine group
20 and 9 in placebo that were permanently discontinued from
21 the study.

22 I'd like to draw your attention to those 14 and
23 16 patients that were transferred to open-label caffeine.
24 We can see that on day 1 there were 2 in the caffeine

1 group. However, at the time of transfer, 1 of these
2 patients had at least a 50 percent decrease in apnea
3 episodes, so at the time of transferring was actually a
4 success as defined by the protocol.

5 5 of the placebo patients that were transferred
6 on day 1, among those none actually had at least a 50
7 percent decrease.

8 Looking at day 2, 11 patients were transferred
9 from the caffeine double-blind group to open-label
10 caffeine. You will note that 5 of these actually had at
11 least a 50 percent decrease at the time of transfer, so
12 again, according to our protocol definition, were
13 successes. 6 were not successes at the time of transfer.

14 Among the 9 patients in the placebo group, 2
15 had a 50 percent decrease at least in apnea episodes and 7
16 did not.

17 I'd like to draw your attention to the bottom
18 of the slide and you will see that among the 14 patients
19 that were transferred from caffeine double-blind to
20 caffeine open-label, approximately 43 percent of these
21 patients, according to the definition of success, at least
22 a 50 percent decrease in apnea events, actually were
23 responding to therapy at that time, or at least I should
24 say had a decrease in apnea events. Whereas, if you look

1 at the placebo, among those 16, only 18.8, or approximately
2 19. So, there was a difference in the decrease in apnea
3 episodes between the caffeine and the placebo patients.

4 Looking at exposure, the mean exposure was 6.13
5 days in the double-blind for caffeine as compared to 5.05
6 for placebo. There was no significant difference between
7 these groups.

8 Now I'd like to talk about success or efficacy
9 as we previously defined it, at least a 50 percent
10 reduction in apnea events. First of all, I'd like to draw
11 your attention to a scale to 24 hours. What we did,
12 because we had different time periods, if there were 6
13 apnea events reported in 12 hours, that would be scaled to
14 12 in 24 hours or any fraction of the 24-hour day they were
15 all scaled so that there would be uniformity across.

16 Also, we conducted a last value carried
17 forward. So, if the patients were a success at the time of
18 discontinuation or transferred to open-label, they remained
19 a success for the succeeding days. The numbers, as you
20 saw, got very small because of the high number of
21 transferred and discontinuations. If they were a failure
22 at the time of discontinuation, they remained a failure for
23 this analysis.

24

1 I'd like to draw your attention to day 2. You
2 will note that there is an approximate 20 percent
3 difference in response rates in favor of the caffeine
4 group, and you will notice that that trend of a 20 percent
5 difference, a 20 percent improvement for caffeine, is noted
6 through to day 10. This resulted in a significant
7 difference in favor of caffeine for days 4, 5, 7, 8, 9, and
8 10.

9 This slide shows that what we were trying to do
10 is how many days did a baby have at least a 50 percent
11 reduction. I'd like to draw your attention to day 10 and
12 you will see the yellow bars are the caffeine. 22 babies
13 had 10 days of a 50 percent reduction as compared to 10 for
14 the placebo. You will see for the other days that caffeine
15 was better on days 9, and actually on day 2 when there is
16 no white bar, it's a zero.

17 There were significant differences in favor of
18 caffeine. You will see that for both the T-test analysis
19 and the Cochran's chi square test for trend. It shows that
20 caffeine was significantly better than placebo.

21 We also did a second analysis, which I
22 previously described, and this shows elimination. At this
23 point I want to tell you that when infants were transferred
24 from double-blind caffeine to open-label, although I showed

1 you that some had at least a 50 percent decrease, none of
2 them had elimination. So, actually for this analysis,
3 those babies with the last value carried forward are
4 failures. So, this becomes a very, very stringent
5 analysis.

6 Again, if you would direct your attention to
7 day 2, you will see an approximate 20 percent difference in
8 favor of caffeine and again, the trend is carried forward
9 to day 10. This resulted in a significant difference in
10 favor of caffeine for day 2, day 4, day 7, 8, and 9.

11 We then compiled the data, and you can see that
12 for days 10, 9, and 7 and day 2, that there were more
13 infants that had elimination of apnea. Again, this
14 difference was significant in favor of caffeine, highly
15 significant both by the T-test analysis and the Cochran's
16 chi-square test for trend.

17 If we compile this data, we look at the
18 caffeine and the placebo in the double-blind, and we look
19 at just 7 to 10 days. We chose that. We thought it was a
20 strict criterion among the 10 days. How many babies
21 actually had success based on this? We find that 69
22 percent had at least a 50 percent reduction apnea in the
23 caffeine as compared to 43. There you see the approximate
24 20 percent difference again. This was highly significant

1 in favor of caffeine.

2 Elimination of apnea, 24 percent had 7 to 10
3 days as compared to 0, again highly significant difference
4 in favor of caffeine.

5 That concludes the efficacy portion and I would
6 now like to turn our attention to the safety evaluation,
7 and this again is in the double-blind. We looked at vital
8 signs, which were taken daily. Temperature, respiratory
9 rate, pulse, blood pressure evaluations were done daily.
10 We looked at daily weight.

11 Laboratory parameters in the double-blind were
12 taken at baseline and when the infant was discontinued from
13 the double-blind, and you can see the parameters which are
14 listed.

15 There was no clinically significant differences
16 between caffeine and placebo, vital signs and weight, and
17 no clinically significant differences between caffeine and
18 placebo for any of the laboratory parameters that are
19 listed there.

20 Adverse events. We looked at overall adverse
21 events. Again, we're looking at the double-blind, and then
22 we looked at the COSTART body systems. If we look at
23 patients with at least one AE, you see the p values on the
24 right-hand side of the screen show there's no significant

1 difference. There were also no significant differences in
2 any of the COSTART body systems, which included body as a
3 whole, cardiovascular system, digestive system, hemic and
4 lymphatic system, metabolic and nutrient disorders, nervous
5 system, respiratory system, skin and appendages, special
6 senses, and urogenital systems. No significant differences
7 looking at the Fisher's Exact Test.

8 We want to draw your attention to the fact that
9 there were some adverse events. Actually there were 10
10 AE's reported in 8 patients that the investigator
11 attributed some association with caffeine.

12 The first one is a little unusual. It says,
13 definitely related to drug, drug level increased. There
14 were some underlying conditions in this baby, constipation,
15 PDA, and this baby, just to give you a little history, was
16 randomly assigned to caffeine, had persistent apnea, was
17 transferred to open-label caffeine, still had persistent
18 apnea. So, the investigator asked for the drug level.

19 These drugs levels of course were not given to
20 investigators in the double-blinds because it would break
21 the double-blind.

22 It was 31.4. Based on this, we can only assume
23 that the investigator thought the drug level was too high
24 based on the literature because the therapeutic range,

1 usually the higher limit is 20 or 25 based on the
2 literature and this is slightly above this.

3 There was no adverse event that was attributed
4 to caffeine, and I'm sure as you well know, there are
5 really no serious toxicities reported in the literature at
6 levels below 50 micrograms per ml, but we report that for
7 full disclosure.

8 Also, possibly drug-related, there was one case
9 of enterocolitis, which was considered severe. The little
10 cross on the one patient means they were in open-label at
11 the time. GI disorder moderate, 1 patient. Feeding
12 disorder mild, 1 patient in open-label caffeine.
13 Tachycardia was reported in 1 patient and possibly
14 associated with caffeine citrate. It was mild, 1 patient
15 in open-label caffeine.

16 Also there were several adverse events that
17 were considered remotely associated with the administration
18 of caffeine. Injection site inflammation, moderate in 1
19 patient. Actually there were about five or six cases, both
20 in the placebo and in the caffeine infiltration of the IV
21 and inflammation. However, this was remotely associated
22 with caffeine.

23 Hyponatremia, severe, one case was reported in
24 open-label caffeine.

1 Lung edema and anemia, mild, was also reported.

2 So, these were 10 AE's in 8 patients.

3 Necrotizing enterocolitis, as previously
4 described by Dr. Mosdell, was also reviewed for this study.
5 As you well know, it's a worldwide problem in preterm
6 infants. According to one investigator, Dr. Aranda, the
7 second most common cause of neonatal death. Although not
8 all authors agree it's the second most common cause, it
9 certainly is a significant cause of mortality in this
10 preterm infant population.

11 The pathogenesis of this disease remains
12 enigmatic. It is characterized by GI and systemic signs
13 and symptoms, feeding intolerance, abdominal distention,
14 poor perfusion. Advanced cases also have acidosis shock
15 and bacteremia.

16 The incidence is inversely proportional to
17 birth weight and age of immaturity. The incidence,
18 according to the paper which I have quoted, Uauy, is 10.1
19 percent. This is a fairly recent paper, 1991, although as
20 you previously heard from Dr. Mosdell, the incidence has
21 been reported as high in previous papers as 14 to 15
22 percent.

23 In this study, in the OPR-001 study, there were
24 four cases of NEC for 8.9 percent. 2 of these babies died,

1 and there were 2 placebo patients, 5.1 percent, and 1
2 death.

3 Three serious adverse events were submitted to
4 the FDA. One infant, 30 weeks gestation, received 5 days
5 of double-blind caffeine, and was transferred to the
6 referring hospital. He was re-admitted 3 days later for a
7 bowel resection for NEC and PDA ligation and died of
8 related causes, complications and prematurity.

9 Another infant, also 30 weeks gestational age,
10 received 3 days of double-blind caffeine, followed by house
11 caffeine, not open-label, but house caffeine compounded by
12 the pharmacy for an additional 6 days. The infant
13 developed NEC and died the next day.

14 A third infant, who was 29 weeks gestational
15 age, received 2 days of double-blind placebo and was
16 transferred to open-label caffeine. It's noteworthy that
17 on the day of transfer an ileal resection was performed.
18 Caffeine was subsequently administered for 10 days, 18 days
19 later the patient died, and NEC was diagnosed at autopsy.

20 We feel that the information, the results that
21 I've just described, indicate that caffeine citrate is safe
22 and effective for the treatment of apnea of prematurity.

23 I thank you and this concludes the sponsor's
24 presentation.

1 DR. LI: I would like to thank the sponsors for
2 their very clear and concise presentation. I'd like to
3 invite our committee members to ask questions to the
4 sponsors.

5 MR. MADOO: If I might note, Dr. Crim, who's a
6 committee member, arrived a little late and we're pleased
7 to have him at the table.

8 Another bit of housekeeping is for people who
9 are unaware of our procedures, we have the full final
10 agenda in your blue folders in front of you, and appended
11 to the agenda will be the finalized questions for committee
12 discussion.

13 You'll also note behind that, by way of
14 familiarization with your colleagues around the table, that
15 there is a comprehensive roster of both consultants and
16 members.

17 Thank you.

18 DR. LI: Questions for the sponsor? Yes, Dr.
19 Jobe?

20 DR. JOBE: I'd like to ask the submitters what
21 information they have about the use of caffeine in the
22 nurseries they were evaluating this drug in, before the
23 initiation of the drug. I think the committee might be
24 interested to know in this population of 28- to 32-weekers,

1 what was the use of caffeine off label. If I can guess I'd
2 say it was 70 percent.

3 DR. ERENBERG: The majority of the nurseries
4 that enrolled in the study were those that were using
5 caffeine as the primary pharmacologic intervention prior to
6 the use of the study though some of them would on occasion
7 use the theophylline or aminophylline, or if they sent the
8 infant home obviously would send them home on theophylline.

9 DR. JOBE: And the use in the nursery, what
10 percent of the babies were --

11 DR. ERENBERG: The actual percentage?

12 DR. JOBE: Because you actually surveyed 1,000
13 infants to get these 80. Do we know how many of those
14 infants were actually receiving --

15 DR. ERENBERG: The 1,000 infants were the
16 consecutive admissions during the study period. The
17 majority of these infants were eliminated because of
18 gestational age or one of the other exclusion factors.

19 I would estimate that the use of caffeine was
20 somewhere between 50 and 70 percent in the 28- to 32-week
21 gestation infant.

22 DR. JOBE: Another point that people probably
23 ought to be aware of is that probably most of the babies
24 that you surveyed were less than 28 weeks gestation and

1 that group between 24 and 28 weeks gestation are frequently
2 treated with caffeine. In fact, probably most of them are
3 on caffeine around the country.

4 Many of those infants in fact are on caffeine
5 on ventilators because the babies are being weaned from the
6 ventilator and are initiated on caffeine therapy. So,
7 those are exclusions from your study but actually it is the
8 major population of infants being treated with caffeine.

9 DR. LI: Do you actually have any numbers of
10 the percentage of infants that were screened and excluded
11 from the study? What percentage of those received
12 caffeine?

13 DR. ERENBERG: I don't believe we have that
14 information. We do not require that of our study centers.

15 DR. LI: Dr. Goldsmith.

16 DR. GOLDSMITH: I have a whole series of
17 methodological questions and I don't wish to nitpick but
18 this is one study that we have.

19 First of all, there is no maternal history of
20 mothers taking caffeine or coffee. I'd like to know that
21 incidence for both placebo and treated patients.

22 Secondly --

23 DR. LI: Maybe we can take these one at a time.

24 If we could have one of the sponsor's representatives

1 address these, if possible, especially if you have a whole
2 series. Otherwise, questions may get lost. Maternal
3 history.

4 DR. WYNNE: We don't have that. We did not
5 collect that information.

6 Dr. Erenberg has something to add.

7 DR. ERENBERG: If an infant had a serum level
8 of caffeine, I think it was greater than 2 microgram per
9 deciliter, they were eliminated from the study as a priori
10 evidence that either they had received the drug or possibly
11 from mom.

12 DR. LI: Why did you want to know that, Dr.
13 Goldsmith?

14 DR. GOLDSMITH: In other words, there was a
15 serum level done before the first dose was given and that
16 would exclude if it was greater than 2. Is that correct,
17 Dr. Erenberg?

18 DR. ERENBERG: Yes, that is correct.

19 DR. GOLDSMITH: All right.

20 Secondly, most apneic episodes have been shown
21 in most nurseries to be missed by nurses. Were hard copies
22 done of printouts for apnea, bradycardia and oxygen
23 saturation so that these could be looked at in a scientific
24 way rather than just on clinical observation?

1 DR. ERENBERG: This was not done. This was not
2 required in our protocol.

3 DR. GOLDSMITH: Number three, were the
4 incidents of patent ductus arteriosus in the placebo and
5 treatment groups looked at? PDA is noted to cause apneic
6 episodes and may be a cause for nonresponse in babies that
7 were either treated or in the placebo group that went to
8 open-label.

9 DR. ERENBERG: If a PDA was diagnosed and was
10 untreated -- in other words if the infant was in the
11 investigator's opinion in congestive heart failure -- that
12 was an exclusion criteria, so they were not started on the
13 study.

14 I do not believe we looked at specifically
15 infants who developed PDA during the process, though I do
16 believe that could have been indicated by the investigator
17 as the cause for removal of the infant from the study.

18 DR. GOLDSMITH: There was one child that was
19 discussed in the previous presentation that had a
20 nonresponse and had a patent ductus arteriosus. Are you
21 saying that that child developed the PDA during the
22 treatment, or was there echocardiographic evidence prior to
23 beginning treatment of no ductus?

24 DR. ERENBERG: That child was one who was

1 transferred from the study site to the original referring
2 hospital and then was transferred back, and at that time
3 the patent ductus had been noted. So, there was a 3-day
4 time period between the infant being in our study site and
5 the infant returning.

6 DR. GOLDSMITH: How about the incidence or the
7 use of gavage feeding tubes and the correlation between
8 bradycardia and hypoxemia leading to apnea versus apnea
9 being the initial event, then going to bradycardia and
10 hypoxemia? In other words, were the nurse clinicians
11 differentiating between apnea as the primary event, or
12 could bradycardia and hypoxemia be the initial event which
13 led to apnea?

14 DR. ERENBERG: I can't guarantee that all of
15 them were like that but the study centers were to identify
16 the infants that had apnea first with subsequent
17 bradycardia and not the reverse, bradycardia with
18 subsequent apnea.

19 DR. GOLDSMITH: And finally, we've noted after
20 prolonged treatment -- the treatment here only went 10 to
21 12 days, but after prolonged treatment with theophylline
22 and caffeine, significantly in babies less than 1,000 grams
23 a very significant hyponatremia. That was reported here in
24 one infant. Both theophylline and caffeine are diuretics

1 and naturetics.

2 I want to know a little bit more about that
3 infant, and if this drug is going to be approved for
4 prolonged treatment, how we are going to monitor sodium
5 levels, especially in these very small infants.

6 DR. WYNNE: We aren't able to describe that one
7 baby with hyponatremia at this time, but we can review it
8 and have it for you a little later for you in the program.

9 DR. GOLDSMITH: Thank you.

10 DR. LI: Les.

11 DR. HENDELES: I was wondering if you could
12 provide some additional information on the relationship
13 between caffeine drug level and treatment failure, and also
14 what kind of range of levels resulted from the loading dose
15 and how that contrasted with the levels from the
16 maintenance dose, and how many patients were greater than
17 20 micrograms per milliliter.

18 DR. WYNNE: Sorry for the delay.

19 You'll see at the point when the serum
20 concentrations were to be taken, basically at baseline
21 after the loading dose on days 2 and 12, and then
22 subsequently as they are listed there.

23 Actually we did not see any consistent pattern
24 between the mean serum concentrations for any of the days

1 in the double-blind and response, whether we looked at a
2 greater than 50 percent reduction or elimination for any of
3 the 10 days.

4 These are the mean serum concentrations looking
5 at a greater than or equal to 50 percent reduction and less
6 than a 50 percent reduction. Looking at the mean
7 concentrations, you can see there is no pattern that we
8 could relate to response.

9 Also, if we looked at the mean concentration
10 and those infants that had no apnea events or had greater
11 than 1 or equal to 1 apnea event, again no consistent
12 pattern could be derived.

13 Dr. Ludden, would you like to make any further
14 comments on this?

15 DR. LUDDEN: The only thing that I would
16 comment about is that in the correlations that we looked at
17 with the pharmacokinetic analysis of this sparse sampling
18 data was that there appeared to be a relationship between
19 the clearance value and body weight that was obvious.
20 There also appears to be, as I understand it from the
21 response data, a correlation between responsiveness to the
22 drug and body weight, the larger children getting maybe a
23 better response the larger they are. Yet they are going to
24 have a higher clearance and therefore lower blood levels.

1 Because there was a very limited range of
2 dosing, in fact it was almost a fixed dose type of study,
3 you don't get the kinds of ranges of concentrations within
4 an individual subject that allow for a good pharmacodynamic
5 type of analysis of the data.

6 But I have personally not looked at the data in
7 that way. But just given that type of correlation, one
8 could imagine a bit of a difficulty in pulling that out.

9 MR. MADOO: Sir, for the benefit of the record,
10 could you articulate your affiliation, your name, and
11 whether you are a consultant of Roxane, your manner of
12 conveyance to this meeting?

13 DR. LUDDEN: Yes, I'm a consultant to Roxane.
14 I am Professor and Chair of Pharmaceutical Sciences at the
15 University of Nebraska Medical Center in Omaha.

16 DR. LI: Any other questions for sponsor? Dr.
17 Osborne?

18 DR. OSBORNE: Dr. Wynne, I hate to say this
19 just as you are sitting down, but just one other question.

20 It certainly struck me reading this -- and I
21 may not have it quite straight and you also mentioned this
22 -- that there were these 20 percent success rates, if you
23 will, both for placebo and for caffeine. Would you care to
24 comment on why? Did you look at those individuals to see

1 if there was anything that could predict success with the
2 caffeine? I can think of a host of variables, but perhaps
3 that's something you have considered already.

4 DR. WYNNE: Yes, we did. Let me just show you
5 the backup slide for that.

6 What we wanted to do when we looked at success,
7 to see if there was anything -- we looked at individual
8 babies, but we wanted to look at baseline characteristics
9 to determine if there were any predicting factors that we
10 could correlate to response.

11 If you see on this slide, we looked at
12 gestational age and we looked at both zero apnea events or
13 elimination and the days 1 to 6, 0. This is of course the
14 strict evaluation, and at least 7 days. If you look across
15 for gestational age, you'll see that they are very
16 comparable. Post-conceptual age, very comparable. Number
17 of baseline apnea attacks. Actually in the last column on
18 your right you'll see that those with at least 7 days of 0
19 apnea events had slightly fewer apnea events at baseline,
20 and actually, as far as weight, you'll see those again that
21 had at least 7 days of elimination of apnea, that they were
22 a little heavier. The other variables are similar. So,
23 those are the variables.

24 We looked at individual babies and we just

1 could not see any correlation. There was nothing that we
2 could say would be a predicting factor for those who might
3 have a spontaneous evolution of apnea as compared to those
4 who would need treatment with methylxanthine.

5 DR. OSBORNE: And did you do any logistic
6 regression adjusting for sepsis or some other causes of
7 apnea that might have confounded the data?

8 DR. WYNNE: No, we did not.

9 Did you want to add anything to that, Dr.
10 Haack? No. No, we did not.

11 DR. ROTHSTEIN: Using the least value carried
12 forward analysis, looking at the data a different way, one
13 could conclude that if there is no effect on the first day,
14 there is no effect with this drug.

15 DR. WYNNE: The results seemed to be predictive
16 of that, yes. Actually I think you see that in the
17 literature too. I know you see that in the literature,
18 that within this 24- to 48-hour period that not all babies
19 but some babies respond.

20 You did start to see that trend but it became
21 stronger, so not all babies would respond in that 24 to 48
22 hours. I couldn't say absolutely if you don't see a
23 response in 24 hours, but there is some prediction that
24 that's when the response occurs.

1 Dr. Haack would like to --

2 DR. HAACK: My name is Dennis Haack and I'm the
3 biostatistical consultant to Roxane Labs. One thing that
4 should be noted, this study was not designed to look at
5 what would happen if you removed caffeine once you saw a
6 response.

7 Again, an aside to your question, if the infant
8 did respond at day 2, we don't know that that response
9 would go away if we removed caffeine. That was not part of
10 the design.

11 DR. ROTHSTEIN: No, I'm looking at the other
12 issue, how long does one treat an infant with caffeine if
13 in fact there's no response by day 1 or 2? This will
14 eventually carry over perhaps into the labeling.

15 DR. WYNNE: Yes. Actually according to our
16 protocol, we did ask investigators to look at the response
17 within 24 to 48 hours. If there was not at least a 50
18 percent decrease, that's when they had the option of
19 transferring to open-label caffeine. So, I think that
20 indirectly answers your question, although as you saw, some
21 of them had responded that were transferred.

22 DR. HAACK: And there were a few that actually
23 responded, had 7 days of apnea-free existence, and we don't
24 know if those were the last 7 days. We haven't checked

1 that. We could do that for you, but there were a number
2 that had 7 days or 8 days.

3 DR. WYNNE: The other thing that I think Dr.
4 Ludden mentioned, this was like a fixed-dose study. They
5 didn't have the option of increasing the maintenance dose.
6 As you well know from the literature, this is often the
7 case in the neonatal unit. They didn't have the option of
8 changing the dose. They had to transfer the baby,
9 discontinue the baby, put them on alternative therapy, or
10 they had to transfer them to open-label caffeine. So, I
11 think that restriction also has to be kept in mind.

12 Did I answer your question?

13 DR. ROTHSTEIN: Somewhat.

14 DR. JENNE: According to the literature in one
15 fairly recent paper on a large population, mean half-life
16 was 144 hours. There is such a tremendous spread in half-
17 life. I was wondering if you had the data. Were you
18 satisfied when you looked at the 2-hour versus the 12-hour
19 levels, that there were not some levels that were really
20 climbing up? I don't have a feeling of the spread of those
21 12-hour levels.

22 DR. WYNNE: Would you like to address that, Dr.
23 Ludden?

24 DR. LUDDEN: Yes. I don't have the definitive

1 data on that. We looked at this more as a whole because
2 the sampling was spread across time and not at fixed times
3 in every infant, so you don't get a nice uniform picture of
4 was going on at some of these specific times.

5 I would say that there was a reasonable spread
6 in the data, though in a given subject, in a given
7 individual the loading dose and the maintenance dose seemed
8 to match up fairly well. There wasn't a lot of variability
9 after the first day or two, looking like there was dramatic
10 accumulation or drop across the plasma levels when there
11 were 10 days' worth of blood levels.

12 The half-life that we get from our data is
13 about 100 hours, which is somewhat less than that previous
14 report in a population style analysis and we're probably
15 closer to, I think, the Thompson paper that was published a
16 little before that in that regard.

17 DR. LI: Thank you.

18 Dr. Szeffler?

19 DR. SZEFLER: I have two questions in two broad
20 areas. In looking at the documentation, there is a mention
21 of sepsis and you mentioned that. It seems to stand out in
22 the caffeine group but it really doesn't stand out in the
23 statistics. Can you comment on what was going on there?

24 DR. WYNNE: Yes, I'd like to do that.

1 Actually while I'm looking for the backup
2 slide, I'll tell you that we looked at the double-blind and
3 I think because of the variation when they are treating and
4 when the infants are getting older, we wanted to look at
5 that first.

6
7 We see that there are two in the caffeine group
8 and none in the placebo group. However, when I reviewed
9 these cases, one of these cases of sepsis actually was
10 either present at the time the baby was enrolled or this
11 baby had a history of sepsis. So, there was only one of
12 these cases --

13 DR. SZEFLER: Does this document the sepsis
14 because it's kind of like rule out sepsis.

15 DR. WYNNE: For the case I'm mentioning, it
16 never said culture-proven sepsis. It doesn't say rule out
17 sepsis. It said history of sepsis. That was a preexisting
18 condition according to what was on the case report form.

19 The second case that we see actually was not
20 present at baseline and was culture-proven.

21 So, what we have in the double-blind portion,
22 which I feel is the way to really evaluate these, although
23 we have to talk about long term I realize, is that there
24 was one case that actually occurred during the double-

1 blind.

2 If we look at the open-label, and we'll go on
3 to that, again, here you see now the open-label, so you see
4 4 patients in open-label that had sepsis. That's for a
5 total of 6. And actually the 2 in the placebo -- placebo
6 means that they were randomized to placebo but this is
7 open-label caffeine, so they are actually receiving
8 caffeine. So, there were 8 cases total when they were
9 receiving caffeine.

10 DR. SZEFLER: And once again these were, having
11 dealt with this in the past, there's like rule out sepsis
12 and then there's a small percentage that are actually
13 documented.

14 DR. WYNNE: Several of these were rule out
15 sepsis. They are not all documented culture-proven sepsis.

16 DR. SZEFLER: The second broad area I was going
17 to ask you about is I know there's another preparation
18 that's out there called caffeine benzoate. My recall is it
19 was used as a respiratory stimulant in adults. Have you
20 done any studies in adults, and do you anticipate that this
21 particular preparation will be used in adults?

22 The reason I ask that, in the population you
23 studied you can't identify subjective adverse effects, but
24 certainly in adults you get a better feel for subjective

1 adverse effects. Do you have any feeling for that?

2 DR. WYNNE: You're talking about the benzoate
3 preparation?

4 DR. SZEFLER: Right. I don't know the extent
5 of its use now, but I remember --

6 DR. WYNNE: As you well know, it's not used in
7 infants because of the toxicity of the benzoate and the
8 benzyl alcohol. At this time we don't have any studies
9 planned at all for benzoate in the adult population.

10 DR. HENDELES: I don't think it's available.

11 DR. LI: Dr. Kelly, you had a question?

12 DR. KELLY: The question was answered primarily
13 but it had to do with the blood levels. You didn't have a
14 response in the first two hours after the loading dose but
15 you got a response later on and that was my question. Do
16 the concentrations of the drug drift up or drift down, or
17 are we just seeing that patients enrolled in this study in
18 general are going to get better and this drug will have a
19 minimal effect?

20 You would think if it has pharmacologic action,
21 direct action, that right after the loading dose, you would
22 see your basic therapeutic response.

23 DR. LUDDEN: This is Tom Ludden again. If I
24 can respond to that.

1 The loading dose gives on average -- if you
2 take the kinetic parameters of volume and clearance, the
3 loading dose given produces an average level of about 12 to
4 14. If you look at the clearance values generated, it's
5 somewhat above that, around 14 to 18. So, there is a
6 possibility we're getting that.

7 You don't see that very clearly in the data,
8 though, because of the variability among individuals and
9 because of the fact that as time goes on in this study the
10 dropout rate from at least the randomized part of this
11 study is quite significant.

12 DR. KELLY: At least one of the trials that
13 compared theophylline to caffeine used two different
14 caffeine doses in the historical trials. They used double
15 the dose that was used in this trial, showed a more
16 immediate effect and a better effect. So, there was an
17 apparent concentration or dose-related phenomenon, but you
18 weren't able to find anything at all?

19 DR. LUDDEN: No. I have not looked
20 specifically at response versus concentration in individual
21 subjects.

22 DR. LI: Dr. Chinchilli?.

23 DR. CHINCHILLI: Yes, I have a couple of
24 questions. The first one has to do with the NEC.

1 You were reporting from the literature, you and
2 Dr. Mosdell, about the incidence that is reported in the
3 literature. My basic question is, does the incidence of
4 NEC increase with earlier gestational age, so the more
5 premature, the higher at risk you are for that. If that's
6 the case --

7 DR. WYNNE: That's what's documented in the
8 literature, yes.

9 DR. CHINCHILLI: You reported incidences of 10
10 percent and possibly even up to 15 percent for the
11 gestational age that you had enrolled in this study, which
12 is 28 to 32 weeks. Is there anything in the literature
13 that says what the incidence of NEC would be for that range
14 of gestational age?

15 DR. WYNNE: Can you answer that, Dr. Erenberg?

16 DR. ERENBERG: The reference that Dr. Wynne
17 referred to was in infants under 1,500 grams, which would
18 be the approximate population that we reported. The
19 incidence of necrotizing enterocolitis is very difficult to
20 determine because it is so episodic within a given
21 institution, where one can go several years without having
22 a single case, and then one can have an outbreak of having
23 several cases, never determine the etiology, and then it
24 disappears.

1 The reference is a review of a very specific
2 population which is infants under 1,500 grams, which would
3 be very similar to the infants that were in our study
4 group.

5 DR. CHINCHILLI: The next questions I have
6 probably Dr. Haack needs to address. The first has to do
7 with the sample size calculation, and I don't know if you
8 were involved with that. I saw somewhere that when the
9 sample size was calculated for this study, it was assumed
10 there would be a 70 percent success rate for the caffeine
11 and 20 percent success for the placebo. This seems
12 extremely ambitious results to expect. Were you involved
13 with this?

14 DR. HAACK: No, I was not. I was not involved
15 in that sample size calculation.

16 DR. CHINCHILLI: I was just wondering what the
17 basis was for this type of expected success rate.

18 DR. WYNNE: Can you answer that question, Dr.
19 Erenberg?

20 DR. ERENBURG: It was a guesstimation. There's
21 nothing in the literature on placebo treatment of infants
22 with methylxanthines, so it was just an estimated guess and
23 that's how we came up with the 20 percent.

24 DR. CHINCHILLI: Didn't you consider that to be

1 rather ambitious, though, to expect such a strong result
2 like that?

3 DR. ERENBERG: We have faith in caffeine.

4 (Laughter.)

5 DR. CHINCHILLI: My last question has to do --
6 I'm sure Dr. Haack can answer this one. This was a multi-
7 center trial with nine different centers but I didn't see
8 anywhere -- if it was, it wasn't very specific or direct --
9 any mention of adjusting for center in any of the
10 statistical analyses.

11 I realize you have small numbers of subjects
12 per center, but did you do any analyses that had looked at
13 center effects and center-by-treatment interactions?

14 DR. HAACK: No, we did not. We did look at
15 changes and percent changes which would eliminate the
16 center effects, but we did not look for center effects in
17 that model to see if there was an interaction. So, that
18 was not done.

19 DR. CHINCHILLI: I'd like to ask a question
20 about the study design and the definition of success. As I
21 saw the presentation, the definition of success in many of
22 your slides was a 50 percent reduction in apnea episodes.
23 I would ask, at what point in the study design was that
24 determined to be the primary efficacy variable, so to

1 speak, and were there other primary endpoints that you
2 considered?

3 DR. WYNNE: Would you like to address that,
4 Dennis?

5 DR. HAACK: I wasn't involved in that earlier,
6 but as was just brought out, the sample size calculation
7 was based on what they thought the 50 percent reduction
8 would be. To my understanding, that was an early success
9 variable. The elimination was an ad hoc analysis that we
10 came up with after the study.

11 DR. LI: But the variable then of the 50
12 percent reduction was decided upon at the time of the study
13 design?

14 DR. HAACK: Yes, it was early on because that's
15 where they calculated. The sample size was based on their
16 best guess as to what the percentage of patients would have
17 a 50 percent reduction in placebo and caffeine.

18 DR. WYNNE: This was based on the literature
19 and discussing with experts. If you look into the
20 literature, most of the literature assesses success with a
21 50 percent reduction in apnea, so that's where we based
22 ours. It's my understanding. I wasn't there at the
23 earlier part of this trial either.

24 DR. LI: In some of the documents there was a

1 reference to the actual rate of apnea episodes during a 24-
2 to 48-hour period, and I take it that was rejected as a
3 success measure early on. Is that correct?

4 DR. WYNNE: Would you like to address that,
5 Dennis?

6 DR. HAACK: Yes, the actual rate. I think
7 early on they were looking at the percentage of success, at
8 least a 50 percent reduction, but the actual rate was
9 mentioned in some of the earlier documents. We did do some
10 analyses on the actual rates but we used the primary as the
11 success, as a 50 percent reduction.

12 DR. ERENBERG: At the initial meetings, the
13 rate was discussed but it was felt going to a specific rate
14 as defined as success without referring to what the initial
15 baseline was would make it difficult to really get an
16 answer to our question.

17 DR. LI: Dr. Rothstein.

18 DR. ROTHSTEIN: This is more of an observation
19 than a question. During your presentation, you mentioned
20 that you thought it would probably be unethical to try and
21 repeat a study like this. During the power analysis, it
22 was felt that there would be a 20 percent effect in the
23 control population, and I presume that you talked to a
24 number of neonatologists when you set up this study.

1 This is probably the most powerful placebo that
2 I've ever seen, where the placebo has in effect somewhere
3 between 40 and 50 percent. It speaks to the necessity of
4 in fact continuing in many areas with blinded placebo-
5 controlled studies, and that some of our clinical
6 assumptions -- we've been working with newborns for years
7 and no one was able to predict that the placebo would come
8 up with an efficacy rate this high.

9 DR. WYNNE: Yes, I couldn't agree with you
10 more. We were very surprised. In fact, when we went back
11 to the literature, there's nothing in the literature of
12 course to determine. There was one study that was
13 described as a placebo but treatment was given very early
14 in that. So, we had no idea what the placebo effect would
15 be.

16 I'm only echoing what neonatologists have said
17 when I said it was difficult to do the study because of the
18 fact that methylxanthines are used so extensively.

19 DR. LI: Dr. Cross.

20 DR. CROSS: I was a little bit unclear on the
21 study population. I'd be interested in the 1,000 patients
22 that were screened. What percent of that 28 to 32 age
23 group that had apnea were excluded because of other
24 reasons? I suspect that the drug will be used in those

1 sicker babies that have other things going on and I was
2 interested, did you recover into your study group most of
3 those that had apnea episodes and were 28 to 32 gestational
4 age? Was in half, was it less than half, was it more than
5 half? For example, in that age group you picked and who
6 actually had apnea, what percent were thrown out as not
7 being appropriate to study?

8 DR. WYNNE: Dr. Erenberg is going to answer. I
9 was not there early enough.

10 DR. ERENBERG: We were looking for a specific
11 population, which is those that have apnea of prematurity,
12 which as I mentioned is a real diagnosis. If there are
13 other etiologic factors, yes, caffeine may be used
14 concomitantly. But for this particular group we wanted one
15 indication and wanted to remove all the other variables
16 such that if you have an infant with patent ductus
17 arteriosus, controlling congestive heart failure could
18 eliminate the apnea. If you give caffeine concomitantly,
19 which one is the one that had the major effect?

20 DR. CROSS: It certainly cleans up your study
21 to do all those exclusions, but can you give any sense of
22 what percent of the babies that had apnea by definition of
23 prematurity, they were in your age group but for other
24 criteria were thrown out?

1 DR. ERENBERG: We have the logs of the infants
2 but we do not have how many of them had apnea and exclusion
3 criteria.

4 DR. LI: Dr. Crim?

5 DR. CRIM: I just have some questions in my
6 mind about this particular condition, and then as it
7 pertains to its treatment.

8 In the literature review that was presented, as
9 I understand the duration of the studies ranged from 24
10 hours to over 3 months, and I guess my question in that
11 regard is, what was the duration of treatment of the
12 infants in these various studies?

13 In other words, I don't have a sense and
14 perhaps the pediatricians can give me a sense for this.
15 How long were these babies treated with caffeine anyway for
16 this problem. I'm trying to get a sense, for instance,
17 does a baby -- as they get older, they grow out of it, so
18 to speak.

19 And then along the same lines, one of the
20 questions that had come up was the babies that have the
21 sepsis as far as this history of sepsis. How old were
22 these babies at the time from birth that they were treated?
23 I can't understand how a person can have a history of
24 sepsis if they are enrolled in a study soon after birth.

1 I'm trying to get a sense in terms of these
2 time lines, in terms of treatment, as well as the time
3 lines, in terms of how old these babies were at the time
4 they were enrolled in the study, as opposed to gestational
5 age, but from birth.

6 DR. WYNNE: You'd like to know in our study how
7 old they were?

8 DR. CRIM: I'll just kind of restate them one
9 at a time.

10 One, as far as the review of the literature,
11 although the duration of the studies range from 24 hours to
12 3 months, do you have a sense of how long the infants were
13 treated in this study? I know your study was approximately
14 10 to 12 days. How long were these babies treated in the
15 studies that were reviewed in the literature?

16 DR. MOSDELL: It is very difficult from the
17 literature to say that there is an average duration. The
18 24-hour study was just trying to -- it was one particular
19 trial that was trying to evaluate the effects within the
20 first 24 hours.

21 There's quite a wide range. I don't really
22 have an average that I can provide to you. Some studies
23 were specifically designed to be 7 to 10 day trials, as
24 ours was. Others treated babies until they responded, so

1 you had very long durations of treatment.

2 Perhaps Dr. Erenberg could talk about the
3 clinical use of the drug, but the literature really has a
4 wide range of durations used and it is difficult for me to
5 say that primarily they were 7 to 10 days or they were
6 longer than that.

7 DR. JOBE: Perhaps I could give you a picture
8 of the practice. Apnea of prematurity is extremely common.
9 The more immature the infant is, the more likely the infant
10 is to have it, and the more dense the apnea is likely to
11 be. In general, normal infants will grow out of their
12 apnea of prematurity by 32 to 34 weeks gestation.

13 So, the standard of practice is that if an
14 infant has apnea, he's put on either theophylline or
15 caffeine. Then at 32 to 34 weeks, if there are no apneic
16 episodes, the baby is tested off the methylxanthines.

17 Then if the apnea recurs, the baby is put back
18 on the methylxanthine and then tried off again before
19 discharge. Some of the babies are sent home on
20 methylxanthines.

21 So, the period of use is from severe
22 prematurity at 24 weeks up to 32 to 34 weeks for most of
23 these infants and then they are taken off and tested.

24 DR. CRIM: Is it initiated at birth?

1 DR. JOBE: It is initiated at a point in time
2 when you want them to breathe spontaneously. So, if they
3 are on a ventilator being ventilated, then it's not given
4 in general, but as you wean the baby, there are several
5 studies reporting the efficacy of using caffeine to get
6 babies off ventilators. So, it is initiated before they
7 are extubated very often in small babies.

8 Now, none of this is done by randomized
9 controlled trials. That's just what practice is.

10 DR. GOLDSMITH: Unfortunately, there is also
11 the confusion between apnea of prematurity and ALTEs, acute
12 life threatening events, or near-miss SIDS, whatever you
13 what to call it. Many physicians continue methylxanthines
14 past the time of 36 weeks, some without testing, some with
15 testing by pneumocardiogram, which has a very controversial
16 background and Allen says is worthless. But in one study
17 on successive days, pneumocardiograms were rated as normal,
18 then abnormal, then normal again in a high percentage of
19 times, so it really is very variable.

20 But we'll see babies on methylxanthines up to a
21 year of age home on apnea monitors.

22 This panel is talking about the use of caffeine
23 in the neonatal unit and properly up to 36 weeks, but in
24 practicality this drug, if it's licensed, I'm sure will be

1 used because of its ease to be given once a day rather than
2 three or four times a day as theophylline is, that will be
3 used as a prescription drug, probably up to a year of a age
4 in children for acute life-threatening events.

5 DR. CRIM: I was trying to get a sense for that
6 in that these babies -- not on mechanical ventilation as
7 part of the enrollment, and that's what I'm trying to get a
8 sense for. How old were these babies in terms of after
9 birth before they were enrolled into this study as far as
10 initiated in the sense of how soon would this apnea have
11 been recognized before they would have been enrolled in
12 this study. That's what I'm trying to get a sense for.

13 DR. ROTHSTEIN: That's one of the questions.
14 Maybe the sponsor can clarify it. Looking at their data,
15 it looked to be that the average time of enrollment was
16 about day 4 or 5 of life. Is that correct?

17 DR. ERENBERG: It was about between 7 and 10
18 days, approximately.

19 DR. CRIM: Would these babies have been
20 recognized as having apnea since they would not have been
21 on mechanical ventilation as part of the inclusion or
22 exclusion criteria? Would they have been recognized as
23 having apnea before they would have been enrolled in the
24 study?

1 Obviously, they would have to have it before
2 being enrolled in the study. I'm just trying to get a
3 sense for how many days they would have had these apnea
4 events before they would have been enrolled.

5 DR. ERENBERG: As soon as they had 6 apneic
6 events within a 24-hour period and did not fulfill any of
7 the exclusion criteria, they were enrolled.

8 Now, these infants may have been ventilated
9 prior to enrollment, but because of the problem that Dr.
10 Jobe mentioned, it is often tradition that infants receive
11 caffeine prior to extubation. We eliminated those infants
12 from our study. In fact, several study sites refused to
13 participate because they felt it was important that they do
14 use caffeine in the extubation process.

15 DR. LI: Dr. Sessler.

16 DR. SESSLER: I have two unrelated questions.

17 The first is in regards to the study itself.
18 What was the duration of enrollment for the nine centers to
19 get these 80 patients enrolled?

20 DR. WYNNE: We started in March of 1994 -- I
21 omitted that from my presentation -- until October of 1995.
22 So, it was approximately 18 months.

23

24 DR. SESSLER: And the second question is in

1 regards to NEC. Looking at it kind of in reverse, are
2 there any studies where large groups of patients with NEC
3 have been evaluated for risk factors and, preferably in a
4 multi-variate fashion, have identified methylxanthines as a
5 significant risk?

6 DR. WYNNE: I think Dr. Mosdell can answer that
7 question. She did research on that.

8 DR. MOSDELL: There is one study. I think the
9 FDA reviewed this in their write-up. The study is by
10 Davis, et al., published in 1986. It was a retrospective
11 review of 275 infants and they compared those who developed
12 NEC to see if they were receiving methylxanthines.

13 In that particular study, they did not find an
14 association between the treatment with methylxanthines and
15 the development of NEC.

16 It has to be countered by the fact that this
17 really wasn't a case match controlled study. It was a
18 retrospective review, and there are some limitations to
19 that type of study design. But that is the one study that
20 evaluated, more in a systematic rather than just reports,
21 the association of NEC with methylxanthines.

22 Certainly there is a large body of evidence
23 that has looked at various parameters that are associated
24 with the development of NEC. By and large, the largest or

1 the primary factor which is always associated with NEC in
2 these trials is prematurity. Other than that, you see
3 quite a range of varying variables that have been
4 identified having association with this disorder.

5 DR. GOLDSMITH: As a clinician, the problem
6 with evaluating NEC and methylxanthines is that apnea
7 causes decreased blood flow, and decreased blood flow is a
8 common denominator in the pathogenesis of NEC. So, if you
9 start with a child who is having apneic episodes and he is
10 having decreased blood flow to his gut and then you add on
11 top of that as treatment methylxanthines, what's the cause?
12 Is the cause the decreased blood flow problem or is the
13 cause the drug?

14 DR. LI: Dr. Jenne?

15 DR. JENNE: Well, we'll probably get into this
16 later, but I wondered what your view was of the therapeutic
17 range. You took a level which is common in the literature
18 and most of these papers that you referred to used
19 calculations based on caffeine citrate, which when
20 corrected to caffeine, is the same dose that you are using
21 basically.

22 But in a large study in Journal of
23 Pharmacologic Therapeutics, 1997 by Lee, the conclusion in
24 their discussion is that many infants require levels in the

1 range of 35 micrograms per milliliter.

2 There's another paper that Dr. Kelly mentioned,
3 a paper by Scanlon, I think, in which 30 was better than 15
4 in severe apnea.

5 Now, you allowed your study patients to break
6 protocol, and apparently some of them went up into the 40
7 range or so after another loading dose, which is what
8 happened.

9 Can you say that in those cases you seemed to
10 get beneficial effects by increasing the dose once you went
11 off label and gave a second loading dose?

12 DR. ERENBERG: I believe, first of all, Dr.
13 Scanlon's study showed that the infants responded quicker
14 to the higher dose, but the success rate may not
15 necessarily have been greater.

16 DR. JENNE: I see.

17 DR. ERENBERG: Dr. Ludden, do we have values
18 with the second loading dose?

19 DR. LUDDEN: Yes, there are blood levels in the
20 data set for that, so I think that could be looked at. I
21 haven't looked at it yet.

22 DR. ERENBERG: We went with the fixed-dose
23 study. One of our original previous versions we were going
24 to look at a multi-dose escalating study for nonresponders,

1 but it was decided ultimately that for this study we would
2 be with a fixed dose with a strong safety net for
3 nonresponders, which is what we put together.

4 DR. JENNE: Well, this will probably be kicked
5 around later in the day.

6 DR. LI: Les?

7 DR. HENDELES: I have some questions about the
8 package insert, the labeling. Is now the appropriate time,
9 or would that be postponed until later?

10 DR. LI: Go ahead and ask your question. We
11 will probably be discussing that in more detail later, but
12 I think it's reasonable to bring it up, Les.

13 DR. HENDELES: One of the questions I have -- I
14 have several, but one of them relates to the fact that
15 there is no information in the labeling on adjusting the
16 dose for decreased renal function. You excluded that in
17 the study design but the drug is actually going to be given
18 to patients who have varying amounts. There's a brief
19 warning sign but it seems to me that there needs to be some
20 very specific dosing guidelines since the drug is as much
21 as 86 percent eliminated from the body by urinary
22 excretion.

23 DR. LI: Does anyone want to comment on that?
24 Otherwise I think we probably will be able to bring that up

1 after we hear from the FDA. Yes, Stan.

2 DR. SZEFLER: I had some questions on the
3 pharmacology of the drug, and it ties in with this NEC
4 question and the observation that Dr. Rothstein made on
5 blood flow.

6 I can't recall where it is, but somewhere in
7 this literature there's a mention that caffeine does not
8 affect cerebral blood flow, whereas theophylline does.
9 That seems to be posed as an advantage of caffeine in
10 treatment. This may tie it together because also there
11 seems to be the observation that the NEC has occurred with
12 theophylline use and not with caffeine.

13 Is there a common link here that should be
14 addressed in terms of the pharmacology of the drug?

15 DR. MOSDELL: I can review those studies that
16 discuss cerebral blood flow.

17 I think in terms of NEC we have to keep in mind
18 that there was one study that stated that there was no
19 statistical significant difference between caffeine and
20 theophylline. There was no frequency in that study so we
21 can't say how many patients in each group developed that
22 adverse event. That seems to suggest it may have occurred
23 in the caffeine group.

24 Nonetheless, the literature has been

1 predominantly associated with theophylline in terms of NEC.

2 I can if you wish go through the data with
3 cerebral blood flow if you are interested in those studies.

4 DR. SZEFLER: I don't think you need to take
5 time. Just to summarize would be fine.

6 DR. MOSDELL: Basically the literature that's
7 out on cerebral blood flow, one study compared caffeine to
8 theophylline on its effects on cerebral blood flow. In
9 that study caffeine was not shown to adversely affect
10 cerebral blood flow, whereas theophylline was shown to
11 decrease cerebral blood flow.

12 There were two additional studies that examined
13 cerebral blood flow. These were caffeine only looking at
14 baseline compared to after treatment. In those two studies
15 caffeine was not shown to affect cerebral blood flow.

16 So, those are the three studies that comprise
17 the data by suggesting there is no decreased cerebral blood
18 flow with caffeine, but perhaps with theophylline.

19 DR. SZEFLER: And these are all neonatal
20 subjects?

21 DR. MOSDELL: The cerebral blood flow studies
22 were all in infants.

23 DR. LI: Yes, Molly?

24 DR. OSBORNE: Again, staying with mucosal

1 injury and the necrotizing enterocolitis and caffeine, it's
2 certainly not a field I'm familiar with. So, I looked
3 through this epidemiology of necrotizing enterocolitis that
4 was included in your documents, Clinics in Perinatology,
5 1994. So, I'm going to say, is this a reasonable
6 hypothesis, and then help you give me feedback to see if
7 this is a way to think about it.

8 My concept of what's going on here is that if
9 someone who is premature, for whatever reason, develops
10 mucosal injury in the GI tract and then has a caffeine kind
11 of drug administered, there's the potential, perhaps in a
12 slight population, for that mucosal injury to occur,
13 perhaps because of a presser effects of the caffeine that
14 would then further decrease blood flow in an area that's
15 already injured. Then with inflammation developing, one
16 could then end up with necrotizing enterocolitis.

17 Is that a reasonable hypothesis? Is that how
18 to best put this information together that in some patients
19 with underlying mucosal injury, caffeine could then have an
20 exacerbating effect?

21 DR. ERENBERG: I think that is a potential.
22 There is no data to substantiate it. One of the proposed
23 etiologies for necrotizing enterocolitis is hyperosmolar
24 ether formula or medications. Caffeine is hypo-osmolar,

1 compared to theophylline, which is hyperosmolar. If the
2 mucosal injury has already occurred then I think that is a
3 potential. Does the oral administration of caffeine cause
4 the mucosal injury, which would then go on, I don't think
5 is.

6 Unfortunately, infants with necrotizing
7 enterocolitis, before they are clinically recognized, may
8 present with apnea, without the abdominal distention and
9 other signs and symptoms of necrotizing enterocolitis. So,
10 therefore, the potential does exist that the clinician may
11 initiate methylxanthine therapy prior to the full-blown
12 picture or the ability to make the diagnosis of necrotizing
13 enterocolitis.

14 DR. OSBORNE: Thank you. I'm just trying to
15 address how we're going to put together a warning.

16 DR. LI: Yes. Maybe the last question for
17 right now. Stan?

18 DR. SZEFLER: Just one question because I'm not
19 sure if we're going to be able to come back to Roxane
20 later.

21 DR. LI: We can.

22 DR. SZEFLER: Okay, good.

23 The quick question is, in the documentation
24 that we have, I didn't get a feel for what the study sites

1 were like. Were these clinical research sites that
2 participated in this study, or were they clinical sites
3 that had the opportunity to participate in research? What
4 was the distribution of the nine sites?

5 DR. ERENBERG: There were nine study sites.
6 All of them were affiliated with universities. None of
7 them had CRC's per se, but all had experience in clinical
8 research, and Dr. Wynne could list her study sites.

9 DR. WYNNE: I would like to refer you to your
10 briefing document. I don't know if you all have it or not.
11 It's actually page 8-19. I'll just go through these for
12 you very briefly.

13 The University of Kansas enrolled 3 patients.
14 Cooper Hospital enrolled 5. Medical College of Virginia,
15 14. Denver, Colorado Children's Hospital, 19. Women and
16 Infants Hospital of Rhode Island, 5. Oakwood Hospital, 3.
17 University of Texas Health Science Center, 12. University
18 of California, Irvine Medical Center, 17. And 4 at the
19 Carolinas Medical Center.

20 So, you can see there are three that enrolled
21 quite a few patients. The others enrolled a few.

22 DR. LI: I'd like to thank the sponsor for
23 their very forthright answers to the questions from the
24 committee.

1 Let's take a 15 minute break and we'll have the
2 FDA presentation at 10:15.

3 (Recess.)

4 DR. LI: Ladies and gentlemen, the sponsor and
5 Dr. Wynne have asked for just one or two minutes to have
6 the opportunity to answer some of the questions that came
7 up earlier this morning. They have been able to find some
8 additional information that might be helpful to us.

9 Dr. Wynne, before Dr. Pina's presentation, if
10 you would go ahead.

11 DR. WYNNE: Yes, thank you very much. One of
12 the questions that you raised earlier was, why were these
13 approximate 1,000 patients excluded from entry into the
14 trial? I do have that information for you.

15 The exact number of patients screened was
16 1,029, 87 of whom were enrolled. The patients excluded
17 then were 942. Reasons for exclusion were, 482 patients
18 did not meet the age requirement or apnea event
19 requirement. 248 were already receiving theophylline or
20 they were on ventilation.

21 Parents refused or were unable to give consent,
22 63 of the patients. Underlying disease, CNS,
23 cardiovascular, sepsis, 55. Death, 52; patient
24 transferred, 17; other, 13; and then there were 12 patients

1 with no reason stated. I think that will give you an
2 overview of the approximate 1,000 patients that were
3 screened.

4 A second question that came up earlier was the
5 incidence of PDA during the study. Actually there were two
6 reports -- I'm talking now about the double-blind -- in the
7 caffeine group and two in the placebo group. An additional
8 2 patients that were transferred from the placebo into the
9 caffeine open-label also were reported to have PDA.

10 I hope that answers the questions that you
11 asked earlier. Thank you very much.

12 DR. LI: Thank you, Dr. Wynne.

13 I'd now like to invite Dr. Pina, who is the FDA
14 medical reviewer, to give the FDA's presentation. Dr.
15 Pina.

16 DR. PINA: Good morning. I am Miriam Pina, the
17 medical reviewer from the Division of Pulmonary Drug
18 Products. I thank the members of the pulmonary committee
19 and consultants for being here today to discuss this
20 important drug, caffeine citrate injection, for the
21 treatment of apnea of prematurity.

22 I also would like to publicly acknowledge the
23 hard work of the other members of my review team: Dr. Jim
24 Gebert, statistical reviewer; Vibhakar Shah, our chemistry

1 reviewer; Misoon Chun from pharmacology-toxicology; Albert
2 Chen from biopharmacology; and our tireless project
3 manager, Lindsay Cobbs. Thank you very much for your help.

4 We heard a detailed presentation of what apnea
5 of prematurity is all about, and the data that the studies
6 with caffeine citrate have generated from the sponsor.
7 Thus, I would like to focus only on some issues that are
8 either complementary for the understanding of the data or
9 of concern from the regulatory point of view regarding the
10 study design and the results of trial OPR-001, and from the
11 data available from the literature. I will end my
12 presentation with a summary of the issues for discussion.

13 I will start with trial OPR-001.

14 As the sponsor explained, trial OPR-001 was a
15 multi-center randomized double-blind placebo-controlled
16 parallel study with an open-label rescue phase.

17 The target population was premature babies
18 between 28 and less than 33 weeks of gestational age, with
19 at least 6 apnea episodes in 24 hours or less. Apnea for
20 this trial was defined as a respiratory pause of 20 seconds
21 or more, with or without bradycardia. These events were to
22 be observed and recorded by the attending personnel.

23 As presented by Dr. Wynne, patients with
24 underlying causes of apnea were excluded from the trial. I

1 would like to explain here that the 2 patients in the
2 placebo group who were excluded because they were not
3 treated, they did not receive any treatment because they
4 were advanced from CPAP to mechanical ventilation before
5 they even started the treatment.

6 During the double-blind phase, the patients
7 received either caffeine citrate or an equivalent volume of
8 placebo. A patient could be rescued with open-label
9 caffeine citrate if the number of apnea events did not
10 remain less than 50 percent of the baseline rate and the
11 investigator felt that continuing double-blind treatment
12 placed the patient at unacceptable risk.

13 The original maximum duration of treatment was
14 10 days, but the treatment period was extended to 12 days
15 in the last amendment, and only 16 patients were enrolled
16 under this provision. As Dr. Wynne explained, only 4
17 patients completed the treatment to 12 days.

18 I should point out here that the primary
19 endpoint defined in the original protocol was the success
20 rate defined as having a 50 percent reduction of the
21 baseline number of episodes of apnea during hours 24 to 48
22 after the double-blind loading dose. But this primary
23 endpoint was revised, was amended to apnea rate on day 2
24 during amendment number 5. So, the final version of the

1 protocol has the primary efficacy endpoint, apnea rate on
2 day 2.

3 As we will see shortly after, both definitions
4 failed to show a statistically significant difference
5 between the treatment groups.

6 Secondary analyses of the apnea rate, the
7 primary endpoint, were number one, the reduction in apnea
8 episodes by at least 50 percent and, number two, the
9 elimination of apnea events, that is, no apnea events
10 reported for that day by treatment day or by total number
11 of days reported without apnea.

12 The secondary efficacy endpoints were, for
13 those patients who continued to have apnea events, they
14 analyzed the lowest heart rate, lowest oxygen saturation,
15 and the duration of apnea events. A sample size of 78
16 patients was chosen based on the original primary endpoint.
17 The sponsor assumed that a 50 percent reduction of apnea
18 events during hours 24 to 48 after the double-blind loading
19 dose would be seen in 70 percent of the caffeine-treated
20 patients and only 20 percent or less in the placebo-treated
21 patients.

22 The difference in success rates was lower than
23 the sponsor had predicted. It was about 20 percent, as we
24 have seen. According to our statistical reviewer's

1 calculations, the study was estimated to have only 44
2 percent power to pick up the observed difference in success
3 rates.

4 Before discussing the study results, let's look
5 at the number of patients receiving double-blind therapy by
6 treatment day as a result of the design of the study.
7 Let's remember that the study allowed for patients to be
8 transferred to open-label caffeine treatment if the
9 investigator considered it necessary.

10 From this light we note the marked reduction in
11 sample size in both groups after treatment day number 2.
12 Here we have study days baseline to day 10, and the number
13 of patients who completed that study day on baseline we
14 have 100 percent of patients in the caffeine and in the
15 placebo group. As you see, there is almost half of the
16 patients by the end of day number 2.

17 The number of patients who were transferred to
18 open-label caffeine or were permanently discontinued from
19 the trial was similar in the caffeine and in the placebo
20 groups, 53 percent in the caffeine group versus 65 percent
21 in the placebo group.

22 As explained before, the protocol-specified
23 primary efficacy endpoint was apnea rate on day 2. The
24 sponsor did not submit this analysis. Therefore, the

1 statistical reviewer performed the primary analysis of the
2 primary protocol-specified efficacy endpoint. For this
3 analysis he used scaling of the duration of baseline and of
4 the study days to 24 hours and the last value carried over
5 method.

6 Here we have the number of apneas in 24 hours
7 and the results on day 2. As we can see, the caffeine
8 group has an apnea rate of about 4.95 apneas in 24 hours.
9 In the placebo group, the apnea rate was 7.2. The
10 difference was not statistically significant.

11 The sponsor analyzed the apnea rate on day 2 by
12 identifying those patients who had a reduction in apnea
13 events equal to or greater than 50 percent of the baseline
14 apnea rate. In this chart we have the percent of patients
15 and the results on day 2.

16 From the total of patients, about 76 percent of
17 the patients had a reduction of 50 percent or more of the
18 apnea rates on day 2, and in the placebo group, 57 percent
19 of the patients met this endpoint on day 2. The difference
20 was not statistically significant.

21 Analyzing the 50 percent reduction of apnea
22 events by treatment days, we have here the percent of
23 patients and the number of treatment days. Each treatment
24 day up to day number 10. We see that on day 2 there was no

1 statistically significant difference, but the difference
2 was significant for days 4, 5, 7, 8, 9 and 10.

3 We should note, however, that this is a post
4 hoc analysis. In addition, it carries forward the apnea
5 rate value of 10 on the last day of double-blind treatment
6 for those patients who were transferred to open-label
7 caffeine or were discontinued from the trial.

8 I would like to explain that 10 patients in the
9 caffeine group, that is, 28 percent, and 6 patients in the
10 placebo group, 25 percent, had a reduction of 50 percent in
11 their apnea rate the day that they were transferred to
12 open-label caffeine or that they were discontinued from the
13 trial.

14 There were several reasons why they were
15 transferred from the trial. These were frequent
16 bradycardic events without apnea, persistent apnea events,
17 although the rate was still less than 50 percent of the
18 baseline period, or the patient was referred to another
19 hospital.

20 Keeping in mind that these are post hoc
21 analyses, we wanted to know how many patients in the
22 double-blind phase maintain the beneficial effect of the
23 drug until the end of the study period, how many patients
24 that had a 50 percent reduction of their apnea events, once

1 they reached the endpoint, how many maintained that effect.
2 Here is the graphic.

3 Here we have percent of patients. This y axis
4 uses as a denominator only the patients who achieved at
5 least once this endpoint. Here we have those patients who
6 maintained the drug effect, and those who did not maintain
7 the effect. That is, some days they had a reduction of 50
8 percent and some others did not reach this endpoint.

9 These two columns do not add to 100 percent
10 because we excluded those patients who reached this
11 endpoint but were transferred to open-label or were
12 discontinued from the trial.

13 The difference between the patients who
14 maintained the effect and those who did not plus those who
15 were discontinued is statistically significant.

16 Another way of analyzing the apnea rate was the
17 percent of patients with zero apnea events reported for 24-
18 hour periods. This table shows the percentage of patients
19 with no apnea events at each treatment day. Here we have
20 on the y axis the percent of patients who reached this
21 endpoint on treatment day number 1 up to day number 10. As
22 we can see, those with the asterisks, the difference was
23 statistically significant in favor of caffeine.

24 I would like to point out at this point that on

1 day 2 the difference was statistically significant. Day 2
2 was the day chosen by the sponsor to measure the primary
3 endpoint.

4 This graphic shows the analysis of the number
5 of patients by the total number of days spent without
6 apneas. That is, on the y axis we have how many patients
7 remained apnea-free for how many days. Here we don't have
8 treatment days, but total number of days with no apneas.

9 I would like to focus your attention on these
10 days, where about 10 patients in the caffeine group remain
11 apnea-free for 8 or more days. No patients in the placebo
12 group remained apnea-free for this long.

13 To answer one of Dr. Rothstein's questions,
14 regarding once the patients remained with no apneas for 24
15 hours, how many patients remained without apnea for the
16 rest of the period, I should say that from these 10
17 patients, 6 of them remained apnea-free continuously from
18 the first time they reached that endpoint.

19 We've also wanted to see how many patients
20 remained apnea-free once they reached that endpoint, and
21 that's what I said before. On the y axis we have those
22 patients who at least once -- is the percent of patients
23 who at least once presented no apneas for 24 hours, and how
24 many of those were able to maintain that effect until the

1 end of the study period.

2 Again, we see at 29 percent of the patients in
3 the caffeine group maintained that effect versus 1 patient,
4 which is 7.6 percent, in the placebo group. This patient,
5 1 patient in the placebo group, achieved this endpoint on
6 the last 2 days of the study period. Really, no patient
7 was in the placebo group apnea-free for more than 5 days,
8 and neither one in a row. There were some days yes and
9 some days no.

10 This table shows some of the characteristics
11 that you were asking before of those patients in the
12 caffeine group who met different efficacy endpoints, and
13 those who never met any of the efficacy endpoints. Here we
14 have some of the characteristics, gestational age, what was
15 the baseline apnea rate, the weight at entry, and the
16 caffeine plasma levels.

17 For those patients, 12, who had a reduction of
18 50 percent for more than 7 days, who had 0 apneas for more
19 than 7 days, and this is the failure group who never had a
20 greater than 50 percent reduction of their apnea rates. We
21 have 9 patients here.

22 As you can see, there is not a particular
23 subset of characteristics other than maybe weight at entry,
24 where those patients who had no apneas for greater than 7

1 days after the treatment was started were slightly heavier
2 than the other two groups.

3 Other secondary efficacy endpoints were lowest
4 heart rate associated with apneas. The mean values between
5 the caffeine and placebo groups were similar and not
6 statistically significantly different. They were between
7 67 to 78 beats per minute.

8 The lowest oxygen saturation associated with
9 apneas. The values were similar in both groups, 78 to 84
10 in the caffeine group and 77 to 87 in the placebo group.

11 The duration of apnea events was another
12 secondary efficacy endpoint. The durations were recorded
13 by the attending nurse once the apnea alarm went off.
14 Because the nurse was not always at bedside at the time the
15 apnea alarm went off, the manner of recording of the
16 duration of the apnea events can be considered unreliable.

17 The sponsor presented the duration of the apnea
18 events by day for the double-blind and the open-label
19 treatment periods for each treatment group, but did not
20 provide the analysis of the data for this endpoint.

21 According to the statistical reviewer's
22 calculations, the overall analysis of the summarization of
23 duration of the apnea events submitted by the sponsor did
24 not show a significant effect of caffeine on the duration

1 of apnea events.

2 From the safety point of view, the sponsor has
3 already presented a detailed description of the results in
4 OPR-001 trial. I would like to focus my discussion on two
5 issues only: some main adverse events and deaths.

6 The assessment of adverse events between the
7 treatment groups in this trial was difficult. Firstly, the
8 complex design of the trial allowed some patients in the
9 placebo group to be exposed to open-label caffeine at
10 different times, and secondly, the high frequency of
11 complications encountered in this population did not help
12 in many cases.

13 We tried to assess the main adverse events in
14 several ways to overcome some of these difficulties. I
15 will present to you the data by analyzing the incidence of
16 adverse events by exposure to caffeine and by
17 randomization.

18
19 The first analysis assessed the incidence of
20 adverse events by exposure to caffeine. The exposed group
21 includes all the patients randomized to the caffeine group
22 plus those patients in the placebo group who were
23 transferred to open-label caffeine. The not exposed group
24 includes the patients in the placebo group who were not

1 transferred to the open-label caffeine.

2 As you can see, no significant differences were
3 noted in the incidence of adverse events analyzed between
4 the treatment groups. It is clear, however, that the small
5 sample size could have made it difficult to pick up
6 significant differences in safety parameters, had there
7 been any. However, it is of note the numerical increase of
8 necrotizing enterocolitis, 5 versus 1; sepsis, 8 patients
9 versus 0; and death, 3 patients versus 0.

10 Another analysis studied the adverse events
11 that occurred to patients by their randomization,
12 regardless of their exposure to caffeine. We did this
13 analysis to overcome the time factor, where some patients
14 in the placebo group were transferred to open-label
15 caffeine quite early, with the possibility that they did
16 not have enough time to develop some complications that may
17 have occurred had they been allowed to continue in the same
18 treatment group for a longer time period. Again, no
19 significant differences were noted between the treatment
20 groups.

21 About mortality, there were 3 deaths reported
22 and all of them had been exposed to caffeine. Again, very
23 small numbers are difficult to interpret the meaning of
24 this.

1 I would like to discuss the data in the
2 literature for efficacy. The database consisted of 27
3 articles to provide data on efficacy, and we have 59
4 articles to provide data on safety. We have more safety
5 articles than the sponsor reported because we did our own
6 search.

7 From the efficacy point of view, 10 controlled
8 and 17 uncontrolled trials were submitted and reviewed. In
9 our review, we noted that no study was placebo-controlled,
10 all were open-label, and several different clinical
11 endpoints were studied. Except for one study, there were
12 no follow-up data after caffeine was discontinued.

13 However, all the investigators concluded that
14 caffeine improved the patients' apnea endpoints, when
15 compared to the patients' own baseline. However, we should
16 note here that apnea of prematurity tends to improve
17 simultaneously over time.

18 At this point I would like to bring your
19 attention to a particular study conducted by Murat, et al.,
20 in 1991. This is perhaps the best designed trial that
21 supports efficacy of caffeine in the literature. 18
22 premature infants were studied in this prospective
23 randomized parallel controlled trial. The dosage regimen
24 was similar to that used in trial OPR-001. Its primary

1 endpoint was apnea index on days 1, 5 and 15. Apnea index
2 was defined as the average number of apneic events per 100
3 minutes, obtained from the total number of events recorded
4 within a 24-hour period.

5 24-hour cardiorespiratory recordings were
6 performed to monitor apnea events on days 1, 5, 15 and on
7 day 8 after the therapy was discontinued.

8 The study by Murat, et al. showed a
9 statistically significant improvement of the apnea index in
10 the treated group on day 1 and day 5. I will show you
11 later the numbers obtained.

12 A substantial dropout of patients in the
13 control group made the analysis not significant at day 15.
14 This study also showed that apnea did not recur on day 8
15 after the discontinuation of caffeine.

16 Here we have the results on day 1, 5, and 15.
17 The apnea index was .24 versus .74 in the untreated
18 controls, and on day 5 we have .11 versus .57. This apnea
19 index of .24 would be an equivalent of about 3 apneas in 24
20 hours versus 10.6 apneas in 24 hours in the control group,
21 and the difference was statistically significant.

22 On day 5 we have an apnea rate of about 1.6 in
23 the caffeine group versus about 8 apneas in 24 hours in the
24 control group. Again, the difference was statistically

1 significant.

2 On day 15 the control group from 9 patients had
3 dropped to 3 patients only. The others had to be treated
4 with caffeine or were intubated. This apnea index is about
5 .5 apnea rate in 24 hours, and this is about 1.7, and the
6 difference was not statistically significant.

7
8 Regarding safety, the database from published
9 clinical trials and from our own search included over 800
10 premature infants exposed to caffeine. Instead of going
11 over the data on safety that the sponsor has already
12 presented, I would like to emphasize two particular issues.
13 The association of methylxanthines with the incidence of
14 necrotizing enterocolitis and the information currently
15 available on drug-drug interactions.

16 In general, the adverse events reported in the
17 literature for caffeine are similar to those reported for
18 trial OPR-001, and when caffeine was compared to
19 theophylline, the adverse events were usually less
20 frequent.

21 Because of its morbidity and high mortality,
22 and the question raised in the literature regarding its
23 association with the use of methylxanthines, I would like
24 now to focus your attention on necrotizing enterocolitis.

1 As the sponsor has explained, NEC is a major
2 cause of morbidity and mortality in premature infants. Its
3 reported incidence ranges from 2 to about 15 percent, with
4 the highest incidence seen in the lowest birth weight
5 groups.

6 The reported mortality varies from 20 to 50
7 percent according to other medical factors involved.
8 Factors like the use of umbilical artery catheters, some
9 pharmacological agents like aminophylline, theophylline,
10 caffeine and vitamin E, in high density formulas have all
11 been implicated with the incidence of NEC and infant
12 survival.

13 Some of the issues obtained from the literature
14 are as follows. Robinson, et al., in 1980 was one of the
15 first ones to suggest the association of xanthine treatment
16 with the development of NEC. The others published three
17 cases of NEC in premature infants after treatment with
18 aminophylline, and postulated that in these cases NEC was
19 related to bacteria overgrowth due to decreased GI motility
20 which followed the use of xanthines.

21 Grosfeld, et al., in 1983 studied the effect of
22 aminophylline in an experimental bowel ischemia model and
23 suggested that aminophylline had an adverse effect in
24 animals with ischemic bowel insults.

1 After these reports, several other studies
2 tried to address this question. In most cases theophylline
3 was the xanthine studied, probably because theophylline was
4 the most widely used methylxanthine.

5 A retrospective analysis by Davis, et al., in
6 1986 demonstrated that 124 infants treated with
7 theophylline had a similar incidence of NEC as did 151
8 infants who were not treated with theophylline.

9 In other papers, theophylline was compared to
10 caffeine. Bairam, et al., in 1986 studied the effect of
11 caffeine in 10 babies compared to those of 10 babies on
12 theophylline. In this trial, 4 infants in the theophylline
13 group were stopped for GI intolerance. 2 of them were
14 reported to have developed signs of NEC.

15 The caffeine group did not develop significant
16 GI symptoms. These results were not compared to a placebo
17 or untreated arm for a background incidence of NEC.

18 Larsen, et al., in 1995 reported no differences
19 in the incidents of necrotizing enterocolitis between the
20 caffeine group -- 82 patients were treated with caffeine --
21 and theophylline, 98 patients. However, the actual
22 incidence of NEC in each group was not published.

23

24 I will close this section by stating that

1 overall the findings in the literature are not conclusive.
2 Whether the exposure to methylxanthines in general and to
3 caffeine in particular is associated with an increased
4 incidence of NEC, nor if there is a subset of patients at
5 higher risk of developing this disease if exposed to
6 caffeine. One of my personal goals for today is to hear
7 your opinion regarding this issue.

8 The second issue on safety derived from the
9 literature is the drug interactions with caffeine. The
10 biopharmacology data base consisted of 71 studies, mainly
11 from adult healthy volunteers or patients. Only 1
12 pediatric patient was submitted for a discussion of drug-
13 drug interactions. This paper reported three cases of
14 increased clearance of caffeine within co-administration of
15 phenobarbital.

16 The data provided very limited information on
17 caffeine dose adjustments that may be needed following the
18 coadministration of drugs prescribed to preterm neonates.
19 Lower or higher doses may be needed following
20 coadministration of drugs like cimetidine, ketoconazole,
21 and phenobarbital. But the manner of the adjustment is
22 not yet known.

23 In summary, study OPR-001 is the only
24 randomized double-blind placebo-controlled trial in which

1 caffeine was studied for the treatment of apnea of
2 prematurity. It failed to show a statistically significant
3 difference in the primary endpoint apnea rate on day 2
4 after the loading dose in favor of caffeine. But it showed
5 a statistically significant effect in reducing or
6 eliminating apnea events in the target population. These
7 calculations, however, were not protocol-specified.

8 Most trials in the literature were small and
9 not adequate and well-controlled. However, caffeine was
10 consistently shown to improve the patients' endpoint
11 studied when compared to the patients on baseline.

12 Based on the results from study OPR-001 and the
13 data available in the literature, do you consider that
14 there is enough evidence to support efficacy of caffeine
15 citrate for the treatment of apnea of prematurity? That's
16 our question.

17
18 Regarding safety, study OPR-001 had a complex
19 design with a high rate of dropouts early in the study that
20 made difficult the interpretation of the data. It showed
21 no clinically significant differences in adverse events by
22 body system between caffeine and placebo-treated patients.

23 The numerical increase in the incidence of
24 necrotizing enterocolitis found in the caffeine-treated

1 group is of concern, admitting that the association of
2 methylxanthines with an increased risk of NEC has
3 previously been questioned in the literature.

4 The data in the literature were consistent with
5 the findings in the clinical trial.

6 Regarding the association of NEC with the use
7 of xanthines, the findings are not conclusive in either
8 direction.

9 And regarding the drug-drug interactions, no
10 data are available to adjust caffeine dose with the
11 coadministration of other drugs.

12 We would like to hear the opinion of the panel
13 whether the effects shown to you today constitute
14 sufficient evidence of the safety of caffeine citrate for
15 the treatment of apnea of prematurity.

16 Thank you very much.

17 DR. LI: Thank you, Dr. Pina.

18 I'd like to ask the committee if they have any
19 questions for Dr. Pina.

20 DR. CRIM: I have a question relating to both
21 the efficacy and the safety from the literature review. I
22 think it would help in terms of my question on the efficacy
23 if you can pull back up your slide 36 that gave the results
24 of that Murat study.

1 The question I had was in terms of the number
2 or frequency in which patients would get better over time
3 anyway. My question as far as this efficacy is, it looks
4 like there's a decrease in this apnea index for both groups
5 over time. Although you don't have either standard error
6 or standard deviation data for day 5, just looking at the
7 control group, is it possible to glean from that study as
8 to whether the difference between day 1 and day 5 for the
9 control group, or between day 5 and day 15 is improving
10 statistically within groups?

11 DR. PINA: Yes, they did check that in the
12 study and it was statistically significant from here to
13 here.

14 DR. CRIM: And what about for the control,
15 between the .74 and the .57, and .57 to .12 for the
16 control? That statistically improved?

17 DR. PINA: It was, yes.

18 DR. CRIM: And then the other thing regarding
19 the safety, which I guess you have on slide 41, was the
20 study by Davis that saw similar incidents of NEC between
21 the theophylline-treated and the non-theophylline infants.

22 I guess my question for that, was there any
23 statement in that study as to the duration of exposure to
24 theophylline in 124 infants?

1 In other words, was this any exposure, or 10-
2 day exposure, or 2-week exposure and an effect not being
3 found, or was this, for instance, 1 day of exposure in the
4 theophylline?

5 DR. PINA: I don't know if the sponsor has that
6 article with you, but this is a retrospective study. This
7 was a study for something else. So, inside of the study
8 they looked for the patients who were treated with
9 theophylline and those who were not treated with
10 theophylline with apnea events.

11 I'm not sure if they evaluated duration of
12 treatment of theophylline.

13 DR. SZEFLER: I'd like to congratulate you and
14 also Roxane for some excellent presentations and
15 interaction on the evaluation of the data.

16 The one question I had was, these primary
17 efficacy variables are very hard to choose and they are so
18 important. In the development of this protocol and the FDA
19 involvement, how much discussion was there around the
20 primary efficacy variable?

21 Is the Murat study the study that was kind of
22 counted on for these estimates of 70 percent efficacy and
23 20 percent placebo? Did you have general agreement or
24 disagreement on the primary efficacy variable?

1 DR. PINA: I know from the sponsor's point of
2 view, nobody there was at the preliminary discussion of the
3 original protocol. From our side, I was not here when this
4 was started.

5 DR. SZEFLER: Because I believe these start
6 from the IND phase.

7 DR. PINA: Yes. We had discussed with them
8 from the beginning the design of this protocol and we went
9 through a lot of arrangements trying to find the ideal
10 design for this trial.

11 I think the sponsor has something to add.

12 DR. LI: Does the sponsor want to make a brief
13 comment?

14 DR. ERENBERG: I guess I have the historical
15 memory because I was at all of those. You are absolutely
16 correct. We did go through what we could glean from the
17 literature, looked at the various endpoints, apnea density,
18 number of apneic events. We tried to come to a conclusion
19 as to what would be reasonable estimates, and we came to
20 the protocol as it is designed here.

21 DR. PINA: The original protocol-specified
22 primary endpoint was the 50 percent reduction, and then it
23 was changed to apnea rate on day 2.

24 What I can say is that even no apneas on day 2

1 are all different analyses of the same event, which is the
2 number of apnea events on day 2 and just a 50 percent
3 reduction or no apneas, or apnea rate per se on day 2.
4 They are just different analyses of the same clinical
5 endpoint.

6 DR. LI: Dr. Goldsmith?

7 DR. GOLDSMITH: If we look at safety as well as
8 drug-drug interaction, I want to come back to a comment by
9 Dr. Osborne before looking at potential causes of
10 necrotizing enterocolitis. If we say that there is mucosal
11 injury and ischemia, and then the potential for something
12 that might cause a change in blood flow, some drug that
13 might cause a change in blood flow, and then in addition a
14 bacterial aspect to this or an invasion of an organism,
15 then I'm concerned about the interaction between
16 methylxanthines and any H2 blockers, any H2 antagonists,
17 where we change the flora in the gastrointestinal system.
18 So, the combination of caffeine and cimetidine, or any of
19 the other H2 blockers would be very important.

20 Is there any information with regards to NEC on
21 that combination drug-drug interaction or safety that you
22 know about or that the sponsor knows about?

23 DR. PINA: Not from our point of view.

24 DR. WYNNE: I think I'm going to address this

1 question to Dr. Mosdell, who just returned. Could you
2 repeat the question please?

3 DR. GOLDSMITH: The question was, is there any
4 information regarding incidence of NEC in combination with
5 H2 blockers, methylxanthines with H2 blockers, since the H2
6 blockers may change the bacterial flora by changing the pH
7 of the gastrointestinal tract?

8 DR. MOSDELL: The primary focus that we did in
9 our literature search involved caffeine and its association
10 with NEC, and also an additional analysis that looked at
11 theophylline and its association with NEC. In none of
12 those trials was it mentioned that histamine blockers could
13 be associated with an increased incidence of NEC, or the
14 combination of the two increased the incidence of NEC.
15 Although our literature search did not focus on histamine
16 blockers, so we may not have collected all the articles.

17 In specifically looking at caffeine or
18 theophylline literature, what I could read didn't have any
19 type of association that was described.

20 DR. HENDELES: To Dr. Pina. You commented on a
21 study on drug interactions involving premature infants, but
22 I don't recall, what were the drugs and what were the
23 findings of that study?

24 DR. PINA: There was only one paper submitted

1 addressing drug interactions. One paper in premature
2 infants. This paper was just a report of three cases of
3 phenobarbital interaction with caffeine, where they didn't
4 find caffeine levels. They had to increase the caffeine
5 dose.

6 DR. HENDELES: The reason why I bring that up
7 is there were all these other papers on interactions in
8 adults. I don't see the relationship. If the premature
9 infant lacks cytochrome P450 1A2, which is the primary site
10 of interaction in adults, I don't know that any of those
11 have any relationship to this population at all.

12 DR. LI: Curt?

13 DR. SESSLER: The high rate of sepsis and NEC
14 in the caffeine-exposed patients may be concerning, but it
15 also might be related to other factors, including severity
16 of illness. Was there any severity adjustment considered
17 in that analysis or other comments you might make in that
18 regard?

19 DR. PINA: I'm sorry. Can you repeat your
20 question?

21 DR. HENDELES: I'm struck by the fact that the
22 sepsis rate was 13 percent in the caffeine-exposed patients
23 and 0 percent in the not exposed patients. But it may be
24 that the not exposed patients were less premature and had

1 less in the way of other medical illness.

2 Did you attempt to adjust for severity in any
3 way in your analysis?

4 DR. PINA: No, we didn't. What I see is that
5 sepsis could be one of these cases where you start having
6 apneas before the child is diagnosed with sepsis. We
7 thought that these patients could have the apnea and then
8 be enrolled in the trial and then start having the culture
9 positive or the other signs of sepsis.

10 It's one of these cases where it is also common
11 to find sepsis in this population and not in the study.

12 DR. SESSLER: If I may follow, I'd be
13 interested in any thoughts really from the sponsor or other
14 members of the committee or others in this room along those
15 lines as far as experience with severity of illness and its
16 relationship to this condition.

17 DR. ERENBERG: I think the neonatologists on
18 the panel would also agree that many infants are labeled as
19 suspect sepsis as soon as they develop any form of
20 symptomatology. We know of only one infant who was culture
21 proven. The question is, of these increased number, how
22 many of them were culture proven and how many of them were
23 suspect sepsis because of just development of apnea, were
24 treated for a very limited time period, and then

1 discontinued.

2 I think you're correct in that if a child does
3 become symptomatic, you automatically list certain
4 potential disease processes, and sepsis is always very
5 high.

6 The key is what happens 48 to 72 hours later
7 after you get your blood cultures back, what was the
8 response of the child to your therapeutic interventions.

9 DR. PINA: What is difficult to know here is
10 that in many cases even when the culture was not positive,
11 the patient did receive complete treatment with
12 antibiotics. I don't know what to say in those cases.

13 DR. SESSLER: May I follow up with further on
14 that?

15 DR. LI: Yes.

16 DR. SESSLER: Let me ask, perhaps to the
17 sponsor again, was any severity of illness scoring system
18 used to further define the population? Typically in adult
19 ICU populations you routinely will use an Apache score or
20 something akin to that.

21 DR. ERENBERG: No, we did not use that. The
22 only thing we used were the number of apneic spells at the
23 baseline for enrollment.

24 DR. LI: Dr. Goldsmith?

1 DR. GOLDSMITH: Throughout this discussion I
2 have not heard any distinguishing features of the apnea,
3 whether it was obstructive or central. In many of the
4 extremely premature infants, obstructive apnea can merely
5 be from body position in an incubator.

6 Were any differentiations made by the sponsor?
7 Did you see anything, Dr. Pina, in any of the literature
8 that would distinguish between the types of apnea as the
9 studies were done?

10 DR. PINA: Mainly they were addressed as
11 central apneas and that was the entry criteria.

12 DR. GOLDSMITH: Defined as what, and proven by
13 what?

14 DR. PINA: It was clinically assessed.

15 I think that you do have some pneumograms at
16 the beginning but we found so many technical problems that
17 at the end it was decided not to continue doing
18 pneumocardiogram recordings.

19 DR. LI: I think based on some of the
20 differences that were found between the treatment and the
21 placebo group, you came to the conclusion that the study
22 was under-powered. Do you have an estimate of how large a
23 study would have been necessary to increase the power of
24 the study from the 44 percent to about 80 percent or so?

1 DR. PINA: Do you want to answer that question?

2 DR. GEBERT: Jim Gebert, Division of
3 Biometrics. I did not do any calculations to see what size
4 study would have been needed to have, let's say, 80 percent
5 power.

6 DR. LI: Dr. Osborne.

7 DR. OSBORNE: Along those lines, just to make a
8 comment and then ask Dr. Pina if I'm off base or this is a
9 correct kind of comment. It strikes me that looking at
10 table 7, which is a very nice way of looking at the
11 patients and the caffeine group and the placebo group, this
12 is page 13 in the document that we got. I actually don't
13 know if you have something comparable for the sponsors.

14 It nicely goes through both the patients who
15 got caffeine and placebo, and as a reminder, the sample
16 size estimates had hoped for a 70 percent reduction, 70
17 percent of the patients having greater than 50 percent
18 reduction in the caffeine group, 20 percent having greater
19 than 50 percent in the placebo group.

20 Although we certainly don't see those numbers,
21 what I see are very consistent numbers for both the
22 caffeine group and the placebo group and they are
23 different. We've talked about two sources of problems that
24 might give us a type 2 error that we might not see a

1 difference that's really there: number one, the small
2 sample size, which has been alluded to, which I think is a
3 crucial factor, and number two, the possibility that in
4 fact the group that got caffeine was sicker.

5 One might think with the open-label modeling of
6 the design that we might actually be incorporating in the
7 caffeine group those that have a higher severity of illness
8 score. Certainly they were, at least by numbers, more
9 patients with sepsis.

10 Those kinds of problems in a small sample size
11 and perhaps a difference in severity in the two groups
12 would actually argue that we would not expect to see an
13 effect. So, I'm actually impressed that we've seen
14 consistent numbers in the two columns, even though it's not
15 quite 70 percent for caffeine, and it's certainly not 20 in
16 placebo. That's my comment.

17 The question is, is that on base? And if it is
18 on base, were any trend analyses done for the very nice
19 data that you did show, the post hoc analyses that did show
20 significant differences in the two groups and zero apneas
21 and so forth because the trend analyses might help with
22 putting together these day-by-day comparisons.

23 DR. PINA: Yes, your analysis of this is
24 correct except that the part of the sicker patients -- this

1 is analysis of only the double-blind phase, where both
2 groups were exactly the same by randomization. When they
3 were transferred to open-label, the value of that day was
4 carried forward. So, it doesn't take into account what
5 happened to those transferred to open-label from the
6 placebo group.

7 DR. OSBORNE: Do you do trend analyses on the
8 data that you showed this morning or just pair-wise
9 comparison?

10 DR. PINA: No, we did not do that analysis.

11 DR. LI: Dr. Kelly?

12 DR. KELLY: It seems to me with the way the
13 study was designed that you can go to an open-label
14 caffeine that sort of a survival analysis would have been a
15 nice thing to look at in terms of separation of the groups.
16 Did you do Kaplan-Meier survival type analysis?

17 DR. PINA: I think we did try to do that but it
18 was not possible due to this design also. It's not one
19 event. The first time you have the event is the event on
20 each day so it was not possible to do that design. I think
21 Dr. Chinchilli will talk about that.

22 DR. CHINCHILLI: Yes, I did an analysis like
23 that which I'll present this afternoon.

24 DR. KELLY: Okay.

1 DR. LI: Dr. Osborne.

2 DR. OSBORNE: One more quick question. In all
3 fairness again, asking if I'm on base here. It sounds like
4 the FDA and the sponsor did agree on these endpoints, at
5 least at some point during the development of this study.
6 Although we might all look back and do it differently, this
7 was something that was agreed upon over several iterations
8 -- is that correct -- over the last few years.

9 DR. PINA: Yes, we did agree on the design.

10 DR. LI: And to follow up on Molly's point, the
11 conclusion of the presentation is that the agreed-upon
12 primary efficacy variables endpoints in fact were negative
13 in result in that there was no statistically significant
14 difference between the treatment group and the placebo on
15 those agreed-upon primary efficacy variables, although the
16 post hoc analysis of various sorts with multiple
17 comparisons did show certainly trends, perhaps even strong
18 trends toward support of the idea that the treatment was
19 more effective than the placebo.

20 Is that a fair characterization?

21 DR. PINA: Yes.

22 DR. SZEFLER: Jim, just to follow up on that
23 line of thought, are there enough variables that you see
24 because if you take enough tests, you're going to find

1 something that works. But in here there seemed to be, at
2 least to me, a pretty large proportion of those kind of
3 numbers. Maybe you looked at larger numbers and this
4 represents a small population of those numbers. Are you
5 pretty convinced that clinically meaningful parameters,
6 that a large proportion of those numbers seem to go in the
7 right direction?

8 DR. PINA: Well, I hope Dr. Chinchilli will
9 talk about that analysis this afternoon, but that's one of
10 the puzzles we have that we are asking you to help us with.
11 If there's really enough evidence, can we extrapolate this
12 small number to a larger number of patients?

13 DR. LI: I think to follow up, I think that's
14 probably the crucial question. For example, with the
15 multiple comparisons that were performed, I see that
16 statistical analyses were done and generally p less than
17 0.05 was used as a cutoff for significance, arbitrarily of
18 course. Is there any reason to think, I guess based on
19 what Stan just said, whether we ought to be using a more
20 stringent criteria for statistical significance based on
21 the multiple comparisons that were done?

22 DR. PINA: Exactly. That's one of our
23 questions.

24 Actually sample size is one of the things that

1 we asked the sponsor if they were sure the sample size was
2 calculated correctly because that was one of our concerns.
3 Is the sample size enough to show the efficacy of caffeine?
4 Now it's one of the things that see is a problem that maybe
5 is the problem.

6 DR. SZEFLER: I think your approach was
7 excellent. Where the lack was was in past data. That's
8 what Vern was asking the question about previously is what
9 literature do you have to make those kind of estimates
10 because I think what we need to hone down on is what was
11 that past literature and what are clinically meaningful
12 results that bear some risk. I'll kind of address those
13 comments later on.

14 DR. LI: Again, along those lines, how much
15 confidence do you have in the data from the Murat study
16 given the analysis is based on published information and I
17 take it you haven't had a chance to analyze the data and
18 certainly didn't proctor the study.

19 DR. PINA: I think that the Murat trial -- one
20 of them, it was an open-label, so it is a negative point.
21 But the recording of the apnea events not only observed by
22 the nurse, which is not always at the bedside -- that's I
23 think one of the deficiencies of the trial OPR-001. But in
24 the Murat trial, they did a 24-hour recording of apnea

1 events. So, that makes an objective evaluation of the
2 primary endpoint. So, even though it was an open-label, we
3 have a reasonable objective primary endpoint that we can
4 talk about.

5 DR. LI: As a follow-up, would it be feasible
6 currently to conduct a study using an apnea monitor rather
7 than counting apnea episodes on nurses' observations? Is
8 that practical and feasible or not?

9 DR. PINA: I would let the neonatologists, but
10 I think that it would have been the ideal if we had a
11 monitor with a recording capability.

12 DR. GOLDSMITH: Absolutely possible now because
13 most of the monitors have memory and you can go back for
14 several days. Probably to prove it, you'd have to hook
15 some sort of printout mechanism to it, but most of the
16 monitors in use now in NICU's all over this country have
17 memory that goes --

18 DR. LI: But was that technology not available
19 a year or two ago?

20 DR. GOLDSMITH: I think that has been changing
21 over the last five years or so. The other neonatologists
22 can comment, but as people have been upgrading their
23 monitoring systems, all the new ones now have memory.

24 DR. PINA: And many babies go home with these

1 type of monitors.

2 DR. GOLDSMITH: Which also has memory.

3 DR. PINA: Right.

4 DR. LI: Dr. Crim.

5 DR. CRIM: My question may have been addressed
6 when the sponsor presented their data. Maybe you can
7 comment upon it.

8 Just take an observation of the high dropout
9 rate over the course of the study such that, for instance,
10 by day 10 there were only 11 in the placebo group, and
11 recognizing that apparently there was a great deal of
12 reluctance of the various study centers to enroll patients
13 just because of the fact it appeared that they felt that
14 the caffeine was standard treatment.

15 Do you have a sense of -- and maybe it was
16 again presented. The subjects who were taken out of the
17 double-blind and put into an open-label -- I'm just
18 wondering whether or not there was some degree of bias on
19 the part of the investigators, since they were not
20 enthusiastic about giving their patients placebo in the
21 first place, to what degree they were inclined to take
22 their patients out of the blinded and put them in the open-
23 label in terms of the number of apnea events prior to them
24 being taken out of the blinded and placed into the open-

1 label. Were there any major differences between the
2 placebo --

3 DR. PINA: I think there was some kind of bias,
4 that investigators felt not sure that this patient is on
5 caffeine because in many cases I could see a drop of the
6 apnea rate below 50 percent of the baseline and this
7 patient was still transferred to open-label caffeine. So,
8 it at least tells me the investigator was blind but was not
9 sure that it was in the right drug, and so many patients
10 were transferred to open-label caffeine even though they
11 were responding, not meeting the endpoint criteria but some
12 of them were meeting a 50 percent reduction.

13 DR. CRIM: In even some of the placebos?

14 DR. PINA: In some of the placebos.

15 DR. LI: It shows the power of the placebo
16 design of the study, as Dr. Rothstein said I think.
17 Clearly the response in the placebo group was greater than
18 one might have anticipated.

19 Stan?

20 DR. SZEFLER: Just to follow up, I think you
21 have an important question. As I was going through the
22 literature, I was asking myself questions on the
23 pharmacodynamics because I hadn't had a chance to look
24 through all the articles, but what doesn't kind of come out

1 is the pharmacodynamics. My understanding, in talking to
2 several people, is the onset of effect is immediate, like
3 within minutes and certainly within hours. So, that time
4 of 24 hours would certainly be an area where you could
5 characterize whether somebody was a responder or
6 nonresponder.

7 I think that gets to be critical because in my
8 understanding of this population -- we'll probably talk
9 about it more later -- there are dramatic responders and
10 there are nonresponders and then there are responders who
11 then become nonresponders later on. This probably is the
12 most detailed observation period in terms of the effect of
13 the drug versus placebo that would be published I think.

14 DR. CRIM: I guess I'll say, along the same
15 lines, were there individuals who responded one day, didn't
16 respond the next, and then responded again a subsequent
17 day?

18 DR. SZEFLER: I think without that kind of
19 monitoring that was mentioned previously, the dynamics
20 wouldn't be as clearly elucidated as you would like.

21 DR. PINA: I think those who responded with no
22 apneas, those who responded well to the treatment,
23 maintained that effect, and 50 percent reduction, we see a
24 little more variability from day to day. I don't think we

1 have data as to onset of effect after the double-blind
2 loading dose.

3 There is one article in the literature where
4 two different doses of caffeine -- if you please look at
5 table 21 from the medical review of the NDA, table 21 and
6 the author is Scanlon, et al., 1992. Two different doses
7 of caffeine were studied versus theophylline, and the
8 higher dose of caffeine seemed to have had a better
9 response earlier than the lower dose, but at the end, the
10 effect was about the same in both groups. The higher dose
11 was similar to the theophylline group. The lower dose, it
12 seemed that it took a little longer to hit in, and then the
13 response was about the same in both groups. That's about
14 what we have regarding onset of effect.

15 DR. LI: Are there any other questions for Dr.
16 Pina?

17 (No response.)

18 DR. LI: Well, we remain ahead of schedule.
19 Let's break for lunch and return at 12:20. That will give
20 us an extra 10 minutes that we can recapture for this
21 afternoon. So, we'll plan to reconvene and begin promptly
22 at 12:20.

23 (Whereupon, at 11:30 a.m., the committee was
24 recessed, to reconvene at 12:20 p.m., this same day.)

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AFTERNOON SESSION

(12:30 p.m.)

DR. LI: Welcome back. I'd like to reconvene our meeting this afternoon.

We've taken the liberty of asking three of our committee members to prepare some comments and thoughts for us. So, we will begin our open discussion with presentations, first from Dr. Rothstein. Then we've already had a tantalizing preview from Dr. Chinchilli, and he'll be able to fill us in on the meat of his presentation secondly. Last but certainly not least, Dr. Szeffler will give us some comments, perhaps give us the big picture on the issues before us today.

I think we will also have time for questions or discussions after each presentation.

So, Dr. Rothstein, do you have some comments and some slides for us?

DR. ROTHSTEIN: Dr. Li asked me to make some comments about the topic, and given some of the questions today, as the expression goes at meetings, I just happen to

1 have a few slides with me.

2 (Laughter.)

3 DR. ROTHSTEIN: For those of you who spend most
4 of your life with the 3,000-week old infants --

5 (Laughter.)

6 DR. ROTHSTEIN: -- newborn encompasses a
7 tremendous range in terms of development and function, and
8 those infants who are born without the benefit of the last
9 trimester, when there are tremendous changes in organ
10 function and development, are working at a disadvantage.
11 But it is very difficult to lump a 28-weeker together with
12 a 37-weeker and come up with any sort of coherent
13 conclusions.

14 The questions were raised about incidence of
15 various diseases. The younger you are, the more likely
16 you're to have any of these afflictions: RDS, patent
17 ductus, enterocolitis, retrolental fibroplasia,
18 bronchopulmonary dysplasia, intraventricular hemorrhage.
19 As you can see, the numbers go up the younger the infant.

20 I've got a couple slides just on sort of
21 developmental pharmacokinetics and dynamics in terms of
22 looking at various parameters. This happens to be response
23 to the drug isoflurane, which most of you do not use but is
24 common in the operating room. I use it only to show that

1 -- these are term newborns here. These are 32-37-weekers.
2 These are less than 32-weekers. And there's not great data
3 on 27-, 26-, 28-weekers in terms of various drugs. But the
4 y axis can represent any drug effect you want, ED50, ED95.
5 There is going to be a markedly different response the
6 younger the infant.

7 This happens to show the development in term
8 infants of the neuromuscular junction. A term infant, when
9 born, does not have the same level of development that you
10 or I do.

11 In terms of variation of response, this happens
12 to be a response to curare, one of my favorite drugs, but
13 looking at the difference in response to a given dose to
14 produce a uniform endpoint, the variation response between
15 newborns is about three times what it is in older kids and
16 adults.

17 What causes some of these differences in
18 response? Drugs that are distributed through the
19 extracellular fluid space -- again, these are neonates.
20 These are term neonates, not even including some of the
21 micro-beings that we're discussing this morning and this
22 afternoon. But the extracellular fluid space is
23 significantly larger than it is in adults.

24 This is steady state distribution volume again

1 for curare which mirrors the extracellular fluid space.

2 People have raised the issue of renal function.
3 Again, GFR is about a third to a quarter of what it is in
4 adults in term newborns. I notice one of the exclusion
5 criteria for this study was a creatinine I believe greater
6 than 1.7. By the time your creatinine is 1 as a newborn,
7 you're essentially approaching renal failure in terms of
8 clearance.

9 Again, 24-hour excretion. Given the low GFR,
10 any drug that depends on renal excretion, there will be
11 accumulation in the young infants.

12 Variability of response. This happens to be
13 elimination half-lives of morphine in a population of
14 newborns, essentially almost a six-fold difference in half-
15 life. So, the differences that are being seen with
16 caffeine or theophylline are no different than seen with
17 any other drug. What it's going to depend on is a given
18 28-weeker or 32-weeker, what was the development of the
19 kidney?

20 And it can vary tremendously. All 32-weekers
21 are not the same. All volumes of distribution are not
22 equal in any given population of 31-weekers. Then you
23 start mixing and matching all these various factors, and
24 one comes up with some parameters with tremendously wide

1 standard deviations.

2 Let's skip these last two and we'll go to the
3 overheads.

4 One of the difficulties in the literature in
5 apnea of prematurity starts with the definition. Even this
6 morning, we heard two definitions of apnea of prematurity.
7 As one goes through the older literature, people introduce
8 concepts of short apnea, apnea defined as 10 seconds, 15
9 seconds, 20 seconds. So, there may be either different
10 processes going on that are being looked at or there's a
11 tremendously broad range of the problem that people have
12 examined.

13 The incidence of the problem, depending on what
14 series and how the study was conducted, in infants under
15 1,000 grams, the incidence of apnea, anywhere between 84 or
16 85 percent and 100 percent. In infants below 2,500 grams,
17 it's quoted as about 25 percent.

18 The peak frequency of apnea occurs by day 7.
19 It's influenced, as was mentioned this morning, by the
20 sleep state or the awake state that the child is in.
21 That's increased in REM states.

22 Another area that impacts on apnea is the
23 tremendously different responses to carbon dioxide and
24 hypoxia in the newborn compared to you and I.

1 This data is from the classic studies of Henry
2 Gaye Rigatto looking at responses to carbon dioxide
3 depending on gestational age. The 32-weeker, as the
4 inhaled CO₂ is increased, has less of a response than does
5 a 37-weeker. One would normally think that one doesn't
6 give CO₂ in the newborn unit, but any process that may
7 increase CO₂ in the newborn, whether it's fever, whether
8 it's hypoventilation from any cause, the response to that
9 is diminished the younger the infant.

10 Looking at it another way, at day of life 2
11 versus day of life 27, there is an increasing response to a
12 given stimulus with chronologic age. One of the problems
13 we're dealing with in looking at apnea is we saw in the
14 data that in the control population there is a decrease in
15 apnea from whenever time 0 is chosen for that infant, but
16 there will also be changes in response to hypoxia or
17 hypercarbia depending on the chronologic age of the child
18 and it will change as one goes farther into the study.

19 This is a composite looking at changes in
20 minute ventilation at 32 weeks versus 37 weeks versus CO₂
21 and then again looking at it with advancing chronologic
22 age.

23 A significant difference in newborns compared
24 to us is the response to hypoxia. Hypoxemia in you or I is

1 a respiratory stimulant. Otherwise no one would have ever
2 climbed Mount Everest. They all would have dropped off
3 when they hit the first base camp. In a premature neonate,
4 there is initially an increase in ventilation in response
5 to decreased oxygen, and then hypoxia becomes a respiratory
6 depressant. This response, as you can see -- with
7 advancing chronologic age, there is an increase in
8 ventilation initially, but there is still then a decrease
9 in ventilation very shortly after the institution of a
10 hypoxic event.

11 The interaction of levels of oxygenation,
12 hypoxia with increase in carbon dioxide, again as one sees
13 with a 15 percent oxygen stimulus, there is a depression of
14 the CO2 response curve.

15 As we do the entire newborn physiology state in
16 10 minutes, this is looking at ventilatory responses in
17 various sleep states given a hypoxic challenge, and one can
18 see in the awake and REM state that hypoxia is a
19 respiratory depressant. It's only in non-REM state that
20 hypoxia is a respiratory stimulant.

21 Finally just to sum up the various treatments
22 that are available and that have been used to treat apnea,
23 one is just having someone standing there flicking the
24 infant's foot every time they slow down. One of the things

1 I did not hear today is with the apnea events, what was the
2 treatment of these events. Was stimulation instituted when
3 the saturation hit 70, when it hit 60, or when the heart
4 rate hit 90 or 80? That I'm not clear about.

5 We've heard a lot about the drug treatment.

6 The use of continuous positive airway pressure
7 as a respiratory stimulant is used in many units.

8 In some cases increasing the inspired oxygen
9 has been used from room air up to 25 percent.

10 Finally, as one increases the hematocrit, one
11 can decrease the incidence of apnea in these kids.

12 In summary, what we're dealing with is a
13 problem where these kids have multiple medical problems,
14 multiple interventions, and whose organ development and
15 responses is changing, and possibly rapidly changing, over
16 a period of time that the infants are exposed to the drug.

17 Thank you.

18 DR. LI: Thank you very much, Dr. Rothstein.

19 What I'd like to do is maybe spend 5 or 10
20 minutes now to open the floor for questions from the
21 committee for Dr. Rothstein. There may be a lot of
22 questions. I'll probably just cut it off and move on to
23 Dr. Chinchilli since we will have time for general
24 discussion. But right now I'd like to open the floor for

1 questions.

2 Dr. Jobe.

3 DR. JOBE: Just as a comment, one of the issues
4 this morning was this issue of the placebo effect, the
5 large effect of the placebo. I think you hit on the
6 probable explanation for most of that, and that was other
7 interventions. Perhaps the sponsors could comment about
8 the use of higher oxygen or CPAP or other kinds of things
9 in these babies because clearly the physicians didn't just
10 give methylxanthines and then sit back and watch, but they
11 intervened. And those interventions are known to be
12 effective ways of decreasing the amount of apnea. So,
13 that's probably the placebo effect we're seeing.

14 DR. LI: If you could put up your last
15 overhead, Peter, maybe if I could ask the question in a
16 slightly different way. How effective are these other
17 nonpharmacologic modalities in treating neonatal apnea?

18 And another question is, just in general what
19 is the standard of care nowadays for this disorder?

20 DR. ROTHSTEIN: In answer to the first
21 question, someone can correct me, but I'm not sure that
22 there are any random controlled trials of any of the other
23 therapies. There are series with small numbers of
24 patients, three in one group, four in another, but there

1 are not numbers to make any coherent --

2 DR. LI: So, that would be true of the
3 stimulation, the CPAP, oxygen, and increasing the
4 hematocrit. Okay.

5 So, the second question, just in your view,
6 what is the standard of care? What is the range of the
7 standard of care for neonatal apnea?

8 DR. ROTHSTEIN: A lot. Since medicine is like
9 religion, it depends which church you believe and pray at,
10 there are some units that will use stimulation. We've
11 heard a lot about the use of methylxanthines in units.
12 People will use multiple modalities in the treatment. I
13 don't know of units that use a single modality in a pure
14 approach, that they will only use methylxanthines or they
15 will only use CPAP. Everyone is constantly kicking the
16 Isolettes to get the kids to breathe.

17 DR. LI: Do you have questions, Dr. Goldsmith?

18 DR. GOLDSMITH: I don't want to be a wet dish
19 rag here. We started with the premise, or at least it's
20 mentioned in the materials sent to the committee, that
21 apnea of prematurity causes brain injury. I don't think
22 that has ever been proven in modern neonatal intensive care
23 units.

24 When that statement was made, probably back in

1 the late 1960's and early 1970's, we didn't have continuous
2 monitoring of babies available, and babies often went for a
3 prolonged period of time with apnea and bradycardia before
4 it was recognized based on the nurse-to-patient care
5 ratios.

6 In modern intensive care units, babies would
7 not be allowed to go past 15 or 20 seconds, wherever you
8 set your alarm, and assuming appropriate care ratios, which
9 most states require in their neonatal intensive care units,
10 babies would respond just by stimulation.

11 So, the question is, what are we treating? And
12 if we are treating it, is it going to make a difference?

13 I assume, although that I didn't hear it this
14 morning, also that there was exclusion criteria of brain
15 injury such as an intraventricular hemorrhage prior to
16 putting these patients into the study.

17 However, without long-term follow-up for
18 injuries such as periventricular leukomalacia, which there
19 is a correlation between apnea of prematurity and PVL later
20 that takes two to three weeks to show up, how do we know
21 the babies who didn't respond didn't have a brain injury
22 associated with an injury that does not show up as an
23 intraventricular hemorrhage or something visible on day 1
24 or 2 or up to day 10 of life?

1 Peter, do you want to comment on those?

2 DR. ROTHSTEIN: There is so much going on in
3 the unit with these kids, and the endpoint may not be even
4 at 3 weeks, as you state. It may be much farther out.
5 Given the I spend most of my time working with kids, we
6 sometimes deal with endpoints that are 1 year or 10 years
7 out from the treatment, and until you start looking, one
8 doesn't know.

9 Case in point. And I know it's going farther
10 afield than this. Back in the 1970's and 1980's, the
11 treatment for transposition of the great vessels was
12 something called a mustard procedure. It was only on 10-
13 year follow-up that people found out that none of these
14 kids were in sinus rhythm 10 years out and all required
15 pacemakers.

16 So, we're looking at endpoints that need to be
17 defined and may not even be known at the present time. I
18 think that, if anything, what's coming out today is there
19 is a tremendous opportunity for long-term, well-constructed
20 trials to try to look at some of these issues, but I can't
21 tell you where one starts and stops.

22 I certainly agree with you. I do not accept,
23 you know, if you don't treat this, the kid is going be
24 brain damaged, which comes up a lot. I don't accept that

1 premise.

2 DR. LI: Molly.

3 DR. OSBORNE: Another obvious question. We're
4 going to be asked to recommend the dosing period and
5 whether it be restricted. That's one of our questions.

6 But just to ask you in terms of a clinical
7 comment, once people are put on methylxanthines, can you
8 comment on duration of treatment just for our edification?

9 DR. ROTHSTEIN: To go way out on the limb, I
10 suspect the treatment and treatment times will bear no
11 relationship to the kinetics or the dynamics of the drug.
12 There is really no data looking at higher dosing, looking
13 at kinetics, looking at the questions that were asked this
14 morning. Is there a correlation between blood
15 concentration and effect? Is there an ED50 or an ED95 at a
16 given blood concentration? I suspect that will not be
17 looked at. I suspect that very few units have ever looked
18 at renal excretion or maturation of renal function versus
19 the dose of drug they're giving.

20 DR. OSBORNE: So, there's nothing like the
21 dose-response curve that we often see in adults.

22 DR. ROTHSTEIN: No.

23 DR. LI: Okay, last question for right now.

24 Dr. Jobe.

1 DR. JOBE: Just as a comment, I don't want
2 people to leave this thinking that apnea isn't a problem
3 because apnea is actually a severe problem in preterm
4 infants and the selection of the therapies is at least
5 clinically driven by least intervention. It turns out that
6 if a small preterm infant gets significant amounts of
7 apnea, the consequences of that are continual stimulation,
8 continual bagging, interference with feeding, and
9 ultimately going on a ventilator. What that gets the baby
10 is basically chronic lung disease. So, there are a lot of
11 down sides to having apnea independent of if it caused
12 brain damage or not.

13 And I would agree that these babies don't end
14 up with brain damage because people intervene. On the
15 other hand, the interventions are not benign.

16 I would think that most people would accept as
17 a standard of practice, that once one thinks that one has
18 apnea of prematurity, the first thing you give is
19 methylxanthines because it's less invasive than continually
20 stimulating the baby and it's less invasive than using CPAP
21 which then can cause stomach inflation and then you can't
22 feed the baby and so on and so forth.

23 So, in general, I think what most people do is
24 assess the baby. If they think it's apnea, they start with

1 methylxanthines. If it doesn't work, then they up the ante
2 with more stimulation or with CPAP or with increasing
3 oxygen or those sorts of things. Again, I think that's why
4 so many of these babies that were in the placebo group got
5 better, is presumably because these other things were being
6 done.

7 DR. ROTHSTEIN: I'm not claiming that any of
8 the other interventions are more or less invasive, and
9 certainly I can tell you about major complications with any
10 of them. If in fact decreasing the incidence of apnea
11 decreases the amount of -- instead of having a nurse
12 assigned to an infant around the clock because he stops
13 breathing every 10 minutes, you can free up personnel, then
14 that may be a major endpoint in terms of treatment also.

15 DR. LI: Okay. Thank you.

16 Next we'll have Dr. Chinchilli give us some
17 comments about his views on the subject.

18 DR. CHINCHILLI: As we know, this was a
19 randomized, double-blind study comparing caffeine citrate
20 injection and placebo with respect to treatment of apnea of
21 prematurity.

22 Because of safety concerns, the patient could
23 be transferred to open-label caffeine citrate rescue
24 between day 1 and day 8 of the randomized treatment phase

1 under two different scenarios: one, if the number of apnea
2 episodes in a 24-hour period exceeded 50 percent of the
3 number of baseline apnea episodes, or the investigator
4 suspected that the randomized treatment placed the patient
5 at risk. And we saw with the data that were presented this
6 morning by the sponsor and the FDA, that there was quite a
7 bit of investigator discretion.

8 Also, the patients in the double-blind,
9 randomized phase could be permanently discontinued from
10 participation due to adverse event, apnea recurrence, or
11 investigator discretion. I've just reproduced here one of
12 the tables that the sponsor provided in terms of how the
13 two randomized groups compared in that regard, again
14 looking at just the numbers they used for the efficacy
15 analysis with 37 randomized to placebo and 45 to caffeine.
16 You can see that there was a higher percentage of caffeine
17 babies that completed the study and a slightly less rescue
18 rate when compared to the placebo.

19 Now, this major feature of the design I feel
20 yields a natural primary outcome variable which should be
21 considered and that's mainly the number of days until
22 rescue or discontinuation. It was I thought a very ethical
23 design. You're worried about placebo in this instance
24 putting the neonates at risk, and so this is an ethical

1 procedure in terms of designing the study. You monitor
2 them very carefully and as soon as there's a problem, you
3 immediately come to their rescue.

4 This is not unprecedented. In some of the
5 asthma studies with which I'm involved, we do that with
6 adult asthmatics, take them off their inhaled steroids,
7 monitor them closely, as soon as they run into a problem,
8 we immediately come rescue them with prednisone or
9 something else. So, it's not unusual to have this type of
10 a design in this type of a situation, but if you do, it
11 seems to me that a natural variable to analyze and what we
12 do with our asthma studies is look at time until rescue or
13 discontinuation.

14 So, that's the analysis I'm going to present
15 right now very quickly. I just got the data on Wednesday
16 from the agency, so I completed this on Friday. So, I
17 don't have a lot of detailed analyses but just some
18 straightforward things.

19 First, if we just look at some descriptive
20 statistics, the median number of days until rescue or
21 discontinuation, you can see there was an advantage to the
22 caffeine group. The median number of days until rescue or
23 discontinuation was 6 for the caffeine group and 3 days for
24 the placebo group.

1 I have the Kaplan-Meier survival plots, as Bill
2 Kelly asked this morning. Again, there's not a big
3 difference here between the two groups, but you notice then
4 later on, as you get out to, say, 3, 4, 5, and 6 -- say
5 days 4 through 8 of the study, you can distinguish a
6 difference here in the survival curve. Remember, survival
7 is surviving the study. You survive being rescued or
8 discontinued. That doesn't happen to you. So, you can see
9 that the caffeine group is doing slightly better in terms
10 of the Kaplan-Meier survival curves.

11 So, the question naturally arises, well, is it
12 statistically significantly better? Obviously, the
13 descriptive statistics indicate there's an advantage to
14 caffeine, but is it statistically significant?

15 That did not turn out to be the case. You
16 probably saw this when I had this up there earlier. I did
17 the usual, the logrank test and the generalized Wilcoxon
18 test, and the p values, you can see, are on the order of .2
19 and .23 in both cases.

20 One more overhead. So, I thought, well, maybe
21 I could get a little bit more precision because -- this is
22 a small sample size, by the way, for doing this type of
23 analysis. I thought maybe I could get a little bit more
24 precision by accounting for investigator site and baseline

1 number of apnea attacks. So, I tried to do a more
2 sophisticated analysis to account for them.

3 So, I did a proportional hazards regression
4 where I had 8 degrees of freedom for the covariates for
5 site and 1 degree of freedom for the baseline number of
6 apnea attacks. I did use the scale baseline number of
7 apnea attacks, the way the sponsor did.

8 The estimated hazard ratio or relative risk of
9 caffeine to placebo in this case is .73. A risk of 1 means
10 there's no difference in terms of the hazard risk for the
11 group when you compare caffeine to placebo. In this case,
12 there's a reduced risk. We saw that with the Kaplan-Meier
13 curves. Numerically that comes out to a relative risk of
14 .73. I did not get increased precision here, getting a p
15 value along the same lines, .28. The 95 percent confidence
16 interval for the relative risk was .41 to 1.30, and you can
17 see that it coincides with the p value because a relative
18 risk of 1 can be embedded within the confidence interval.

19 So, although there seems to be a numerical
20 advantage to the caffeine in terms of this type of
21 analysis, again it wasn't statistically significant, as the
22 other analyses with the primary variables that the FDA
23 considered this morning.

24 So, I did do a calculation if you designed the

1 study in this way and planned to do this type of primary
2 analysis, what sample size would be necessary to have 80
3 percent statistical power. My calculations were that we
4 would need a sample size of 210 patients, which is sort of
5 like two and a half times the size that the current study
6 was done.

7 Just one other comment about the analyses that
8 were done. There was some question this morning about
9 whether or not multiple comparison adjustments should be
10 made since the sponsor and the FDA both looked at analyses,
11 say, at day 2, day 3, et cetera, all the way up through day
12 10.

13 My feeling is that that's not really critical
14 in this instance simply because the analyses that were done
15 used this last value carried forward approach. That
16 approach works relatively well when you don't have a lot of
17 dropouts as we did here. When you have 5 percent, 10
18 percent dropouts, that type of data imputation of missing
19 values works reasonably well.

20 In this case, since we had such a high
21 percentage of dropouts, I wouldn't recommend that type of
22 analysis anyway. So, I think it's interesting to look at
23 the results in terms of descriptive statistics, but I
24 wouldn't rely on that type of analysis looking at what

1 happens, say, at day 8, 9, 10, when so many values are
2 being carried forward. I think this is a natural approach
3 to take in terms of the way to analyze this particular
4 study simply because of the design, but again it was a
5 little bit -- well, quite a bit under-powered to detect a
6 difference, although it did show a numerical advantage to
7 the caffeine group. So, I think it's supportive and gives
8 similar results as the analyses we've seen this morning,
9 but again there wasn't a statistical significance.

10 DR. LI: Thank you very much, Vernon.

11 Any questions from our committee? Yes, Dr.
12 Hendeles.

13 DR. HENDELES: Could you help me understand why
14 there was such a large placebo response? Was that an
15 artifact of how the data was analyzed?

16 DR. CHINCHILLI: No. I think one of the
17 reasons this happened -- I don't know obviously all the
18 physiology here, but I think there's a regression to the
19 mean effect, and I've mentioned that to a couple of people
20 on the board already this morning. A lot of these infants
21 are detected to have high levels of apnea episodes early on
22 at their peak. You get to the point where they're having a
23 lot of episodes, and so naturally they're going to fall and
24 come back down. So, I think that's what's happening. Part

1 of the placebo response could be that there's a regression
2 to the mean effect. You're catching these infants when
3 they have a high number of episodes, and then they're going
4 to naturally going to start coming back down.

5 DR. HENDELES: What do you think of just
6 analyzing the number of apneic episodes right at the early
7 period right after the loading dose and not carrying that
8 data forward?

9 DR. CHINCHILLI: Well, I think that's why the
10 FDA was focusing on that primary analysis of, say, the
11 number of episodes at day 2 or a 50 percent reduction, how
12 many infants had a 50 percent reduction in number of
13 episodes at day 2. I think that's why the sponsor
14 indicated that was the primary response as well.

15 DR. LI: Vernon, it would seem to me that there
16 would be at least two ways to interpret the data that you
17 presented, which is the same data, of course, that we heard
18 from the sponsor and the FDA. That's actually almost
19 easier to think about it in the way that you presented it
20 to us.

21 So, one interpretation would be that, indeed,
22 the caffeine is effective and more effective than placebo
23 in reducing apneic episodes but that the study was in some
24 way under-powered to show that, 80 patients instead of

1 perhaps a necessary 210 or so.

2 The other hypothesis would be that the drug in
3 fact is no different from placebo, and the small
4 differences that we do see that fail to reach a statistical
5 significance is simply because there is no effect or the
6 effect itself is minuscule.

7 Do you have any sense of which one of those
8 hypotheses may be correct?

9 (Laughter.)

10 DR. LI: Or is there a way to think that
11 through from a study design or statistical point of view?

12 DR. CHINCHILLI: Well, we laugh when
13 statisticians always get asked that particular question.
14 There's incomplete observations. A study, it turns out,
15 either had a design flaw or was under-powered, and so
16 you're asked to make a determination based on incomplete
17 information. It's easy for me to stand up here and
18 criticize this issue and that issue because I'm not the
19 ones doing the study. But still, it comes down to the
20 point, as we have to today. We have to come to some kind
21 of recommendation and decision.

22 I think given the amount of consistent results
23 in the literature, even though most of the studies, if not
24 all of them, were uncontrolled studies or not double-blind

1 or placebo-controlled type of studies, I think there are
2 indications in the literature that this is effective.

3 DR. LI: That it is or isn't?

4 DR. CHINCHILLI: That it is effective. I think
5 there's indications of that. I'm not saying it's
6 convincing, but I'm saying there are indications that it's
7 effective.

8 So, I think given that this study too -- given
9 that this is double-blind and randomized and placebo-
10 controlled, showing similar types of results, maybe not as
11 strong an effect as we had anticipated seeing, but given
12 that there is this effect that's consistent with the
13 literature, I'd say, yes, there is very good evidence that
14 this is effective.

15 However, I could be wrong too. Again, I'm
16 using my subjective judgment based on incomplete
17 information, just as the rest of you will be asked to do.

18 DR. LI: If I can put the question in a
19 slightly different way. We look at the post hoc analyses,
20 which are very much more convincing.

21 DR. CHINCHILLI: Right.

22 DR. LI: To what extent is that analysis flawed
23 by the very basis of the post hoc nature of it?

24 DR. CHINCHILLI: Well, just the way you've

1 indicated. Given that it's post hoc, that there's a chance
2 to look at the data and decide are there other things we
3 could identify -- now, some were identified as secondary
4 variables by the sponsor and they weren't, I wouldn't say,
5 entirely post hoc. They were identified as secondary
6 variables, and they did come out to be significant.

7 This is really a judgment call. I don't think
8 here is a situation where a statistician is much help.

9 (Laughter.)

10 DR. LI: Well, you have helped us so far.
11 Thank you.

12 Peter.

13 DR. ROTHSTEIN: In response to some of your
14 comments, if you have a treatment that's being widely used
15 for a condition that is widely present, but where there are
16 other interventions going on or the natural history of the
17 course of the disease is to get better on its own, then
18 many of these previous studies will come up with a
19 positive effect.

20 DR. CHINCHILLI: That's true.

21 DR. ROTHSTEIN: But we are over-estimating the
22 effectiveness of a particular treatment, in this case the
23 caffeine or the theophylline or whatever.

24 DR. CHINCHILLI: Yes. I think the one study

1 I'm really relying on too is that Murat study that was
2 discussed this morning by the FDA.

3 DR. ROTHSTEIN: Who, I should point out, went
4 on also to be a pediatric anesthesiologist.

5 (Laughter.)

6 DR. CHINCHILLI: So, I think although that was
7 open-label and it's a small study size, much smaller even
8 than this study we're discussing, it did show a significant
9 effect. You have to wonder how much bias there is given
10 that it was open-label, but there was something there.

11 DR. LI: If you look at the Murat study, that
12 study might have been judged as under-powered too. There
13 were only, what, 18 patients or so, and yet they were able
14 to find a fairly sizable effect with good statistical
15 significance.

16 DR. CHINCHILLI: You have to wonder how much is
17 due to bias. Given it's open-label, it's hard to really
18 quantify how much of this was really due to some bias.

19 DR. LI: Courtney.

20 DR. CRIM: Just from a statistical standpoint
21 you mentioned about the median days before they went to the
22 open-label. I think it was 3 and 6 for the two groups.

23 DR. CHINCHILLI: Right, either rescue or
24 discontinuation.

1 DR. CRIM: With the number of subjects from the
2 nine institutions ranging from, I think, 3 to 17 max, to
3 what degree could that difference or any of the other
4 differences be related to, let's say, a bias at one
5 institution, thinking that they should be in an open-label,
6 basically moving the bulk of their patients to an open-
7 label, and therefore that would affect -- see, I don't know
8 to what degree these outliers in terms of a hospital moving
9 their three or four patients to an open-label would make
10 those differences.

11 DR. CHINCHILLI: Right. I didn't do those
12 kinds of sensitivity analyses to see, well, let's eliminate
13 this site or that site and see if the results change in any
14 way.

15 They're going to be very sensitive doing that
16 simply because the overall sample size is small. So,
17 typically the types of multi-center trials you see here
18 where you have a couple of hundred subjects or even close
19 to a thousand subjects in a trial, you do those types of
20 sensitivity analyses to see if one or two or a cluster of
21 centers has that type of impact.

22 Here I'd expect that, yes, one or two centers
23 do have a big impact. I think there were three centers
24 that had, say, more than 15 subjects or close to that.

1 You're going to see that. You remove those three and
2 obviously things will change. Or if you remove a couple of
3 the smaller ones. Given that the overall sample size is so
4 small, I think that's probably why I didn't pursue that
5 endeavor because I would be able to find things along that
6 line.

7 DR. LI: Yes, Dr. Osborne.

8 DR. OSBORNE: Certainly sometimes when there
9 are small sample sizes, in many studies meta-analyses are
10 done. Are there obvious reasons why a meta-analysis would
11 not be helpful in this case?

12 DR. CHINCHILLI: Well, you have the precursor
13 to a meta-analysis. You have both the sponsor and the FDA
14 doing sort of a very thorough literature review. But I
15 think the studies were so different. You have to decide
16 which studies you're going to use in the meta-analysis.
17 Are you just going to use randomized studies? Well, that's
18 going to eliminate most of them. Are you going to use
19 placebo-controlled studies? Well, then we've got a
20 problem. We've got one. So, I think that's probably why
21 they didn't pursue that, and that was prudent on both the
22 sponsor's and the FDA's part not to try to do a meta-
23 analysis.

24 DR. LI: Yes, Curtis.

1 DR. SESSLER: Vern, did you look at any of the
2 safety data in terms of reworking the statistics?

3 DR. CHINCHILLI: I didn't do that. Obviously I
4 noticed the -- I forget it now. What is the --

5 DR. OSBORNE: Necrotizing enterocolitis.

6 DR. CHINCHILLI: Yes, that thing.

7 (Laughter.)

8 DR. CHINCHILLI: Yes. I had some concerns
9 about that as well, and I realize the analysis that was
10 presented this morning -- I'm trying to remember now. I
11 guess there were five or six in the caffeine group. If you
12 looked at safety in terms of whether or not they received
13 caffeine at all, even if they had been switched, I think
14 the percentages gave you something that wasn't
15 statistically significant. But again, given the small
16 sample size, that probably is the reason why.

17 I don't know enough about this to know if this
18 is a cause-effect relationship or if this is something
19 concurrent that happens with these neonates. I think
20 there's reason for concern, and my recommendation would be,
21 obviously, this needs to be closely monitored. If this is
22 approved and gets on the market, I think in the phase IV
23 type of studies I think this really would have to be
24 monitored very closely as to sepsis and this side effect as

1 well. So, I didn't analyze them just because the numbers
2 were small, but there is concern about the proportions.

3 DR. LI: Dr. Kelly?

4 DR. KELLY: In the Murat study, their entry
5 criteria was three apnea episodes in a 24-hour period
6 versus the six in this. I know that we heard previously
7 that there was not a relationship or predictive phenomenon
8 of baseline apnea levels or severity. I guess my question
9 is, is there a more sensitive way of looking at that in
10 terms of controlling for the level of the baseline apnea
11 episodes or number than was looked at by the groups here?

12 DR. CHINCHILLI: Well, the FDA did an analysis
13 where they used that as a covariate, and that's mentioned
14 in the biostatistical report. I did something similar here
15 with the proportional hazards regression to try to adjust
16 for the baseline level, and it wasn't significant. When I
17 looked at the p value for the covariate, it was well above
18 .5. So, it's not to say that it's not an important factor,
19 but I think there was a good balance between the placebo
20 and caffeine groups in terms of the baseline levels.

21 DR. KELLY: But if you just looked at the
22 patients who got caffeine and looked at who responded and
23 who didn't respond, would that be a better way of doing it
24 than just comparing the two groups the way they did? It

1 just seems like the dramatic effect of the Murat study was
2 -- they took in potentially significantly less severe
3 patients than they did in this study.

4 DR. CHINCHILLI: I mean, that could be the
5 case. I don't know. I'm still concerned about the bias
6 too with an open-label study of the Murat as well.

7 DR. LI: Dr. Pina?

8 DR. PINA: I just would like to clarify that
9 the entrance criteria for the Murat study was three
10 episodes of apnea associated with bradycardia less than
11 100. So, the definition is not exactly the same as in this
12 trial which was just apneic events with or without
13 bradycardia. So, that was the difference.

14 DR. LI: Okay. Thank you very much, Vernon,
15 for that helpful discussion.

16 Next on our agenda is Dr. Szefler who I've
17 asked to give some comments on his view of the evidence
18 presented before us. Dr. Szefler is Director of Clinical
19 Pharmacology at a major medical center.

20 DR. SZEFLER: Thank you, Dr. Li.

21 I received a package in the mail about 10 days
22 ago. It was about this thick with all the information, and
23 I said, well, I'll get through this before the meeting.
24 Then I think the following Monday, Dr. Li called me and

1 said, I've got a challenge for you here and I want you to
2 be the primary reviewer. It was a little shocking for me,
3 and I asked him, well, why? He said, well, you're a
4 pediatrician. You're a clinical pharmacologist. You've
5 published on theophylline and you're in a respiratory
6 center. I said, well, let me clarify a few things here.

7 (Laughter.)

8 DR. SZEFLER: Theophylline is not caffeine and
9 the respiratory center I deal with works with asthma and
10 not neonates.

11 But, nevertheless, I really enjoyed the
12 experience because one of the other things that I do in my
13 spare time is I'm on the Committee on Drugs for the Academy
14 of Pediatrics. I've been on this committee for a year and
15 a half and I've seen several areas discussed. I'm
16 beginning to associate Dr. Jenkins with landmark
17 discussions in pulmonary medicine.

18 I think this one here is a landmark because
19 this is an area that has been largely -- I would not say
20 neglected, but poorly defined, the neonates and the young
21 children in product information. So, I really congratulate
22 them on taking the challenge to discuss this issue because
23 it has great impact for the future.

24 As you all know, the legislation has been

1 moving to get better information on medicine in children,
2 and on that ground, I'd like to congratulate Roxane for
3 taking on this challenge because, as you heard this
4 morning, it's really a challenging area with a lot of new
5 information to be identified.

6 Having not touched a neonate for about 20
7 years, the approach that I took was to look at the
8 literature and to call two people that I respect very much
9 in terms of their opinions in this area. To this point
10 their names haven't been mentioned.

11 One is Jacob Aranda, who's in Montreal, who has
12 published more extensively in the area of caffeine than
13 anybody else that's listed there. I would recommend that
14 his opinion be solicited, if this is approved and if
15 guidelines are developed for its use, if it hasn't already.

16 The second person is Robert Ward who's the
17 chair of the Committee on Drugs in the Academy of
18 Pediatrics and also is a neonatologist at the University of
19 Utah.

20 Both of them gave me the impression that if
21 this preparation was available, one, they would feel it's
22 important and, two, they would use it if it was FDA
23 approved.

24 So, what I'd like to do is take you through

1 some steps in approaching this issue.

2 I got the impression from reading this
3 literature that the incidence is, indeed, high in terms of
4 this problem. It occurs in 25 percent of preterm infants
5 with a birth weight under 2,500 grams, and there does seem
6 to be a relationship to the extent of prematurity in that
7 it occurs in approximately 84 percent of those with a birth
8 weight less than 1,000 grams. So, I think this is a
9 significant medical problem that deserves attention because
10 of its high prevalence in this population.

11 Risk. I got the impression from reading the
12 literature that there was significant risk in terms of
13 morbidity, that this can lead to irreversible neurological
14 damage secondary to hypoxia and acidosis.

15 Mortality also is mentioned in the literature
16 and that it may lead to death if it's untreated, for
17 example, in 23 percent of cases where no treatment is
18 administered or postponed due to mild apnea, and about 34
19 percent required mechanical ventilation. Again, these are
20 points that can be discussed because this is a population
21 of patients at risk for a number of disorders that kind of
22 tie together.

23 What are the available methods of management?
24 Some of these were discussed, but I don't think they were

1 really compared. There's monitoring, physical stimulation,
2 bagging which would also include use of CPAP. I think this
3 study is an excellent format for doing a pharmaco-economic
4 analysis if the data is there in terms of looking at
5 comparative care because, as physicians, we're all being
6 faced with cost effective management.

7 The treatments available are theophylline for
8 those who want to use an approved drug in an unapproved
9 application. It has the disadvantage of a narrow
10 therapeutic range, significant forms of toxicity with
11 overdose, including mortality.

12 Caffeine sodium benzoate was another choice,
13 but Les said it's not on the market, plus it's not an
14 applicable preparation here because it interferes with
15 bilirubin binding which in and of itself can result in
16 neurological damage if it's not recognized and controlled.

17 What is being used in this patient population
18 -- and it's used quite extensively, and perhaps a fact
19 analysis should be conducted. Caffeine citrate by
20 extemporaneous formulation seems to be the medication of
21 choice. This is fraught with problems in terms of it's
22 prepared in the pharmacy. It has poor stability. I'm told
23 that it only is stable for about 24 hours, and the quality
24 control can be poor. There are reports of toxicity in the

1 literature with overdose due to errors in extemporaneous
2 formulation. So, that in itself highlights a problem.

3 What are the potential benefits of this type of
4 preparation? If this is approved, it will come under FDA
5 guidance in terms of application of safety principles for
6 the commercial preparation, and it will also come under the
7 guidance that would facilitate better information and
8 better stability of the product, a better quality
9 controlled type product.

10 Continued monitoring of the use of this
11 medication would improve its application. I think today --
12 I've been away from it, but I've heard the best discussion
13 of this type of problem and the medical management of this
14 problem focused on a specific drug that I've heard in a
15 very long time and probably in this area of management.
16 So, I think it opens the door for continued improvement and
17 continued evaluation of this medical disorder.

18 What are the benefits over available
19 preparations? I touched on that, but the long half-life of
20 this drug facilitates once-daily administration and reduces
21 day-to-day and within-day variability of serum caffeine
22 concentrations. That in itself is an advantage over
23 theophylline.

24 The stability and quality control would be an

1 advantage.

2 Caffeine is a medication of choice based on the
3 communication of several opinion leaders. I asked Jack
4 Aranda and Bob what their feeling would be if this
5 medication was approved, and both of them indicated to me
6 that if this preparation was available, this would be the
7 one that they would use in their nursery. So, I think it
8 would have application.

9 There was another point that I mentioned
10 earlier that caffeine has no effect on cerebral blood flow,
11 whereas theophylline appears to have that effect.

12 What's the information that's there to support
13 the application? Extensive past literature and I think
14 very nice analyses were done both by the company and by the
15 FDA showing some pretty strong evidence that it does have
16 some effect. However, there was no placebo-controlled
17 trial with caffeine in the past literature.

18 It appears, from reading the literature, that
19 both the sponsor and the FDA worked pretty closely to
20 develop a plan to look at this drug very carefully. It
21 followed some of the initiatives that have been proposed in
22 looking at medications in a small population in an area of
23 need and also seems to support the movement in terms of
24 getting better medications in children. So, I think the

1 steps were taken and it seemed like it was a friendly
2 exchange of knowledge to get us where we are today. It
3 followed the orphan drug step, carefully reviewed the
4 supportive literature, and a single study was conducted was
5 recommended in the design that was also recommended.

6 As a result of that, the overall efficacy, even
7 though the key variables didn't work out, seemed to support
8 the past literature.

9 The adverse effect profile for this medication
10 seemed to be pretty reasonable. The central nervous system
11 effects -- again, these are objective findings. We have no
12 way of assessing subjective findings unless adult studies
13 were done in terms of this preparation. But the objective
14 findings were irritability, jitteriness, restlessness which
15 appears in the literature, and it's also indicated that
16 tolerance to these adverse effects can develop. Again,
17 that comes from the literature.

18 The literature doesn't point to any long-term
19 effects on growth and neurological development. Seizures
20 can occur with overdose, but prior to this study, there
21 were no deaths reported. The literature with theophylline
22 indicates seizures can develop and there have also been
23 reports of death with theophylline.

24 The clinical experience shows that it also

1 seems to have a very good profile. Rapid onset of effect.
2 It seems to be the drug of choice with the ones available.
3 It has a better safety profile than theophylline with
4 equivalent efficacy, the advantage of once-daily
5 administration, potential therapeutic advantages. Again, I
6 haven't looked at the pharmacology literature, but better
7 CNS preparation.

8 The extemporaneous preparations are widely used
9 indicating, at least to me, that a number of people feel
10 this drug is effective and they're using it whatever way
11 they can get their hands on it.

12 The area of concern, as we discussed, is that
13 the primary efficacy variable was not met. Maybe this was
14 just bad luck or poor study design, but I think Vern kind
15 of alluded to numbers of patients that would be required
16 and I think you alluded to the difficulties in obtaining
17 these kind of patients. So, I think the efforts were made,
18 but just the primary efficacy variable didn't come out.

19 The risk of necrotizing enterocolitis. Reading
20 the literature provided, this seems to be the second most
21 common cause of neonatal death. So, it's not a side effect
22 that we can ignore. However, it is a concomitant disorder
23 in this patient population. It has about a 10 percent
24 incidence. The patient population is at risk with or

1 without the methylxanthines. Unfortunately, there are no
2 good studies that show the relative prevalence.

3 I think based on your discussions and the IRB
4 discussions, it would be hard-pressed to think in terms of
5 doing a study that would give us the kind of numbers that
6 would be needed and it would take a long time to design the
7 study, get the approval, and if that was held back, we'd be
8 holding back about two or three years before the drug could
9 be approved. I don't know if there's anybody else that's
10 ready to stand up to the plate with a product with the kind
11 of studies that would be used to allay our anxieties about
12 this.

13 It seems to be that caffeine has less risk than
14 theophylline, the approved medication.

15 If indeed this drug was approved and could be
16 available, what kind of information should be out there to
17 the physicians to prevent any catastrophic episodes?
18 That's where we get to the product information.

19 In terms of the dosage guidelines, the doses
20 that were recommended and studied seem to be consistent
21 with the past literature and seem to be adequate for the
22 target population. However, I think the product
23 information could benefit by some information on
24 pharmacodynamics in relationship to the onset of effect,

1 the time of maximum effect, the expected time of maximum
2 effect, and the offset of effect when discontinued.

3 It should indicate that there are responders.
4 In talking to Drs. Aranda and Ward, they seem to paint the
5 picture that there are responders, dramatic responders,
6 there are nonresponders, and then there are patients who
7 respond initially but then kind of break through later on.
8 I think that kind of discussion needs to come out so that
9 there's some information on how to use the drug because you
10 have to remember it will be used in academic centers, but
11 then it will also be carried on in other types of centers.
12 So, the more information available on how to use the drug
13 safely, the better.

14 Also discussing the duration of treatment I
15 think came up earlier. Dr. Jobe addressed the extent of
16 use, that a 12-day limitation won't be realistic in terms
17 of its application. So, some guidance in terms of
18 discussing the duration of treatment, when to consider
19 stopping and how to do it, whether a tapering schedule
20 should be used or just discontinuation when the time seems
21 appropriate.

22 There are some precautions in terms of
23 approving this drug that should be considered. It is a
24 limited study population. There is an absence of data in

1 adults. As I mentioned before, I think there are
2 situations -- and maybe Dr. Jenne can address this that in
3 some of the patients on respirators, apnea in adults, that
4 preparations like this may be used, and if there is
5 anticipated use, studies should be programmed.

6 There is an absence of data in premature
7 newborns. Dr. Aranda pointed out to me that the literature
8 has been very scarce in the population less than 1,000
9 grams, and I think this study has that population in it and
10 maybe some analysis to see what kind of efficacy it has in
11 that young group would be helpful. There's a Scandinavian
12 study that he alluded to that I think is in our information
13 in 1995 that also includes some information on these
14 younger patients.

15 There was mention that there are some subset
16 differences, and this needs to be explored a little bit
17 more in terms of some of the populations. The Hispanic
18 population has higher volume of distribution, and patients
19 with higher frequency of apnea have higher clearance. It
20 would be interesting in the future to explore this in terms
21 of its pharmacodynamic implications.

22 Also I think there needs to be some better
23 information on guidelines for monitoring levels. I forget
24 the term that's in the product information now but it's

1 kind of loose in terms of being recommended to obtain it,
2 but some kind of general knowledgeable guidelines like
3 obtaining a serum concentration once a week would be
4 useful.

5 In terms of this issue about tolerance, Dr.
6 Aranda mentioned that in some of the patients who initially
7 respond and then break through that an increase in dose is
8 helpful. That doesn't come through in the product
9 information and potentially needs to be addressed.

10 If it was approved and the product information
11 was developed, what would be the considerations in terms of
12 post-marketing surveillance? Information to date does not
13 indicate long-term adverse effects, but this needs to be
14 followed, particularly for the drug and for the
15 preparation. I think a new drug out there in a new
16 population would recommend cautions in terms of some
17 surveillance systems being set up. I don't know how to do
18 them but that would be useful.

19 Limited use of product to date. The extent has
20 been only in these 46 patients in terms of the clinical
21 experience. So, that in itself would merit some long-term
22 follow-up.

23 The product would be used if available and
24 would likely become preparation of choice for the

1 management of apnea of prematurity. I think monitoring its
2 use would be very helpful in setting up some kind of system
3 to see if it is being used in populations. I would hate to
4 have this kind of legislation kind of be the way of getting
5 drugs approved for the future, to take the simple way out,
6 get a drug approved for the simplest indication, and then
7 have more extensive use. So, I think the FDA should watch
8 out for that kind of application. I'm not sure, based on
9 the discussion here, that it has application in older
10 patient populations.

11 It would be useful, as I said before, to assess
12 the pharmacodynamic implication of the patient subsets with
13 varying pharmacokinetics.

14 I think this particular drug, if it's approved
15 and the nature that it's approved, is a landmark
16 initiative. It seems to fulfill the intention of the new
17 and emerging initiatives in better medication guidelines
18 for children. As such, this application and potential
19 approval needs to be monitored in terms of its application
20 and use to develop principles for other medications that
21 will be coming along in the same direction. So, I think
22 there are a lot of lessons to be learned in terms of this
23 particular process.

24 DR. LI: Thank you very much, Dr. Szeffler, for

1 those thoughtful comments.

2 Are there any questions for Dr. Szeffler? Yes,
3 Brenda?

4 MS. CONNER: This one really isn't for Dr.
5 Szeffler as much as maybe the neonatologists in the group.
6 If you would clarify for me -- we've talked about
7 management methods, and we've seen that methylxanthines are
8 used regularly. What percentage of the time would someone
9 choose an extemporaneous formulation of caffeine over a
10 standardized theophylline product, and does that change on
11 discharge when you're sending a patient home?

12 DR. JOBE: I can try to address that only
13 because I recently moved from UCLA to Cincinnati where
14 there are two different practice styles.

15 In many institutions, a theophylline
16 preparation is used not because people like it but because
17 it's easier to get plasma levels, and that's what happened
18 at UCLA. Basically we used theophylline because we didn't
19 have a caffeine assay.

20 In Cincinnati all the babies for a 50-mile
21 radius are on caffeine. It's made up extemporaneously and
22 they have an in-house assay. So, it's used there because
23 it's felt to be less toxic, more effective, and because
24 there's an assay for measuring drug level.

1 MS. CONNER: Are those formulations available
2 for discharge?

3 DR. JOBE: Actually the pharmacy makes them and
4 they're prescribed as outpatient medication.

5 DR. GOLDSMITH: It really depends on the
6 institution. There are a lot of institutions that will not
7 make up caffeine because it has to be made on site, and
8 stability and the problems.

9 Dr. Szeffler, Alan touched on a problem and that
10 is most institutions have the ability to do levels in house
11 because they are monitoring theophylline levels for older
12 people and asthma, et cetera. I would dare say less than
13 20 percent -- maybe less than 10 percent -- of hospitals in
14 this country have the ability to do caffeine. Is that our
15 concern or will that naturally follow if this drug gets
16 approved and everybody will put those procedures in place?

17 DR. SZEFLER: Les will address this but I think
18 they have the availability. It's just a matter of getting
19 the right kit.

20 DR. HENDELES: Yes. The Abbott TDX method of
21 measuring drug levels and drugs of abuse in the urine is
22 the most common. It's a fluorescence polarization
23 immunoassay, and there is a caffeine kit for it that can be
24 obtained. It's expensive to do that if you only have one

1 level a month and labs may not be willing to do it unless
2 you can increase the number of levels. But it is
3 commercially available.

4 DR. LI: Stan, did you come across any evidence
5 that the homemade preparations of caffeine have actually
6 caused clinical problems?

7 DR. SZEFLER: As I read through the literature,
8 there was reference to a couple of publications on that. I
9 didn't get a chance to read them to see exactly what was
10 going on there and tease them apart, but it's mentioned
11 several times in the document.

12 Perhaps the company would want to comment on
13 that.

14 DR. MOSDELL: These are two cases of overdoses
15 which resulted from errors in extemporaneous compounding.
16 You can see that some of the errors were fairly
17 significant.

18 The first error was actually a tenfold
19 calculation error made by the pharmacy which was discovered
20 66 hours after the end of the overdose. The level was 160
21 milligrams per liter.

22 The second level -- it didn't say the amount of
23 an overdose it was. However, at the time that the error
24 was recognized, the caffeine levels were 346 milligrams per

1 liter.

2 In both of these cases, the infants had
3 significant adverse events during the course of the
4 overdose.

5 DR. LI: Thank you.

6 Any other questions for Dr. Szeffler? John?

7 DR. JENNE: Well, I just wanted to mention in
8 regard to caffeine in adults and respiratory failure that
9 Dr. Szeffler mentioned in his comments.

10 I know that about 10 years ago Supinski -- I
11 forget his first name -- in Cleveland published some
12 studies in dogs in which caffeine was considerably superior
13 to theophylline as far as increasing force of contraction.
14 When I was at Hines, theophylline was not the most popular
15 drug in patients being ventilated, despite my efforts,
16 although we did have some patients on it.

17 But it seems to me that this would be an ideal
18 population to study not only in ventilated patients, but
19 patients with severe COPD such as Obay has done with
20 theophylline to see what effects it has on pCO₂ and so
21 forth. There may be others that have some better
22 understanding of the literature to date than I do.

23 DR. LI: Thank you, Dr. Szeffler, for those
24 thoughtful comments. I know you took a lot of time

1 preparing this for us.

2 I'd like to continue our open discussion of the
3 use of caffeine citrate. Rather than just right at this
4 moment focusing exclusively on the questions that we would
5 like to address for the FDA, let's see if we can just focus
6 just somewhat on the broader areas of efficacy and safety,
7 and keep the discussion open, not necessarily exclude
8 comments. Then maybe in another 20 minutes or so we can
9 address in a very much more focused way the questions that
10 we have on our handout.

11 Yes, Dr. Cross.

12 DR. CROSS: I'd just like to mention something
13 that hasn't been discussed probably. Many intensive care
14 units -- and our hospital is among them -- do review and
15 keep a record of their problems with drugs or drug
16 reactions and complications. In our neonatology unit, on
17 many occasions the number one drug problem has been
18 calculation errors in dosing the drug being administered,
19 and number two has been methylxanthines often.

20 I think that this is one thing that has to be
21 taken into consideration as quality control measures are
22 more rigorously reviewed in intensive care units. We meet
23 once a month and discuss such things as the aggregate total
24 of reported drug complications in the patients, units,

1 deaths, et cetera.

2 This is a possible retrieval of information,
3 and I'm sure our hospital wouldn't be the only one where
4 methylxanthines continue to be high on the list of drug
5 complications in hospitalized patients.

6 DR. LI: So, how do you see that as
7 impacting --

8 DR. CROSS: I would see both of those issues
9 impacting the neonatology unit. The methylxanthines are
10 tremendously hard to dose. I'm sure that the young neonate
11 is sort of like the very aged patient. It's hard to know
12 what dose to give a 90-year-old and it's hard to say what
13 dose to run the other way. We're all used to this 10 to 20
14 or 5 to 20 dose range, but 15 may be toxic to a 90-year-
15 old, and we see kids that have had no complications and
16 their theophylline level is 30.

17 Now we move down this slope, and we've seen it.
18 I have a problem with Dr. Szeffler's wanting a lot of
19 monitoring in dosage in a range where there's tremendous
20 individual variability at one age, and now we're on that
21 steep neonate curve which is going down from 36 months
22 downward where not only are we dealing with individual
23 variability but tremendous variability, I suspect, on
24 gestational period in terms of the kinetics of a drug that

1 most of our hospitals, including UCLA, aren't even
2 monitoring the drug level.

3 So, I think it would be very, very difficult,
4 and I think it probably points to the complications of
5 theophylline administration in this same age group. I
6 suspect if one looked at neonatology intensive care units,
7 they'd find that methylxanthines were pretty high up on the
8 list of drug complications.

9 DR. LI: So, is the basic idea that if caffeine
10 is available, it would reduce the use and therefore the
11 errors associated with theophylline or aminophylline?

12 DR. CROSS: Yes, I think that would be a very
13 important point and that you would have the data because I
14 think it's probably collected.

15 DR. LI: Dr. Rothstein.

16 DR. ROTHSTEIN: A question for our pharmacology
17 friends. If you had a hospital that's got, say, 40
18 newborns and 10 or 15 of them are on caffeine, and so the
19 lab is being sent 5 or 10 assays every couple days, how
20 easy would it be to set up those assays?

21 DR. HENDELES: It would be real easy. Again,
22 if they use the TDX machine, it's just buying the kit, and
23 if they don't, it's a very simple, cheap HPLC assay.

24 DR. GOLDSMITH: With regard to the

1 complications of theophylline, I also sit on a drug review
2 committee. Most of the ones we see are minor overdoses
3 without tremendous clinical significance, but because in
4 assay it was greater than what our limit is, if it's 15 or
5 20 for theophylline and the child has a symptom, which
6 could be tachycardia alone which will resolve over a few
7 hours, it gets brought to the committee.

8 The ones that are devastating -- at least the
9 ones that we've reviewed -- had to do with packaging in
10 that the packaging of the product in different
11 concentrations is very similar. I don't know if that has
12 been changed or not recently, but it can vary by 25-fold in
13 the amount of drug per unit volume. If that's done
14 incorrectly, then you have a disaster.

15 So, we're not here to discuss theophylline, but
16 obviously if you're going to do different packaging with
17 different concentrations per unit volume, that's an
18 extremely difficult problem for the neonates who have,
19 obviously, limited ways of excreting the drug.

20 DR. HENDELES: I think what Dr. Goldsmith is
21 referring to is the fact that aminophylline is a 25
22 milligram per cc solution. So, if you want to use it in a
23 neonate, you really have to dilute it down to 1 milligram
24 per cc. You increase the risk of errors when you

1 extemporaneously prepare a preparation as opposed to
2 getting it commercially from a company.

3 I think that's just one of the many reasons why
4 bringing a product like caffeine on the market will really
5 reduce the risks to this patient population for serious and
6 potentially fatal toxicity because it's very clear that
7 caffeine at levels of 50 micrograms per milliliter seem to
8 not cause any serious neurologic problems, whereas
9 theophylline at that same level can cause very devastating
10 effects.

11 DR. GOLDSMITH: What I'm suggesting is that if
12 we're approving this or moving towards approval for a
13 neonatal indication, then it should be packaged in a
14 neonatal volume that's appropriate, not to be put into an
15 adult volume that has to then be diluted on site by the
16 pharmacist.

17 DR. HENDELES: Well, it's 10 milligrams per cc,
18 and the dose for an adult would be in the 300 milligram
19 range. So, you'd have to use many vials.

20 DR. LI: I have a question on a slightly
21 different topic and that has to do with looking at the
22 information that's available to us now and maybe just
23 looking at one of the future questions having to do with
24 future studies.

1 My question really to the panel would be, what
2 is the feasibility and how realistic is it to expect or
3 request a study involving 200 patients using computerized
4 monitoring in order to at least get a chance of getting
5 additional data that would perhaps make this decision
6 easier? The question would be, what is the feasibility
7 given the difficulties with the study that was already
8 conducted? I just want to maybe have a guess or an opinion
9 from some of our panelists. We'll start with Stan.

10 DR. SZEFLER: It sounded like it would be
11 difficult. It sounded like the study design was
12 reasonable. It just feel short in terms of the efficacy
13 variable and the number of patients. It sounded like you
14 lost sites, one because of their IRB's.

15 I guess the other question would be how long
16 did it take to recruit because if the nine centers
17 fulfilled their quota in one month, then I would say
18 there's a lot of population available, but if the deadlines
19 were extended, then it sounds like recruitment was very
20 difficult in some very good centers.

21 DR. LI: Dr. Sessler.

22 DR. SESSLER: I had similar questions. I guess
23 I'd like to ask in a fashion that gets to some of the data
24 that might help us come to conclusions. If we had

1 somewhere between 16 and 18 months at nine centers, that's
2 what? 15 center-years or something. How many centers are
3 there that are out in the United States that are capable of
4 doing this sort of work, looking specifically at the
5 neonatologists here who might be in the know as to how many
6 more than nine? Are there 100? Are there 50? Are there
7 12?

8 DR. GOLDSMITH: Well, it depends on who you
9 ask. Because the protocol was written so narrowly and with
10 great constraints, it was very difficult to sign up
11 patients. Roxane did the best they could and I
12 congratulate them on it, but it's a very difficult
13 protocol.

14 If we're looking at babies per year, 1.1
15 percent of babies in this country are born less than 1,500
16 grams and fall into what we call the very low birth weight
17 group. I would imagine 50 to 70 percent of those babies --
18 let's say 50 conservatively -- are going to get on some
19 sort of methylxanthine at some point in time. That's
20 20,000 babies a year. So, if we're looking only at safety
21 issues, how many of these babies versus another population
22 are going to get NEC or any other kind of safety issues,
23 that information should be easy to come by.

24 To get the kinds of effects that Roxane tried

1 to get, in terms of a very narrow protocol with so much
2 methylxanthine already being used and with all the other
3 problems and all the exclusion criteria, that's very
4 difficult.

5 There are probably 1,200, 1,300, 1,400 neonatal
6 intensive care units in this country. I would imagine
7 probably 1 in 5 to 1 in 10 is capable of doing this kind of
8 study or wants to do this kind of study, to be involved.

9 They are now beginning to have some consortiums
10 like groups of institutions looking at problems together
11 like the Vermont Oxford group and the NIH group, but it's
12 difficult to get a study like this to get the power that
13 you need, the numbers of patients that you need.

14 DR. SESSLER: May I ask the sponsors how many
15 centers they approached to get their nine centers that
16 agreed to participate?

17 DR. ERENBERG: I don't remember exactly, but I
18 think it was somewhere in the 2 to 1 range. I think we had
19 approached 15 to 18 different centers looking for people
20 who would be willing to follow the narrow protocol with all
21 the various constraints that have been cited.

22 DR. GOLDSMITH: Has the company made an
23 estimate of the amount of use that this would have if it
24 were approved in terms of manufacturing and how many babies

1 a year would get this? I mean, is 20,000 unreasonable?

2 DR. ERENBERG: Mr. Gunn?

3 MR. GUNN: My name is Ed Gunn. I'm Marketing
4 Manager for Roxane Laboratories.

5 The potential patient base for methylxanthine
6 therapy right now currently, looking at babies that would
7 be actually available to treat, would be around the 70,000
8 patient range a year. Of that, obviously there would be a
9 portion that would go to caffeine. Looking at how many
10 neonatal intensive care units out there that are currently
11 using caffeine to treat, we predict of those 70,000 in NICU
12 units, approximately 10,000 of those patients are receiving
13 caffeine now.

14 DR. ERENBERG: As Mr. Gunn did focus groups,
15 one of the major problems has been availability of caffeine
16 levels, and if this were resolved, I think people would
17 look at the data and look at dosing, the cost of getting
18 multiple theophylline levels versus one caffeine level a
19 week and look at the medical economics, as has been stated
20 before.

21 DR. HENDELES: Dr. Erenberg, it's not clear
22 that you'd need to do that if the patient was responding
23 and had normal renal function. Would there be any
24 rationale for doing a caffeine level under that

1 circumstance?

2 DR. ERENBERG: I think those of us who have
3 used caffeine for a long time feel very comfortable with
4 it. I think people who are going to be switching from
5 theophylline, where it is required to do levels to know on
6 an individual baby, especially when you first start, where
7 they are -- I think people will probably want to do a level
8 until they get comfortable with the use of the drug and
9 know what the clinical response is.

10 DR. LI: Yes, Molly?

11 DR. OSBORNE: I have a question actually about
12 the labeling since this seems to be just a open period of
13 discussion here just because I don't know very much about
14 the cytochrome P450 1A2 system in neonates, let alone in
15 adults, I'm ashamed to say. I'm confused about how the
16 drug interactions will actually work. I certainly know
17 them for adults, but it seems that for the neonate it might
18 be different. I know that there were exclusion criteria in
19 the studies that Roxane performed, the sponsor performed,
20 and so I'm wondering how to best approach what should be in
21 the package insert since it might be different depending on
22 a neonate or somebody -- I don't know -- early-life infant,
23 et cetera.

24 DR. KELLY: The major problem is that caffeine

1 is excreted primarily unchanged in the kidney, and so most
2 of the drug interactions that are related to both
3 theophylline and methylxanthines in adults aren't going to
4 happen because all of those are metabolic in nature. You
5 can see from the literature search that they did that you
6 don't achieve adult levels till about 6 months of age, at
7 which time, if it's apnea of prematurity, you're not going
8 to have any more apnea of prematurity.

9 So, it's unclear to me as well how they're
10 going to address these interactions because in the patient
11 population that they're using the drug in, it's very
12 unlikely that these drug interactions may occur except for
13 in patients whose mothers got phenobarbital and they have
14 then some enzymes in their liver and are metabolizing. But
15 other than that, it's very unclear.

16 Just to list them all I think would actually
17 create some false information that these actually even have
18 a potential for occurring.

19 DR. LI: Yes, Les?

20 DR. HENDELES: On the other hand, the package
21 insert doesn't contain any advice on how to adjust the
22 dosage if a patient has renal dysfunction. Since in your
23 study you eliminated all of those patients, there's a huge
24 population of these patients that have varying degrees of

1 renal dysfunction and are going to get the drug once it
2 becomes commercially available.

3 So, I think it's really essential that both a
4 dosage guideline be provided for reduced renal function
5 since that's a major way of getting rid of the drug, and
6 then secondly, some advice on when to measure levels and
7 how to use that information to adjust dosage, similar to
8 what we have in the theophylline package insert.

9 DR. JENNE: We're talking about the package
10 insert now, and one of my impressions is that it comes down
11 a little too strongly that the therapeutic range is 8 to
12 20. I think this may have real legal ramifications -- I
13 mean, to state it as positively as it is stated. There
14 should be some buffer there or some reference to higher
15 levels being relatively safe in certain series and so
16 forth.

17 The other thing in regard to the necrotic
18 enterocolitis, there was one study mentioned here in the
19 review where there was a comparison between theophylline
20 and caffeine on enterocolitis I believe. It seems to me
21 that a better way to state the caffeine situation is to say
22 that there is no evidence at this time that it's associated
23 with enterocolitis, whereas there is a question whether
24 theophylline is associated with enterocolitis. In other

1 words, I think we're tending to condemn the drug a little
2 prematurely here on the basis of what we know right now.

3 DR. LI: I think it's a reasonable time now to
4 proceed to the very specific questions that the committee
5 has before them, and we'll start with the first question on
6 efficacy and again open with just a discussion but
7 discussion now focused on this particular question, which I
8 will read.

9 Do the effects shown in study OPR-001 and the
10 published literature constitute sufficient evidence of the
11 efficacy of caffeine citrate for the treatment of apnea of
12 prematurity? I suppose the key word here is "sufficient."

13 I'll again open it up for discussion. Then
14 maybe we'll have a comment or an opinion from each of our
15 committee members, and then finally we'll actually take a
16 vote. Dr. Chinchilli.

17 DR. CHINCHILLI: Yes. I have a question for
18 Dr. Jenkins which I warned him about at lunchtime.

19 (Laughter.)

20 DR. CHINCHILLI: And that is, what are the
21 ramifications of something like this? If the committee
22 recommends approval in terms of efficacy and safety based
23 on one multi-center trial where there wasn't statistical
24 significance for efficacy with the primary response

1 variable, is this going to set a precedent for the FDA, and
2 is it going to cause ramifications for other drug products
3 and biological products that's going to cause problems for
4 the agency?

5 DR. JENKINS: I think that is a very important
6 question and it's one that we have debated internally quite
7 a bit. Since you provided me warning at lunch that you
8 were going to ask me this, I provided my boss warning that
9 I was going to defer the question to him --

10 (Laughter.)

11 DR. JENKINS: -- because he has so many more
12 years of experience in the area than I do.

13 But before I let Dr. Bilstad address some of
14 those issues, we should go back and look historically. The
15 sponsor presented this morning that there was a literature
16 review conducted in the mid-1980's for the agency. The
17 agency concluded that the data at that time based on the
18 literature were not adequate to support the efficacy of
19 caffeine in this indication, and that's why we requested
20 that adequate and well-controlled trials be conducted.

21 We actually did take some heat for that
22 recommendation because some people thought it was unethical
23 to have a placebo-controlled trial in this disease because
24 they were so convinced that caffeine was effective and was

1 standard of care.

2 To Roxane's credit, they did take on the task
3 and complete the study we've heard about today.

4 The agency did agree at that time that given
5 the literature-based evidence of efficacy, that one
6 adequate and well-controlled trial could potentially serve
7 as the basis for an approval action if the data were
8 favorable for the effectiveness of caffeine.

9 It's correct that generally we focus on the
10 primary endpoint that's specified by the sponsor and
11 hopefully agreed to by the agency in advance in the
12 protocol before the data are unblinded in making our
13 determinations of efficacy in clinical trials. We usually
14 expect that there will be prespecified analyses plans also
15 in place before the data are unblinded.

16 However, that does not mean that the agency
17 doesn't have some flexibility in how we can interpret the
18 overall results of clinical trials. We're not bound to
19 limiting ourselves just to the prespecified primary
20 endpoint/primary analysis.

21 Finally, in anticipation that this question
22 would come up, you'll notice that in our package to the
23 committee from the agency, we included a draft guidance
24 document that the agency issued recently which tries to

1 spell out some information for the industry about what the
2 effectiveness standard is for the approval of drugs.
3 Hopefully you had a chance to look that over and see some
4 of the legal and scientific bases for the standard that has
5 generally been two adequate and well-controlled trials, but
6 also there was a lot of detailed descriptions in there of
7 situations where the agency could or has made
8 determinations based on a data set of less than two
9 adequate and well-controlled trials which met the primary
10 effectiveness endpoint.

11 Dr. Bilstad has had a lot more experience in
12 this area than I have, and I think he has been thinking
13 about this most of the day and I'll let him give you some
14 of his thoughts on what level of flexibility there is in
15 the effectiveness standard and also what, if any, precedent
16 an action favorable to caffeine might have on the agency
17 and the industry.

18 DR. BILSTAD: Well, there currently are some
19 weaknesses in the efficacy database provided for this drug,
20 and we see that as a regulatory challenge. Is there enough
21 evidence to be able to say that the drug is effective for
22 approval for marketing?

23 At the same time, I think it's fair to say that
24 we don't view the data on its face as being completely

1 inadequate. If we viewed it that way, we would not have
2 presented it to the committee for review. We believe this
3 falls into a gray area where judgment really is needed.

4 The Food, Drug and Cosmetic Act, which provides
5 the framework under which we operate, refers to substantial
6 evidence consisting of adequate and well-controlled trials.
7 As Dr. Jenkins mentioned, we have interpreted that in most
8 circumstances to mean that there needs to be some sort of
9 independent substantiation of the results, data from more
10 than one source.

11 At the same time, we believe that we have some
12 flexibility in how we can interpret that legislative
13 standard, and we believe that we can take into
14 consideration expert judgment that the studies and the
15 database, taken as a whole, do provide substantial evidence
16 of effectiveness.

17 There are some factors that can be taken into
18 consideration in this situation, factors of multiple
19 sources of data, looking at the data as a whole. To some
20 extent, feasibility can be addressed, although that's a
21 difficult one. Feasibility is a factor in all drug
22 development programs to some extent, somewhat more in
23 programs that deal with orphan drugs, and sometimes there
24 is the ethical question on the feasibility of conducting

1 studies which can be taken into consideration.

2 So, I guess I would say in summary we believe
3 that we, from a regulatory standpoint, have some
4 flexibility in this situation, but we certainly would like
5 your expert judgment, taking all the data as a whole,
6 whether there really is in your view substantial evidence
7 of effectiveness.

8 DR. LI: Thank you for those comments, Dr.
9 Bilstad.

10 Yes, Dr. Osborne.

11 DR. OSBORNE: Specifically I'd just like to say
12 that the attachment that we received, the draft guidance on
13 level of evidence, I thought was absolutely outstanding.
14 It helped me. It clarified certainly in my own mind
15 exactly how the FDA does look towards drugs in terms of
16 safety and efficacy and would also, of course, point out
17 that for me it was very helpful to read that our expert
18 judgment could conclude that studies together represent
19 substantial evidence of effectiveness. This leaves us a
20 tremendous amount of flexibility, in the case where there's
21 substantial evidence in the literature, to help make a
22 recommendation here. Somehow it doesn't mention statistics
23 at all.

24 (Laughter.)

1 DR. LI: What I think we'll do next is go
2 around the table, and I'll ask for an opinion and thoughts
3 about the issue that's before us on evidence. Is there
4 substantial evidence or sufficient evidence of efficacy in
5 order to move forward toward a possible vote toward
6 approval or approvability?

7 If you feel strongly, feel free to actually
8 voice what your vote will be. I'm not asking for a vote
9 right now. I'm just asking for thoughts and impressions
10 and what you think the major issues are. Perhaps we'll go
11 around the table and hear from everyone, starting with Dr.
12 Goldsmith.

13 DR. GOLDSMITH: You would make me start.

14 (Laughter.)

15 DR. GOLDSMITH: I just want to point out that
16 there's a substantial difference between question number 1
17 and question number 2. I know we're not at question number
18 2. But it says in question number 2, short-term use. It
19 doesn't say short-term use in question number 1, and I
20 think that needs to be added because that's basically what
21 we're looking at. I am concerned that once the drug is
22 there, it will be used for months rather than days.

23 But I think given the literature review, my
24 tendency at this point is to say that the published

1 literature in conjunction with the one study, despite the
2 flaws of the study and the lack of power, is adequate
3 information at this point.

4 DR. LI: Brenda?

5 MS. CONNER: I think the literature review that
6 we have with us, as well as the post hoc evaluation after
7 the study, and the anecdotal information that Dr. Szeffler
8 provided us from his other experts that he talked with, as
9 well as who I consider the experts on the panel, the
10 general consensus that it would be used and that it is
11 needed, I think that helps substantiate the efficacy.

12 DR. SESSLER: I have some difficulties with it.
13 I think the "sufficient evidence" is the key phrase there,
14 and we're bending two rules. I think we're moving away
15 from using two randomized controlled trials to one, and I
16 think in order for that to work frankly, that the one
17 randomized controlled trial should be of sufficient
18 strength to stand pretty firmly on its own.

19 I think there are serious questions about the
20 powering of this current study. Some of the other
21 literature is consistent, but again it's almost entirely
22 open-label.

23 If we went with these criteria, I think we
24 would have several monoclonal antibodies or similar such

1 agents available for adult critical care in treatment of
2 sepsis. I know we'd have interleukin-1 receptor
3 antagonist, for example, and probably many others. So, I
4 think we need to look clearly at whether bending both rules
5 is the right thing to do.

6 DR. CROSS: I, like Molly, read parts of the
7 document that the FDA prepared as their draft on the way
8 out here from the coast, and I thought it was outstanding
9 and was amazed at the flexibility. I thought that was
10 great.

11 I also appreciate Dr. Goldsmith's proviso that
12 we should maybe consider short-term on this first question.
13 I still have problems of mechanism, general CNS stimulant,
14 tolerance, et cetera, et cetera on the longer-term studies.

15 It's interesting that their electrolytes didn't
16 show any changes in CO₂ which I might have expected if it
17 was a long-term stimulant driving respiration.

18 I feel much more comfortable with the short-
19 term use approval rather than long-term use.

20 And that's all my comments.

21 DR. SZEFLER: I reviewed my comments there, and
22 what I was alluding to is the literature seems to support
23 its efficacy and seems to support the need for a product
24 out there that could be used safer than what's being used

1 right now.

2 DR. CHINCHILLI: Well, I definitely think
3 there's evidence and whether or not it's sufficient is what
4 I'm debating internally right now. I guess if I had to put
5 a probability on it, I'd probably say there's a 65 percent
6 chance I'll vote yes.

7 (Laughter.)

8 DR. LI: Spoken like a true statistician.

9 (Laughter.)

10 DR. ROTHSTEIN: I like waffles for breakfast.

11 (Laughter.)

12 DR. ROTHSTEIN: I think there's evidence for
13 some efficacy of this drug.

14 I'd also throw out a problem with drugs and
15 with kids. Let's say you have two drugs, both of which
16 have absolutely no effect at all but are used widely
17 because of the belief that the drug has some effect, but
18 one of those two drugs is safer than the other. If
19 approving a second drug will drive the first less safe drug
20 off the market, then there may be a rationale for approving
21 the drug.

22 But going back to the efficacy, I think there's
23 some efficacy. I think it's overrated but there is an
24 indication of efficacy.

1 DR. LI: I'll just voice my own opinion. I
2 think it's again a tremendous asset that we have this
3 placebo-controlled trial before us so at least we have some
4 evidence on which to base a decision.

5 I do share some of the concerns that were
6 voiced earlier, and as I looked through the FDA guidelines
7 on what constitutes sufficient evidence, again I'm struck
8 that the usual standard is two well-controlled, placebo-
9 controlled trials and in certain cases a single trial can
10 be considered sufficient generally when that single trial
11 is especially strong or the results are especially strong.

12 I'll add that more likely than not I would
13 support the idea of having the indication include some
14 duration of treatment, be it, say, 10 to 12 days or 10 days
15 or so. My opinion there is based on the evidence that's
16 available to us that was presented which goes up to about
17 10 days or so. So, it would be to me difficult for us
18 later on to advocate an indication for longer than 10 days.
19 So, I support the idea of including the short-term caveat.

20 I think our decision today is going to be based
21 on the particulars with this drug in this setting. So,
22 there are extenuating circumstances in this case that are
23 in some ways unique in terms of the orphan drug, the
24 difficulty in conducting this trial and future trials. As

1 Dr. Rothstein said, we need to consider the risk of
2 approval, as well as risk perhaps of not recommending
3 approval.

4 I think the theoretical down side perhaps would
5 be that, if we recommend approval and actually eventually
6 the drug becomes available on the market, the drug in fact
7 is not effective because that's certainly a possibility
8 that we have to entertain whether that's true or not.

9 But even theoretically, even just as Dr.
10 Rothstein said -- I think my rationale is the same. Even
11 in a worst case scenario, so to speak, if the drug turns
12 out to be no better than placebo, in some ways we're still
13 better off. So, I guess my own view is --

14 DR. ROTHSTEIN: Excuse me. I didn't say no
15 better than placebo. No better than theophylline, and if
16 this replaces theophylline and the attendant problems with
17 theophylline, then --

18 DR. LI: Right, fair enough.

19 Actually my own view would be even if the agent
20 turns out not to be better than placebo, with the current
21 practice as it is, it still may be of benefit to our
22 patients. That's what I think is the main issue here.

23 DR. CRIM: I think there's circumstantial
24 evidence to suggest that caffeine may be beneficial in

1 patients with this problem. Because of the way the studies
2 that were reviewed in the literature were conducted, I
3 don't think that's convincing but I think it's indeed
4 suggestive of it. Likewise, I think that the current study
5 that we're reviewing is also suggestive of it although not
6 convincing, and that's because I think the biggest concern
7 I have is the small size of the groups and particularly the
8 dropout rate and the concern I have about the biases of the
9 investigators both in enrolling patients into the study, as
10 well as keeping the patients in the study.

11 So, I think there's circumstantial evidence to
12 suggest that it's probably effective, but I'm not convinced
13 that it really is. I would have liked to have seen the
14 primary efficacy variables met.

15 DR. OSBORNE: I think there is sufficient
16 evidence of efficacy. My only comment would be that my
17 guess is there is a number of responders, which is not the
18 entire population, but that will be sorted out in the
19 marketplace.

20 DR. CRIM: The one thing I'd like to add is
21 that the circumstantial evidence is for short-term use, as
22 far as I'm concerned, definitely not long-term.

23 DR. JENNE: Well, I would come down on the side
24 of efficacy. I'm particularly affected, although we should

1 probably think independently of this, but the comparison
2 with theophylline, which is in wide use, is a reason to not
3 dally further I think. When it was decided to study this
4 drug, it was a number of years ago, and these studies take
5 a long time. I think there's a down side to continuing to
6 do studies like this.

7 I think we need to give credit to the
8 practitioners, many of them who have personal experience,
9 and it's likely that many of these finer points that have
10 been brought up will be solved with this drug in smaller
11 studies that focus on some particular issue.

12 So, that's what I have.

13 DR. JOBE: I find the evidence for efficacy in
14 these trials and in the historical review to be basically
15 circumstantial, as pointed out by the other people.

16 I think there's a large safety issue with
17 having caffeine available.

18 I think everyone needs to realize that this is
19 really a unique population of patients that cannot be
20 generalized to other folks.

21 There's one thing that really hasn't been
22 talked about today and that's the clinical evidence for
23 this which is very common where infants are put on
24 theophylline or caffeine and their apnea resolves, and as

1 they get older, it's withdrawn. Very often they have apnea
2 again and the drug is restarted, and that's a very common
3 clinical observation which sort of demonstrates efficacy to
4 me.

5 DR. KELLY: I think just so I can say something
6 different than everybody else said, I've spent 20 years
7 teaching people, residents, students that use of a drug in
8 and by itself does not indicate appropriate use.

9 Then having said that, I think the primary
10 endpoint or the primary goal of therapy is to end apnea
11 episodes. In that endpoint, the double-blind, placebo-
12 controlled trial was successful in terms of showing more
13 patients got rid of their apnea. So, I think there is
14 sufficient evidence, although not a lot -- sufficient
15 evidence -- of efficacy.

16 DR. HENDELES: Well, I think there's sufficient
17 evidence of efficacy. I think hindsight is always 20/20.
18 If the sponsor and the agency knew what they knew today,
19 they probably would have designated a different endpoint
20 and this may have been less of an issue.

21 I'm comfortable that the drug is both safe and
22 effective. I think there needs to be some precautions.
23 The association with NEC needs to be included as a
24 precaution in the package insert, and I think the

1 indications need to be explicitly limited because I can see
2 where anesthesiologists might use caffeine to reverse
3 medazolam sedation and other things because it's an
4 adenosine receptor antagonist. So, it may be used for many
5 other purposes, and so I think there needs to be an effort
6 to restrict it to this indication unless the company is
7 willing to conduct other studies.

8 DR. LI: Thanks for everybody's comments. We
9 can still stay open.

10 Dr. Bilstad?

11 DR. BILSTAD: I just wanted to make a comment
12 to the comment that was made earlier that the FDA's usual
13 standard is two randomized placebo-controlled studies. In
14 fact, we talk about adequate and well-controlled studies,
15 but we very definitely do not say that these need to be
16 randomized placebo-controlled studies. In fact, there are
17 a number of controls that are mentioned in the regulations
18 as possible controls, and one is even the historical
19 control where a study may not have a concomitant control
20 group but the results might be compared to historical
21 experience with the drug. So, I just wanted to make clear
22 the usual standard is not necessarily two placebo-
23 controlled randomized studies.

24 DR. LI: Right. Thank you for that

1 clarification.

2 We can still stay open for discussion if anyone
3 wants to make comments or question any one of the other
4 panel members based on comments that you've heard already.

5 What I might suggest is a question for our
6 panel and that is whether we want to modify the question to
7 include the short-term qualifier that I've heard at least a
8 couple of the panel members raise as an issue. For
9 example, as an example only, we could slightly alter the
10 question to address the question of whether the evidence
11 constitutes sufficient evidence on the efficacy of the
12 short-term use of caffeine in the treatment of apnea. Is
13 there any favor toward that issue? Yes?

14 DR. ROTHSTEIN: I don't want to restrict or
15 remove the drug for use in the population that Dr. Jobe has
16 described or withdrawn from the drug, the drug is stopped,
17 and then have a recurrence of their apnea and are started
18 treated again. So, I'm not sure where this short-term
19 stops and long-term begins.

20 DR. LI: That's a good point. On the other
21 hand, the data that we're basing our decision on really --
22 at least the study data -- ends at 10 days, does it not?

23 DR. ROTHSTEIN: I understand that, but the 26-
24 or 27-weeker who's born hasn't read the insert yet.

1 (Laughter.)

2 DR. ROTHSTEIN: And his apnea is not going to
3 resolve necessarily in 10 days, and it may be possible to
4 reduce the episodes from 7 to 2 in that infant. He may get
5 treated for 3 or 4 weeks.

6 DR. CRIM: But I guess caffeine is not FDA
7 approved for apnea of prematurity now, is it?

8 DR. ROTHSTEIN: No.

9 DR. CRIM: So, physicians are using it how they
10 want to use it anyway. So, if we approve it for short-term
11 use, it's still not going to stop physicians from doing
12 what they're going to do anyway. Correct?

13 DR. JOBE: The way it's worded I think is good
14 because it's not treatment of apnea, but it's apnea of
15 prematurity, which by definition means that as the child
16 approaches term, they ought to be bringing the babies off
17 the drug.

18 DR. GOLDSMITH: I would agree with Dr. Jobe.
19 Peter, I'm not as concerned about babies being treated up
20 till 36 even 38 weeks post-conceptual age. What I'm
21 concerned about is being treated for a year while they're
22 on home monitors with virtually no other kind of monitoring
23 because it's the easiest way out and they got sent home on
24 it or discharged on it. As we're starting to discharge

1 children now at 34 to 36 weeks post-conceptual age, many of
2 them are going home on methylxanthines, and very honestly,
3 the practicing pediatrician may be a little different from
4 the practicing neonatologist and doesn't know when to stop.
5 So, the easiest thing to do is not to stop, just continue
6 on.

7 So, I think we have to be very careful about
8 opening the doors too wide.

9 DR. LI: What would be your recommendation for
10 indication?

11 DR. GOLDSMITH: I think short-term use and some
12 caveat about treatment beyond 38 weeks post-conceptual age
13 has not been studied or is beyond the scope of the
14 information available, or something along that line.

15 DR. JOBE: Yes, or prolonged apnea beyond the
16 newborn period or something like that.

17 DR. ROTHSTEIN: What about apnea of
18 prematurity?

19 DR. JOBE: That says it all I think.

20 DR. GOLDSMITH: But when does apnea of
21 prematurity stop? The problem is for the practicing
22 pediatrician who gets handed these babies post-discharge.
23 Apnea of prematurity on the discharge summary he may think
24 continues on 52 to 56 weeks post-conceptual age.

1 DR. ROTHSTEIN: But then that's something that
2 the neonatology community needs to communicate to the
3 pediatricians. I don't want to incorporate that into a
4 restriction or start writing science into the package
5 insert that doesn't exist.

6 DR. HENDELES: As I understand it, the labeling
7 guideline really regulates what the manufacturer can
8 promote this for, not what a physician -- any approved drug
9 just regulates the manufacturer's promotion. It does not
10 regulate the physician's practice.

11 DR. GOLDSMITH: I would agree but I think
12 physicians are more aware of the medical-legal consequences
13 of using drugs for non-approved uses and that some
14 indication in there would be helpful in terms of not having
15 the drug continued for months and months after discharge,
16 which I think is very common, extremely common.

17 DR. HENDELES: It sounds like an educational
18 problem.

19 DR. LI: Courtney, then Molly.

20 DR. CRIM: I guess the viewpoint I take of that
21 is because I'm not concerned about the safety issue, at
22 least the long-term safety issue, since we don't have that
23 kind of data and the data we do have is for the short-term
24 use up to 12 days, I guess I would go along with the

1 recommendation in terms of short-term use because to me
2 we're talking about circumstantial evidence.

3 My sense is that I'm concerned about the
4 clinician -- again, not being a pediatrician, I guess my
5 concern would be about the pediatrician who would keep this
6 person on it for months or a year. And whether or not the
7 clinician should know about those medical-legal
8 ramifications doesn't help that baby that dies because of
9 he or she was kept on it for a prolonged period of time;
10 whereas if you put a short-term limitation on it, then
11 neonatologists or the person who's experienced with it will
12 know the ramifications in terms of when they can or can't.
13 But for the person who is relatively ignorant of it, at
14 least perhaps having that short-term use will cause that
15 person to pause and think and if they have this patient on
16 it for longer than what it's approved for will seek
17 consultation to say, what can we do with this particular
18 type of medication as opposed to leaving it on them willy-
19 nilly.

20 DR. LI: I'll add that it may be possible for
21 us to recommend that some limitation or a caveat be
22 included in the directions for use whether or not the
23 actual words "short-term" are used. For example, it's
24 possible to put into the indication or the labeling that

1 controlled studies beyond 10 days of use have not been
2 performed. That already would be a warning or a caveat.
3 So, we probably don't have to decide on the wording but I
4 think the concept is important since it's raised by
5 several.

6 Molly.

7 DR. OSBORNE: Yes. My opinion would be that
8 the way number 1 is worded, for me personally, is adequate
9 to make a decision, and that on 5a about the dosing period,
10 which has to do with the labeling specifically, my opinion
11 would be that we discuss that fully. My opinion would be
12 that there be something in there about it being reevaluated
13 around the time of birth, or whatever the best wording is,
14 and that reevaluation is warning signal to a pediatrician
15 that something needs to be done. If they don't know what
16 it is, they might actually ask for help.

17 DR. JENNE: In fact, Dr. Jobe really was
18 talking about repeated short-term use I think. In other
19 words, it could be stated that one should evaluate before
20 further short-term use is necessary or further trial is
21 necessary.

22 DR. LI: Stan or Peter, any final thoughts on
23 either this issue or any other issue?

24 (No response.)

1 DR. LI: I think I'll take Dr. Osborne's
2 suggestion and let's address the question as it is written,
3 and we discuss approvability on item 5, then we can again
4 more specifically outline what our concerns are about
5 warning or duration or use.

6 So, in fact, now I will ask for a vote, and the
7 question is, do the effects shown in study OPR-001 and the
8 published literature constitute sufficient evidence of the
9 efficacy of caffeine citrate for the treatment of apnea of
10 prematurity? So, all in favor, raise your hand.

11 (A show of hands.)

12 MR. MADOO: How about all who are not in favor?

13 DR. LI: All opposed?

14 (A show of hands.)

15 MR. MADOO: So, do we have two opposed? We
16 have 14 who are eligible to vote, so I would suggest that
17 we have 12 in favor --

18 DR. LI: Any abstentions?

19 (No response.)

20 MR. MADOO: So, the vote outcome is 12 in
21 favor, efficacy demonstrated; 2 opposed.

22 DR. LI: So, Courtney, was your vote opposed?

23 DR. CRIM: No. I agree with that statement.

24 MR. MADOO: Okay, so it's 13 --

1 DR. LI: Let me rephrase the question. Do the
2 effects shown in study OPR-001 and the published literature
3 constitute sufficient evidence of the efficacy of caffeine
4 citrate for the treatment of apnea of prematurity? So, all
5 agreed, all in favor of this statement in the affirmative,
6 please raise your hand.

7 (A show of hands.)

8 MR. MADOO: I'm seeing 12 hands.

9 DR. LI: All opposed?

10 (A show of hands.)

11 MR. MADOO: I'm seeing one opposed.

12 (Laughter.)

13 DR. SESSLER: I'm between an opposed and an
14 abstain.

15 (Laughter.)

16 DR. SESSLER: I am unhappy with the scientific
17 evidence. I respect the neonatologists' observations at
18 the bedside and opinions. I don't believe that there's
19 sufficient evidence. What I'd like to do is abstain
20 because I think this is an important drug perhaps to that
21 group.

22 DR. LI: Twelve in favor, one opposed, one
23 abstention.

24 MR. MADOO: Duly noted for the record.

1 DR. LI: Let us now address in an open fashion
2 the second question which deals with safety, and I'll read
3 the question. Does the NDA database, together with the
4 data available from published literature and the
5 spontaneous reporting system experience, demonstrate the
6 safety of the short-term use of caffeine citrate in
7 patients with apnea of prematurity?

8 I'll open this for any comment. Yes.

9 DR. CHINCHILLI: Yes. I have a question for
10 our colleagues. Was the incidence of sepsis a surprise? I
11 take it with the NEC, that wasn't a surprise because that's
12 obviously a complication with the pre-term infant, but with
13 the sepsis, was that a surprise or is it out of the range
14 that you would expect for these neonates? I guess the
15 range was 6 out of 6 or 8. Dr. Pina, you had the numbers.
16 I can't remember what they were.

17 DR. PINA: Eight patients, all of them exposed
18 to caffeine.

19 DR. LI: Right, and none in placebo.

20 Stan?

21 DR. SZEFLER: But I think as we talked about
22 before, having had experience in the past but not recently,
23 sepsis is a diagnostic suspicion and then the confirmation
24 -- in this case, it sounded like there was only one case

1 that had bacterial confirmation. To my knowledge, whenever
2 it's suspected, blood cultures are obtained. So, it's not
3 as if it wouldn't be found if it wouldn't be there unless
4 the cultures weren't sensitive enough. So, it's actually
5 one out of eight cases, and the seven cases were suspected
6 sepsis and suspected sepsis is considered rule out sepsis.
7 So, again, I kind of like --

8 DR. LI: Is it concerning that all eight that
9 were suspected or had sepsis were in the treatment --
10 received the caffeine?

11 DR. ROTHSTEIN: The study set up criteria for
12 inclusion in the study -- to my reading, the study did not
13 define sepsis, and so it did not define a positive blood
14 culture or a regaining of ability to maintain temperature
15 or a rise in the platelet count following institution of
16 antibiotics. So, I don't know how to define or then
17 interpret what sepsis is.

18 DR. GOLDSMITH: That's a big problem. The
19 nosocomial infection rate for VLBW babies can approach 20
20 percent and be within the norm and prolonged
21 hospitalizations. The problem is that sepsis is a
22 diagnosis that's difficult to make. We draw very small
23 blood cultures and we generally do them once before
24 antibiotics are initiated. In some literature, you see

1 where babies who truly have supportive evidence of sepsis,
2 all kinds of white blood cell counts, abnormalities and
3 clinical deterioration, et cetera, and 30 percent of those
4 infants have negative blood cultures. So, it's very
5 difficult to interpret the data.

6 I'm not uncomfortable with the data to that
7 point where I would believe that caffeine offers a
8 disadvantage towards babies to getting sepsis.

9 DR. LI: What about the issue of the
10 necrotizing enterocolitis? Are you concerned that there
11 may be an increased risk with caffeine?

12 DR. GOLDSMITH: Not on the basis of the
13 information we have, not in my personal information. I
14 still remain very, very concerned about the interaction
15 with other drugs and causing NEC specifically the H2
16 blockers. I'm concerned that that's an issue that many of
17 these babies will be on histamine blockers, as well as
18 methylxanthines of some sort, and that interaction will be
19 a new interaction, and possibly in a stage 4 time that
20 these things should be reported back. I don't know how we
21 could know that now, but I am concerned about it.

22 DR. LI: Yes, Curtis.

23 DR. SESSLER: I'm particularly struck by the
24 one-sided nature of the exposure data. I don't know how

1 good it is and that relates back to the question that I had
2 earlier about severity of illness and if there were other
3 explanations for this. But one might argue that the best
4 drug now to avoid the onset of sepsis, necrotizing
5 enterocolitis, and death is avoidance of caffeine, because
6 it was 0, 22 in all three categories.

7 The concern I have I guess about approval,
8 based on the safety data or in light of the safety data, is
9 that we've already heard that there is a lot of variation
10 in management of this condition and that there's little
11 good science so far. A lot of it is observational.
12 Without a doubt, this would become the drug of choice and
13 would become very widely used.

14 If we guess wrong about the safety data, I
15 think there's potentially significant damage that can be
16 done. So, I disagree with some of the earlier statements
17 that if we do approve it, there's no loss. It's either a
18 gain or it's not going to be harmful. So, I have concerns
19 about the safety information there. It's far more one-
20 sided I guess when one looks at the exposure data than the
21 randomized data.

22 DR. CROSS: You preempted my statement. I was
23 going to say the same thing, that the way to get at the
24 safety issue is to approve it. It's being very widely

1 used, and perhaps the stage 4 surveillance will produce
2 better data than what we have now. I think approval
3 probably is safer than nonapproval and 70 percent use.

4 DR. OSBORNE: I'll tease Curtis a minute and
5 just point out in the adult ICU with your logic, we
6 wouldn't be giving oxygen either.

7 (Laughter.)

8 DR. OSBORNE: Let me go on to point out as a
9 person who works with --

10 DR. SESSLER: We need to go back 20 years and
11 do those studies again.

12 DR. OSBORNE: It's a deal.

13 I'd just make my opinion which is that
14 certainly the FDA recommendation was for safety. At least
15 on the basis of the information we have, the concept was
16 that caffeine was well tolerated by patients in the
17 population studied.

18 DR. LI: Dr. Jobe?

19 DR. JOBE: The issue of safety I think is
20 something that we all have to be worried about. It turns
21 out that in the neonatal business now, there are two very
22 large networks, the NICHD network that has approximately
23 20,000 infants registered less than 1,500 grams, and the
24 Vermont Oxford trial network. A lot of that database has

1 been mined for a lot of different things. One is for
2 sepsis, and I'm not aware that there's an association with
3 methylxanthines. But I'm not sure it has been looked at
4 that way. That's information that could be probably
5 requested by either the FDA or the sponsor to better flush
6 out that sort of an issue.

7 I am aware that H2 blockers are associated with
8 increased infection in babies looking at a database from a
9 recent glucocorticoid trial that's unpublished presently,
10 but that interaction has turned up as well.

11 The point is I think that in neonatology, in
12 contrast to a lot of other diseases, we have very large
13 databases that are out there that can be looked at.

14 DR. LI: For those who have a concern about the
15 safety regarding in particular the necrotizing
16 enterocolitis, would a label warning and a surveillance
17 study be adequate to allay some of those concerns?

18 DR. SESSLER: I guess you're looking at me,
19 aren't you, Jim?

20 (Laughter.)

21 DR. LI: You don't have to respond.

22 DR. SESSLER: It's interesting because in
23 thinking about this, you wonder if it one includes the
24 exposure to caffeine data in the labeling, it might bring

1 up more healthy questions actually to its automatic use.
2 That is, if you are getting ready to prescribe this drug to
3 your patient and see data that the likelihood of death is 0
4 percent without it and 4 and a half percent with it, and
5 sepsis, 0 percent versus 13 percent, and on down the line,
6 it may perhaps appropriately bring questions about making
7 sure the indications are correct. So, without a doubt,
8 appropriate labeling would have to include extensive data I
9 think about this potential side effect.

10 The concern I have I think is not just that
11 it's something that doesn't make sense. It's a random
12 finding, but there's potential rationale for that in terms
13 of whether it's neonatal models or adult models in terms of
14 GI mucosal injury and the potential for bacterial
15 contamination or bacterial products, quote, translocation.

16 So, the rationale is there and it's something
17 that I have significant concerns about that we may be
18 missing something given the striking nature of the data.
19 So, it definitely does need to be prominently displayed I
20 think.

21 DR. JENNE: I don't think the data is very
22 striking. That's my problem. The exposure to caffeine in
23 one of the open labels, the person had a small bowel
24 resection almost simultaneously with his beginning

1 caffeine. At autopsy the diagnosis was made. So, I don't
2 consider that a case -- I think that's very questionable as
3 exposure being associated. That's two cases in the placebo
4 versus four in the caffeine exposure.

5 You're starting from a different total
6 sufficiently between those two denominators in those cases,
7 that you end up with worthless statistics. It's so close
8 to being random, I can't take it seriously.

9 DR. SESSLER: It's very strikingly one-sided I
10 guess would be the thing that catches my eye. You have a
11 bunch of zeroes in the not-exposed column and significant
12 numbers in the other.

13 DR. JENNE: Well, how about the statisticians
14 discussing this?

15 DR. KELLY: I agree with John Jenne. The thing
16 that increases it really is the exposure data which is the
17 sicker patients getting put on caffeine, the bias there in
18 terms of who do you enter and who gets left off of caffeine
19 altogether, those patients that are doing fine and not sick
20 and doing well. That's one of the problems that you have
21 with a study like this. When you take people off, your
22 placebo group keeps getting better and better and better
23 all the time. But if you just look at the very baseline in
24 terms of who got randomized, you don't see that difference.

1 I agree with you. There is that striking
2 difference, but that's after things have been unblinded to
3 the clinicians.

4 DR. HENDELES: I'm wondering if Dr. Jenkins can
5 clarify whether the agency can even require the company to
6 do some type of surveillance after it's approved. Is that
7 logical?

8 DR. JENKINS: I'm not sure what type of
9 surveillance you're exactly talking about.

10 DR. HENDELES: To see whether there's an
11 increased risk of NEC with the use of caffeine.

12 DR. JENKINS: Well, we certainly can enter into
13 agreements to do phase IV studies which could be controlled
14 trials or they could be some sort of looking at
15 epidemiologic databases.

16 We're interested in hearing your ideas or your
17 suggestions on what would be useful to either better
18 clarify the safety or efficacy of caffeine, if it were to
19 be approved, in the post-approval phase or also any
20 epidemiologic studies you might suggest.

21 But we could require a phase IV commitment for
22 that type of study.

23 DR. HENDELES: Given that, then I think I'll
24 make my comment when we get to item number 6.

1 DR. LI: Stan?

2 DR. SZEFLER: John, by the post-marketing, you
3 wouldn't be able to require another placebo-controlled
4 trial. Is that right or is that within the purview?

5 DR. JENKINS: I think that goes to what the
6 question is you're trying to answer.

7 DR. SZEFLER: Because I think in order to
8 answer Les' question, you have to have a database to
9 compare to to say whether it's increased or not unless it's
10 a striking number like 70 percent of the infants all of a
11 sudden.

12 DR. JENKINS: Well, phase IV commitments can be
13 placebo-controlled trials, but they should not be placebo-
14 controlled trials to answer the question of whether the
15 drug is safe and effective because we need to answer that
16 before we approve the drug. But they could be placebo-
17 controlled trials to better ferret out various areas that
18 are still left questioned such as dosing regimens in
19 different subpopulations, that type of information. But we
20 certainly should not go into this with the thought that we
21 could require a phase IV commitment to do another placebo-
22 controlled trial to determine whether this is really safe
23 and effective. That we need to do before we approve the
24 drug.

1 DR. SZEFLER: Because in order to get those
2 population differences, it would beg the question to the
3 neonatologists to come up with figures to say what's the
4 incidence of necrotizing enterocolitis, say, at certain age
5 groups in the absence of methylxanthine. I don't know if
6 that data is out there.

7 DR. JENKINS: Also keep in mind that the
8 ability to do placebo-controlled trials, if this drug is
9 approved, may even be more hampered than if the drug is not
10 approved.

11 DR. SZEFLER: Right. It was hard enough to get
12 it to an IRB without its approval. It's going to be even
13 harder with an approval.

14 DR. JENKINS: Well, this study had to be
15 designed with a very strong open-label rescue component,
16 and in order to do another placebo-controlled trial, that
17 may even have to be increased. You saw the effect of the
18 very rapid dropout rate on this study of that open-label
19 rescue provision. If it's an approved drug, even if you
20 could get people to randomize to drug versus placebo, they
21 may only do that in the scenario where the open-label
22 rescue was very liberal, which may compromise severely what
23 you could learn.

24 But there may be designs that could be useful,

1 such as dose titration studies or parallel group differing
2 dosing regimens looking to see if there is incremental
3 benefit. You could have targeted plasma concentration
4 studies to see whether there is really a therapeutic range
5 that makes a difference. So, you could do studies where
6 you could have different dosing groups. Placebo may be
7 difficult.

8 DR. LI: Dr. Crim, did you have a comment?

9 DR. CRIM: It's more a comment/question. It's
10 regarding the concern about NEC, and maybe, Dr. Rothstein,
11 you found this when you reviewed the literature.

12 Recognizing the problem with historical
13 controls, was there any sense what the incidence of NEC was
14 in the pre-caffeine days compared to the caffeine days?

15 DR. ROTHSTEIN: Caffeine has been around and
16 used in newborn units before I even started practicing.

17 DR. SZEFLER: I think that's part of the
18 problem because NEC I think just became a diagnostic
19 disorder --

20 DR. ROTHSTEIN: But again, looking historically
21 caffeine sodium benzoate was used as a respiratory
22 stimulant. Until the institution use of continuous
23 positive airway pressure, newborns didn't survive long
24 enough to have NEC. So, NEC only becomes apparent once

1 these kids are living long enough for this disease to take
2 its toll.

3 DR. SESSLER: Are there any preclinical data
4 related to that at all as far as the effects of caffeine on
5 an NEC equivalent in an animal model or anything?

6 DR. LI: Yes, Dr. Pina.

7 DR. PINA: I mentioned one study, but it was
8 not used -- they did not use caffeine. It was
9 aminophylline. There is one animal study where they did
10 show that aminophylline increased the risk of NEC when
11 there was an injured GI mucosa.

12 DR. HENDELES: But that could be from the
13 ethylenediamine. We don't know that it's from the
14 theophylline component.

15 DR. JOBE: Just a comment for perspective.
16 Methylxanthines became common for apnea of prematurity
17 about 1975, so they've been used for a very long time.

18 DR. SZEFLER: That's about the time NEC was
19 popularized.

20 DR. ROTHSTEIN: The use of positive pressure
21 was introduced in 1970, so it's shortly thereafter.

22 DR. SZEFLER: Let me ask another question in
23 terms of this area because I think what seems to be
24 emerging is that this is an interesting drug that needs

1 refinement, and what is the potential for that? I know in
2 my area in terms of asthma, there's been networks
3 developed. NIH has supported networks in terms of doing
4 studies on questions that may not be taken up by industry
5 because of the type of question or because of financial.
6 Is there that type of network available in neonatology?

7 Second, are there guidelines that are published
8 in terms of management of the newborn like we have now
9 guidelines in terms of management of asthma, and if there
10 are these guidelines, what do the authorities recommend in
11 terms of the management of this disorder?

12 DR. JOBE: I guess you asked the right person.
13 I'm actually the chair of the Neonatal Network for NICHD.

14 Interestingly, of all the things we've
15 considered studying, caffeine or theophylline has not been
16 one of them because it's considered by everybody I think
17 standard of care, accepted, and in all the manuals for
18 neonatal care, there are recipes for how you give
19 theophylline or caffeine. So, if you look at Neofax or any
20 of these other drug delivery studies or the textbooks of
21 neonatology, this is considered a non-issue.

22 DR. SZEFLER: After hearing this discussion --

23 DR. JOBE: Yes, I think after hearing this
24 discussion, there are a lot of issues about dosing, about

1 duration.

2 DR. SZEFLER: Could your network benefit by
3 some interest in terms of --

4 DR. JOBE: The network could benefit. Again,
5 these are the kinds of studies that industry perhaps could
6 be encouraged to do in terms of dosing and so on. Sure.

7 DR. SZEFLER: Because I guess I see what is
8 emerging out of here is this drug is provocative in terms
9 of its effect. It's convincing in terms of some of its
10 application, but there's a lot of room for improvement in
11 terms of its application and safety. Perhaps the marriage
12 of the Network and the FDA and industry support to do these
13 kinds of studies would help refine the guidelines and make
14 everybody feel a little bit more comfortable.

15 DR. JOBE: I think that's true.

16 DR. LI: Dr. Sessler.

17 DR. SESSLER: Sorry about getting back to the
18 NEC question and the sepsis. If there are well-established
19 risk factors from previous studies, is it possible -- and I
20 guess this is directed to the sponsors -- to query the
21 databases to try to determine whether in fact this
22 observation is explained and is that data available? Can
23 one do that without having to conduct prospective studies?
24 I guess that's a question for the sponsors.

1 I think this is still an unknown and there may
2 very well be good alternative explanations. That would be
3 marvelous if there is.

4 DR. LI: Would anyone from Roxane like to
5 address that? Dr. Wynne?

6 DR. WYNNE: Yes. Those data are not available
7 in our database. As Dr. Erenberg previously said, we often
8 don't have culture-proven sepsis. So, we could maybe
9 expand the information a little bit to give you a little
10 bit more, but I don't think we have the information --
11 well, in fact, I know we don't -- that you're looking for
12 because we just don't have that culture-proven bacteremia.

13 DR. JOBE: Just as a comment, there is the NIH-
14 sponsored IVIG randomized controlled trial which was
15 published about four or five years ago. That data has just
16 been released to the public sector by NICHD, and that is in
17 fact a sepsis study. I assume they coded in
18 methylxanthines, but I don't know that for sure. So, that
19 is in the public sector now and it's a very large database
20 of approximately 2,000 infants.

21 DR. GOLDSMITH: Part of the problem was
22 mentioned this morning by Dr. Jobe was that NEC in various
23 nurseries is very episodic. So, although generally the
24 practices of giving methylxanthines is not episodic,

1 although it might vary from attending to attending, it's
2 generally pretty consistent. You may go a year or two in a
3 very large nursery with no cases of NEC and then have an
4 epidemic. So, the numbers here are going to have to be
5 quite large and the time frame over which it's looked at is
6 going to have to be relatively long.

7 DR. LI: Yes, Dr. Osborne.

8 DR. OSBORNE: I must say my opinion for
9 question number 2 for using this drug, is it safe for the
10 short-term use of caffeine citrate in patients with apnea
11 of prematurity, I would say yes.

12 I would say when we get to talking about number
13 6, there are several ways we could go about it. For
14 example, the two papers on necrotizing enterocolitis point
15 out it's about 1 in 1,000, and certainly the frequency in
16 this study is within keeping of what has been described in
17 many other studies. If it's possible to have a registry
18 database mined, what you do is you could set up a case-
19 controlled study with multiple controls, so you might have
20 one case where NEC is infrequent and then three or four
21 controls. Then you can do a sophisticated analysis of
22 several kinds of variables that you think might be
23 important in particularly not only the single medication,
24 but medication regimens and multiple effects, such as the

1 H2 blockers, and aminophylline and theophylline and
2 caffeine might come into play in that kind of setting. But
3 I think that's a question I'll address in number 6.

4 DR. LI: I think we're ready to take number 2
5 to a vote. Does the NDA database, together with the data
6 available from published literature and the spontaneous
7 reporting system experience, demonstrate the safety of the
8 short-term use of caffeine citrate in patients with apnea
9 of prematurity?

10 So, all in favor, raise your hand please.

11 (A show of hands.)

12 DR. LI: Did you get that, Leander?

13 MR. MADOO: Who was against?

14 DR. LI: All against?

15 (A show of hands.)

16 DR. LI: Abstentions?

17 (No response.)

18 MR. MADOO: We have 13 in favor of that
19 statement and 1 opposed.

20 DR. LI: All right. Let's take item 3 as a
21 question. Taking into consideration the overall benefits
22 and risks of using caffeine citrate for the treatment of
23 apnea of prematurity, do you recommend that this drug be
24 approved for marketing?

1 Discussion? Yes, Les.

2 DR. HENDELES: I thought you were calling for a
3 vote.

4 DR. LI: We will in a minute.

5 (Laughter.)

6 DR. LI: So, this question of course has to do
7 with approvability. I guess the key word in this question
8 is "overall" taking into account the efficacy and the
9 safety evidence that we reviewed.

10 Again, before the vote, are there any comments,
11 any questions? Yes, Dr. Szeffler.

12 DR. SZEFLER: I have a question back to the
13 other one that I should have asked before the vote. But
14 there's no drug that's completely safe and is there a
15 liberal definition of safety or is that just kind of
16 gestalt?

17 DR. LI: My interpretation is safety based on
18 the opinion of the committee, but perhaps Dr. Jenkins would
19 like to comment on that.

20 DR. JENKINS: Well, I think you're correct in
21 pointing out that there is probably no drug that's
22 completely safe, or if there is such a drug, it's probably
23 not effective.

24 (Laughter.)

1 DR. JENKINS: Usually safety becomes a question
2 of a risk-benefit analysis, so you're analyzing the risk to
3 the patient populations who may be receiving the drug
4 versus the benefit they may be receiving by having the drug
5 administered. So, there is no absolute definition of
6 safety because what may be a safe drug for patients with
7 ARDS where there's no approved therapy would not be
8 considered safe for use as an antihistamine for allergic
9 rhinitis, for example. So, you have to take in the
10 indication, the available treatment option, as well as the
11 actual data and do a risk-benefit type of analysis.

12 DR. LI: That's a good question. That's the
13 essence of this question number 3.

14 All right. Let's go ahead and vote on the
15 question. I guess I won't read it again. All in favor,
16 raise your hand.

17 (A show of hands.)

18 MR. MADOO: Is there anyone opposed? That
19 makes it easier.

20 (A show of hands.)

21 MR. MADOO: Okay, so there are 13 in favor of
22 approval of this agent and 1 who's not in favor of
23 approval.

24 DR. LI: Number 4 we will skip.

1 Number 5 has to do with labeling. We'll take
2 part a separate from part b. If caffeine citrate were to
3 be approved for the treatment of apnea of prematurity, in
4 the labeling would you recommend that the dosing period be
5 restricted to 10 to 12 days?

6 DR. SZEFLER: I don't know who the one opposed
7 was, but I was interested, if that person was opposed, is
8 number 4 applicable? Because we're a recommending panel.
9 We're not a confirmatory panel, and if there is useful
10 information for number 4, maybe it should come from that
11 question.

12 DR. LI: That's an invitation, Curt. What
13 additional studies, if any, would be useful to you?

14 DR. SESSLER: I think additional studies would
15 be problematic certainly. I guess part of my questions
16 that I asked before, without going too far down the field,
17 is we had nine centers that enrolled over 18 months and
18 trying to get a grasp on overall issues of the difficulty
19 in actually performing a second clinical trial. I
20 understand the feelings around the room that that would be
21 very difficult to undertake, and given that this is kind of
22 standard therapy. In my mind, there are some uncertainties
23 in both safety and efficacy, and that would clarify it.

24 My concern I guess is that by going into the

1 acceptance of this as the state of the art and the gold
2 standard, that the important thing is that we don't become
3 complacent about readdressing safety and efficacy.

4 DR. SZEFLER: I guess my question is one of
5 extent because if you have kind of like one vote standing
6 out there, it's useful to kind of know is that because
7 you're convinced it has no effect, or you're just not
8 convinced that there's enough data to make a conviction?

9 DR. SESSLER: Right. I think that there is --
10 well, there are a couple things.

11 I think that there are clearly some indications
12 that this is likely to be effective. Thus, I move to an
13 abstention on the first question.

14 Having said that, the evidence is weak in my
15 view. I guess I'm tainted by being exposed to a lot of
16 negative clinical trials in adult medicine, adult critical
17 care, where similar a sort of findings would not have been
18 borne out by large scale, randomized clinical trials. I
19 cite the several different sepsis studies where the phase
20 II studies looked very promising and where subsequent
21 pivotal clinical trials were performed and proved that the
22 drug had no value.

23 None of them were based on the clinical
24 opinions and bedside experience. Thus, that's why that

1 weighed in in terms of the neonatologists' opinions in my
2 decision there.

3 I still have questions. I think this is
4 unsettled and I feel bad that if in five years we discover
5 that there is some clear-cut relationship between this drug
6 and sepsis and necrotizing enterocolitis, that we perhaps
7 have not been rigorous enough today in apply the standard
8 of actually determining that.

9 DR. LI: Do you have a comment, Dr. Rothstein?

10 DR. ROTHSTEIN: Just that the agents that have
11 been first used by the community and then eventually
12 submitted to randomized studies for ARDS I believe are a
13 lot more toxic than the drug we're talking about here. The
14 numbers of infants who would have to have induced sepsis on
15 the basis of caffeine would have to be elevated quite high
16 in order to start matching some of the drugs that we've
17 been throwing around the adult ICU's.

18 DR. SESSLER: The other factor, I guess, in
19 that decision that I'm made to vote as I did was the fact
20 that this is already approved. It's something that by not
21 approving it, the standard remains.

22 DR. HENDELES: It's not an approved drug.

23 DR. SESSLER: No, it's not an approved drug.

24 I'm sorry. It's in use.

1 So, the advantage of course is that we now have
2 a very standardized preparation and that is clearly worth
3 something, but it is not the same as perhaps denying
4 something that may be a lifesaving drug since it is
5 available. My opinion.

6 DR. LI: Yes, Dr. Crim.

7 DR. CRIM: I would just comment since I was one
8 who also voted -- well, did not support the efficacy
9 question. Again, my not supporting that question is
10 because I considered it was more the circumstantial
11 evidence.

12 In terms of number 4, again what Curtis
13 mentioned, if the technology is now available in neonatal
14 ICU's to objectively measure these parameters better, then
15 I think it may be possible to do that type of a study.
16 That is, if the neonatologists in the unit have better
17 monitoring equipment, then it may in fact be possible to do
18 those types of studies, but you can do a controlled placebo
19 type of a study with larger numbers.

20 DR. LI: Say, Courtney, did you vote
21 affirmative for approvability?

22 DR. CRIM: Yes, I voted affirmative for
23 approvability, but I voted negative for the efficacy
24 question.

1 DR. LI: Would you like to elaborate on the --
2 (Laughter.)

3 DR. CRIM: No. Because number 3 was taking
4 into consideration the overall benefits.

5 DR. LI: No, absolutely.

6 DR. CRIM: And that's why I voted for approval
7 overall, but getting back to the question that was raised
8 in terms of number 4, if you do not recommend approval, I
9 did not support the first question about the efficacy.
10 That's once again my reasons for voting overall but not for
11 the efficacy in terms of what I would like to see. Ideally
12 what I would like to see would be if the technology is now
13 available to do a better efficacy which will also include
14 safety studies.

15 So, I think there are still questions about the
16 safety in terms of the data that was presented both in
17 terms of the literature and in terms of this pilot study
18 here in terms of the numbers and the way the study was
19 controlled. I don't think the data is good, but I don't
20 think the data suggests that the safety of the caffeine is
21 worse than placebo.

22 DR. LI: I understand. Thank you.

23 Let us address as a discussion the question on
24 labeling. A, would you recommend that the dosing period be

1 restricted to 10 to 12 days? We had discuss this briefly
2 and deferred it until now.

3 Yes, Alan.

4 DR. JOBE: I realize the study was designed as
5 a 10- to 12-day study for practical reasons. I think the
6 difficulty here is in clinical practice. Again, the
7 clinical practice is to initiate caffeine or
8 methylxanthines or whatever they're using when a baby
9 presents with apnea of prematurity once the baby is off the
10 ventilator, and then therapy should be discontinued at a
11 point when you anticipate that the baby is mature enough to
12 no longer have apnea of prematurity. That's usually in the
13 32- to 34-week window.

14 In terms of clinical practice, if one has a 26-
15 week infant that you've just extubated, and you treat him
16 for 2 weeks, he'll be 28 weeks gestation and it's unlikely
17 that anybody would stop caffeine at that point. So, I
18 think it's a practical issue of the physiology of apnea of
19 prematurity in that it's a developmental disease and it
20 tends to resolve by 32 to 34 weeks.

21 So, I don't know how to deal with that because
22 the study design wasn't intended to answer that question.

23 DR. LI: Yes, Peter?

24 DR. ROTHSTEIN: I think you've in fact just

1 dealt with that, that the labeling state that this study
2 lasted 10 to 12 days, that this is a developmental issue,
3 that infants born at earlier gestational ages may in fact
4 not have resolution of their apnea until they are 32 or 34
5 weeks, and just leave it at that.

6 DR. HENDELES: I like that.

7 DR. GOLDSMITH: I think you need to take out
8 the word "restricted" from that phrase from a, that you
9 recommend that the dosing period be restricted. If you
10 recommend that the dosing period -- only that 10 to 12 days
11 has been adequately studied or has been studied and that
12 evaluation should come sometime at 34 to 36 weeks post-
13 conceptual age, I think that handles the problem. I don't
14 think I would restrict it to use because that really does
15 lead to problems for clinicians.

16 DR. LI: So, I'm not hearing a lot of support
17 for actually including a restriction as it's written in
18 this particular question. So, the indication, for example,
19 can be apnea of prematurity as the indication. Since there
20 is primarily this one study which is the basis for most of
21 the information that we have, we can recommend that a
22 synopsis or a table or information from that study
23 indicating that the study itself was limited to 10 days.
24 That can be in labeling without writing in a restriction,

1 as Dr. Goldsmith indicated.

2 DR. JOBE: But I think Dr. Goldsmith is
3 recommending putting in the indication that the baby should
4 be tested for need after the period he's likely to have
5 apnea of prematurity, sometime between 32 and 36 weeks.
6 The recommendation would be then that the baby be assessed
7 for need rather than put on continuous drug.

8 DR. ROTHSTEIN: And to answer some of Jay's
9 other concerns, efficacy for other causes of apnea other
10 than prematurity has not been demonstrated.

11 DR. GOLDSMITH: That's right, specifically
12 ALTEs and for weaning from ventilators which I think,
13 although we haven't discussed that today, most children in
14 our unit get started before they demonstrate apnea. They
15 get started while they're still on the ventilator in order
16 to enhance rapid weaning.

17 DR. CRIM: So, if I understand what's being
18 proposed is that we take out the restriction but include in
19 the package insert that the drug has only been studied for
20 10 to 12 days?

21 DR. LI: Yes, something to that effect.

22 Is there an opposing view? John.

23 DR. JENKINS: Dr. Li, I was just going to
24 suggest that since you all have modified the question so

1 much, it's really not entirely necessary that you try to
2 take a vote. I think we've heard a lot of different ideas
3 and we can incorporate those. But if you want to try to
4 write the question in your own words and then take a vote,
5 that's fine also.

6 DR. LI: Thank you.

7 Yes.

8 DR. SZEFLER: I was just going to mention
9 there's kind of another soft area in there that probably
10 requires some looking at right up front. In terms of
11 description, it mentions bronchodilator activity and then
12 it kind of pops up later on. That is distant from the
13 apnea aspect and again kind of creates potentials for
14 creative application. John?

15 DR. JENKINS: Yes, if I could comment on that
16 also. The label that you have in your briefing package is
17 simply the label that was written by the sponsor and
18 submitted. The sponsor generally submits their proposed
19 labeling and that will undergo a rather extensive review.
20 So, that has not been reviewed and modified by the agency
21 as yet. So, if that helps to allay some of your concerns.
22 You can be guaranteed that the labeling will be
23 substantially revised because we always substantially
24 revise what the sponsor sends in.

1 (Laughter.)

2 DR. SZEFLER: That part caught my attention. I
3 don't want to have everybody running around that this is a
4 new bronchodilator that was approved.

5 DR. LI: Rather than take a vote on the 10- to
6 12-day restriction, I would like to have the panel address
7 three items that I had jotted down from our previous
8 discussions earlier this afternoon and this morning that
9 had to do with labeling.

10 One had to do with whether we wanted to
11 recommend drug levels be performed, and if so, at what
12 intervals?

13 The second had to do with whether the
14 importance of the patient's renal function should be taken
15 into account.

16 And the third was whether there was a
17 therapeutic level or a therapeutic range that we wanted to
18 include.

19 Again, these are items that came up from our
20 discussion earlier, and I just wanted to revisit them at
21 this point because it is appropriate to address those.

22 Yes, Dr. Hendeles.

23 DR. HENDELES: I think what prompted those
24 comments was reading the sponsor's labeling, and just

1 letting the FDA know that we're concerned about that they
2 be taken into account is really all that I feel the need to
3 do.

4 DR. LI: So, for example, with the issue of
5 drug levels, is there any opinion or any proposal for
6 including anything about drug levels in the labeling?

7 DR. ROTHSTEIN: I think that's one of the
8 wealth of phase IV studies. Some fellows can have a career
9 over this.

10 (Laughter.)

11 DR. HENDELES: I think there's information in
12 the literature, and the way I would deal with that issue is
13 simply to recommend that there be a section on when they
14 should be drawn and what should be done with the results
15 and leave it to the agency.

16 DR. LI: Do you have an opinion about that,
17 about when it should be drawn and how the results should be
18 used?

19 DR. HENDELES: Yes, but I don't feel it's
20 appropriate here.

21 DR. LI: All right.

22 Dr. Cross.

23 DR. CROSS: At the levels they're suggesting to
24 use, they didn't find any really high levels that looked

1 inappropriately high, at least from what I saw.

2 DR. HENDELES: Dr. Pina's review had indicated
3 that there were some levels above 30.

4 DR. CROSS: But not any that were really
5 concerning.

6 DR. HENDELES: I don't know.

7 DR. CROSS: I mean, one option is just to say
8 if higher dose -- I'm sure we'd all agree if higher than
9 recommended doses are used, blood levels should probably be
10 checked.

11 DR. HENDELES: Or what if the patient doesn't
12 respond to therapy? They are giving a loading dose. It
13 might be because their level is too low. We don't know if
14 there's a relationship, and under item number 6, I would
15 recommend that since they have that data, that they examine
16 it with that intent, to look and see whether those patients
17 who failed to respond to the initial loading dose of
18 caffeine had lower levels than the patients who did
19 respond.

20 DR. SZEFLER: Just to follow up on your point,
21 it's hard to kind of write that levels should be obtained,
22 but levels are the only safety valve that you have with the
23 restrictions of the study. The study was done in a certain
24 age group, certain population, numerous exclusion factors.

1 The levels are something you can use to kind of
2 individualize the dose for your children less than 1,000 or
3 less than 28 or on concomitant therapy. But I don't know
4 exactly, without getting into the details you're referring
5 to, Les, how to write those statements in there, but it's
6 something that it would be nice to have some information
7 around it.

8 DR. LI: Dr. Crim first.

9 DR. CRIM: I guess I'm of the opinion that as
10 far as levels, I don't see a great need to have that in the
11 package labeling as far as the company is concerned.
12 That's because since we don't have any type of
13 pharmacodynamic data, I don't know what to recommend or
14 that the company should recommend since the company doesn't
15 have the data. I think what has been done is what the
16 clinicians have been doing over the years. They'll just
17 titrate the dose up until they get a response or a side
18 effect. If one wanted to just put a general statement that
19 perhaps monitoring may be warranted, to me I think it
20 should be left as nebulous as that because we don't have
21 any pharmacodynamic data.

22 DR. KELLY: Yes. It's like digoxin. You dose
23 till they throw up, and then you back off.

24 When you do therapeutic drug monitoring, what

1 you usually aim at is efficacy. So, you would load the
2 patient. If they don't respond, you would probably reload
3 them. If they then responded, you would get a serum
4 concentration at that point to determine what that
5 patient's therapeutic level was because it's that patient's
6 therapeutic level. You can't write that into a package
7 insert that I can see. Then you want to maintain that
8 therapeutic level and it may take any number of different
9 dosages.

10 People like me have made entire careers out of
11 doing that on a daily basis in other types of patients.
12 So, I don't want to take that away and put it in a package
13 insert.

14 (Laughter.)

15 DR. LI: All right. Well, I don't hear a lot
16 of support for including a very specific directive toward
17 measurement of drug levels nor implicitly for a stated
18 therapeutic range.

19 DR. JENNE: My first comment was that we
20 shouldn't specify these levels so precisely, but I still
21 think that they're worth doing. The question of they're a
22 check, for example, on renal elimination problems. They
23 may be accumulating. I've got in this pharmacokinetic
24 paper they happen to be going up over 12 days or so.

1 They're continuing to go up.

2 But I don't think we should be so dogmatic
3 about the upper level as if anything over that is a
4 disaster because there should be some flexibility in the
5 package insert, it seems to me.

6 DR. LI: So, perhaps a vote for a more general
7 inclusion of a statement on drug levels rather than
8 something specific. Fine.

9 On the issue of renal function, Les, did you
10 think that a comment or a mention of that in the labeling
11 is important?

12 DR. HENDELES: I think in general there needs
13 to be more specific dosing guidelines than what's in that
14 package insert, including an adjustment for patients who
15 have decreased renal function.

16 DR. LI: Do others agree with that suggestion
17 from Dr. Hendeles? Carroll nodding. Okay.

18 Let's now move on to 5b which is one of the
19 important issues that is before us today. Would you
20 recommend a warning considering the concern of necrotizing
21 enterocolitis and caffeine? We did touch on this earlier,
22 but we need to revisit the idea. Yes.

23 DR. HENDELES: I think there should be a
24 precaution or some statement in there that reviews what the

1 animal and human data is in a few sentences so that it
2 informs the clinician of that information but not a warning
3 which to me implies a black box.

4 DR. LI: Is there agreement or dissention?

5 Yes.

6 DR. ROTHSTEIN: I've just got a follow-up
7 question. If an infant develops enterocolitis or abdominal
8 distention, should treatment be stopped?

9 DR. HENDELES: Well, if you stop the treatment,
10 it's still going to go on for five days.

11 DR. ROTHSTEIN: Oh, yes.

12 DR. KELLY: What do you do now?

13 VOICE: Keep going.

14 DR. ROTHSTEIN: So, that's my question. One
15 can say that sicker infants will have more severe apnea.
16 There may be an increased incidence of sepsis in infants
17 with increased apnea, but there is no firm association
18 between the treatment of the apnea and exacerbation of
19 enterocolitis or sepsis. Somehow acknowledging that these
20 two conditions may run together and therefore, people have
21 raised the issue, well, but caffeine or theophylline was
22 used, therefore it's associated. It may or may not.

23 DR. LI: Right. So, you would propose or
24 recommend some indication of a potential association with

1 acknowledgement that that association hasn't been proven.

2 DR. HENDELES: Right, a just a disclosure of
3 the problem.

4 DR. SESSLER: I think I'm comfortable with
5 that, for whatever that matters, in the sense that
6 unfortunately we don't have definitive data. What we have
7 is worrisome findings that may be easily explained
8 somewhere else. Obviously it doesn't require something
9 that's a very high level proven association type of
10 warning, but it certainly does need to be mentioned that
11 that was an area of concern in my opinion.

12 DR. LI: That would satisfy you, Dr. Sessler?

13 MR. MADOO: Couched as a warning or as a
14 precaution? How are you are you going to couch this?

15 DR. LI: Well, we heard from Dr. Hendeles a
16 suggestion for more of a comment. I'm not sure you even
17 used the word "precaution."

18 DR. HENDELES: I probably did.

19 DR. ROTHSTEIN: I don't think it merits a boxed
20 warning.

21 DR. LI: So, no support for the warning.

22 Yes.

23 DR. OSBORNE: I would agree, if I read the
24 numbers correctly, that is, the FDA document pointed out

1 there was no statistical difference between the groups
2 whether the caffeine group or placebo or by original
3 randomization or adverse events of all patients. In none
4 of those cases was there a statistical difference. We've
5 talked about the small sample size extensively and this
6 certainly could be a type 2 error.

7 But I'd also point out that in the literature,
8 with all the problems that the literature has, there are
9 huge ranges of either prevalence or incidence of NEC, but
10 they range easily within the percentages we're seeing here,
11 which are less than 10 percent. They're often much higher
12 in the kind of population that seems similar to this one.
13 So, at least if it is occurring by association, the numbers
14 are not dramatic, and so I would agree with no warning.

15 DR. LI: Curtis.

16 DR. SESSLER: I would ask that someone look at
17 the statistics again just to clarify that in terms of this
18 garbage area, the exposure area. Granted, it's an unknown
19 but before we categorically state that patients by
20 randomization or by exposure had no statistical difference
21 in these, 0 percent versus 13 percent looks to me by a
22 Fisher's Exact Test that it might be significant, and the
23 same for the sepsis and for the NEC. So, I would just do
24 that before we make the statements that we know.

1 DR. LI: Were those studies done, Dr. Jenkins
2 or Dr. Pina?

3 DR. JENKINS: I'll let Dr. Pina answer that
4 question. Then I have a clarification I'd like to make for
5 the committee.

6 DR. PINA: I think I will defer that question
7 to Dr. Gebert.

8 DR. GEBERT: Yes. I did a Fisher's Exact Test
9 on those data and they were not significant.

10 DR. SESSLER: Thank you.

11 DR. JENKINS: The clarification I'd like to
12 offer for the committee is a boxed warning and a warning
13 are not the same things. You can have warnings and they
14 will not be in black boxes. A black box warning is a much
15 higher level of a warning that are reserved for certain
16 circumstances and have the desired impact of conveying the
17 severity of the warning but also they have impacts with
18 regards to how the sponsor may promote the product without
19 providing the entire package insert for the physician.

20 So, just to clarify, there was some discussion
21 earlier that it didn't merit a black box. Other people
22 seemed to equate black box and warning being the same.
23 Almost all drugs have a warning section in their labeling,
24 and often things such as patients who are hypersensitive to

1 the drug, it's contraindicated. That may be in the
2 contraindications or it may be in the warnings.

3 But I just wanted to clarify a warning is not
4 necessarily a black box warning. A black box warning is
5 usually reserved for much more significant definite
6 associations and more severe potential adverse effects.

7 DR. HENDELES: How does a precaution differ
8 from a warning?

9 DR. JENKINS: I don't have the regulatory
10 definitions of those sections here with me, but warnings
11 are generally viewed as things where if the adverse event
12 occurs, it could be serious or life-threatening, whereas
13 precaution is a little bit lower standard. There are
14 specific definitions of those in the CFR, and I don't know
15 if Dr. Bilstad knows the definitions. He's indicating that
16 he doesn't.

17 DR. BILSTAD: Well, it's really just a matter
18 of degree of how strong we think that the message should
19 get to health care providers. If there's concern about a
20 safety problem, the milder concern is to put it into
21 precautions, draw it to health care providers' attention.
22 If the concern is stronger, it may warrant going into the
23 warnings section, and as John indicated, if we have a great
24 deal of concern about it and it's potentially life-

1 threatening or has been demonstrated to cause mortality,
2 then it may merit a boxed warning which again can be in the
3 warnings section, or if we're really concerned, we'll put
4 it up front at the beginning of the labeling. So, there's
5 sort of a spectrum of ways in which we can get across the
6 concern in the labeling.

7 DR. LI: Well, John, would it be useful to get
8 a sense from the group how concerned the panelists are
9 about the risk of NEC?

10 DR. JENKINS: Yes, I think that would be useful
11 because it's clear that we've gotten the feeling that there
12 should be something in there stating what is known about
13 the association between methylxanthines and NEC, and it
14 would be useful to hear from this panel what your level of
15 concern is. I think Dr. Bilstad almost laid out a
16 hierarchy of no concern, therefore no statements;
17 precaution; a warning; a black box warning in the warnings
18 sections; a black box warning in the front of the labeling.
19 So, it would be useful to know what your level of concern
20 is and how much you'd like to convey that information to
21 the prescribing clinician.

22 DR. LI: Why don't we go around the table?
23 Actually, Les, you had your hand up, so you'd like to make
24 some comments.

1 DR. HENDELES: I have a precaution level
2 concern.

3 DR. LI: Thank you.

4 DR. KELLY: Precaution.

5 DR. JOBE: I would just like to see that
6 clinicians know that there's a potential association so
7 that that could be followed up if necessary.

8 DR. JENNE: I'd just say that we're uncertain
9 and at least it should be mentioned.

10 DR. OSBORNE: I'm somewhere between precaution
11 and warning. I don't have the clinical experience, but I'm
12 certainly concerned there's an association. I'll say
13 precaution.

14 DR. CRIM: Precaution.

15 DR. LI: Precaution for myself.

16 DR. ROTHSTEIN: I'll leave it for the
17 discussions between the FDA and the sponsor to work out.

18 DR. CHINCHILLI: Yes, I agree. I think the FDA
19 needs to make that judgment, based on the fact that it's
20 not clear-cut, whether or not there is an association.

21 DR. SZEFLER: I lean towards precaution.

22 DR. CROSS: I'm leaving it to the FDA but note
23 that their indication of the difference between precaution
24 and warning is the severity of the complication, not the

1 certainty of the complication or uncertainty.

2 DR. SESSLER: I agree. I think precaution is
3 about right, but it is a very severe thing. We're hampered
4 by a lack of clear-cut data unfortunately.

5 MS. CONNER: Precaution.

6 DR. GOLDSMITH: I would agree with precaution.
7 One or two other comments.

8 I know Dr. Sessler has been concerned about the
9 adverse events, and those babies who were exposed -- I
10 don't know how many of them because I didn't take notes on
11 this -- were rescued. So, I wonder whether they truly had
12 apnea of prematurity by that point or whether they were
13 suffering from NEC or sepsis when somebody switched them
14 out from their possibly being in the not-exposed category,
15 in the placebo category, because they weren't responding
16 and they already had the beginnings of sepsis. So, one of
17 the things that might be put in the precaution is that
18 nonresponders should be looked at for other causes such as
19 sepsis and necrotizing enterocolitis.

20 The second thing I would add would be that
21 again drug interactions -- the use of caffeine in
22 association with other drugs as potential causes for NEC or
23 sepsis has not been investigated so that it's not just
24 caffeine in itself, but in association with other drugs.

1 MR. MADOO: It looks like we had eight at the
2 precaution level and seven at the let FDA take care of it.

3 DR. LI: Thank you, Mr. Madoo.

4 Let's tackle question number 6. If caffeine
5 citrate were to be approved for this indication, what, if
6 any, post-marketing studies would you recommend be
7 completed by the sponsor? We did actually tackle this to a
8 limited extent. Let's try to give as much assistance as
9 possible.

10 Yes.

11 DR. JENKINS: Jim, if I could just ask the
12 committee, it would be very useful to us if we could hear a
13 discussion of what studies you think should be a condition
14 of approval, in other words, a required phase IV study, a
15 phase IV commitment, versus studies that might be nice if
16 someone would do them. So, it's kind of what's needed as a
17 condition for approval, given that the committee has
18 recommended approval, versus what would be nice in the
19 broad spectra of things which you really wouldn't put it at
20 the level that it had to be agreed to before you would
21 recommend approval.

22 DR. GOLDSMITH: Maybe as an introduction to
23 this -- and I'm not exactly sure of my numbers, but the
24 neonatologists here are very familiar with working with

1 other people's drugs. We get to use all the drugs that
2 have been approved for adults and for children, but never
3 looked at for neonates. I think, if I'm not right -- Alan
4 may correct me on this, but surfactant probably is the only
5 drug that has been approved specifically for neonates, and
6 this may be the second.

7 DR. JOBE: Indomethacin for PDA is another one.

8 DR. GOLDSMITH: Okay. So, two or three drugs.

9 So, what we wind up with is giving all kinds of
10 drugs. We gave indomethacin for a long time before it was
11 approved. I remember back in 1976 that discussion at the
12 SPR's on giving it and what the consequences were.

13 In surfactant, there were 10,000 children
14 looked at before it was approved by the FDA or some huge
15 number in trials before we got a chance to use it
16 clinically in 1990 I guess.

17 Several people said that this is a very
18 important step because we're beginning to take some drugs,
19 orphan drugs and other drugs, and say they have neonatal
20 indications for use and they should be looked at, but we're
21 beginning to see, as this committee has heard all day, what
22 the tremendous difficulties of this are when you have drugs
23 that are already in clinical use, that people won't take to
24 an IRB that physicians want an easy opt-out. So, we have,

1 I think, some real considerations here that we should have
2 some definite stage 4 studies required.

3 Now, I don't know whether you can do any more
4 stage 4 efficacy studies, but certainly safety has to be
5 required and some way of monitoring safety over the next 12
6 to 24 months at a minimum, if we have 20,000, 30,000,
7 40,000 kids a year treated with this, has got to be done so
8 that as we approach these drugs that are now being offered,
9 to compare 10,000 children treated with surfactant and I
10 don't know how many thousand with indomethacin versus the
11 small numbers here, I think we do have tremendous safety
12 concerns in going forward.

13 DR. LI: Dr. Rothstein?

14 DR. ROTHSTEIN: The two areas that I would like
15 to see commitments to is, one, the developmental
16 pharmacology of this drug, the blood concentrations and the
17 accumulation of this drug in the 27-weeker versus the 32-
18 weeker, and then anticipating what's going to go on in the
19 community, what happens when the dose is increased? Is
20 there some sort of pharmacodynamic effect that we're going
21 to see when the loading dose, instead of 10, becomes 15,
22 when the maintenance dose is increased by 50 or 100
23 percent? Do we see a change either in the efficacy of the
24 drug or do we see a change in the side effects?

1 DR. LI: Would those suggestions be under the
2 required or nice-to-know categories?

3 DR. ROTHSTEIN: Well, I think the company is
4 going to very much like to know about how their approved
5 drug is now being used. I think the FDA might want it
6 also, but I think the company has a vested interest in
7 knowing what's going on with the drug.

8 DR. KELLY: Like the neonatologists who believe
9 this drug works, I believe that there is a concentration-
10 effect relationship, and I think there should be dose
11 ranging studies. I don't know the design of those, but I
12 think that's one area that we really need to know more
13 about. I think there's evidence in the literature that
14 there are differences in response rate, and so I think a
15 dose ranging study is necessary.

16 DR. HENDELES: In response to Dr. Jenkins'
17 question, I think before the drug is approved, that the
18 available literature needs to be analyzed and a lot of
19 these questions can be answered, such as the relationship
20 between renal function and half-life of the drug so that
21 one could scale down the maintenance dose.

22 I think that through the network, there ought
23 to be after approval some attempt to see whether there's an
24 increased incidence of NEC in association with the use of

1 this drug as opposed to CPAP or something else. If there
2 is, I do support what Dr. Kelly said about looking at the
3 relationship between concentration and effect. If there is
4 no strong relationship, it may be that you can give a
5 smaller dose of the drug and decrease any risks from it.
6 So, I think that would be nice to know afterwards.

7 But right now I think that we have sufficient
8 information to approve it and I think the dosing that's in
9 the package insert could be adjusted based upon the
10 knowledge of the biopharmaceutics and pharmacokinetics that
11 is available.

12 DR. LI: Curt, did you have a comment you'd
13 like to make about this?

14 DR. SESSLER: I think the safety part is
15 certainly key. I would include sepsis with NEC just
16 because of the observation in the database that we have
17 before us. Even though this may not have received
18 attention so much in the past, I think we're obligated to
19 look at that along with the NEC question in terms of
20 follow-up safety.

21 DR. LI: Vernon, do you have any thoughts about
22 whether any additional studies should be required as a
23 condition for approval?

24 DR. CHINCHILLI: No. My main concern is the

1 safety. So, I have similar concerns as Curtis.

2 DR. CROSS: Yes, mine is safety. I'm unclear,
3 though, how one would handle sepsis because sepsis syndrome
4 and suspected sepsis and bacterial proven sepsis and how
5 you do the blood cultures, et cetera gets to be pretty
6 complicated to deal with even in the adult ICU. So, I'm
7 certainly interested in my own feeling on the safety in
8 terms of the enterocolitis aspect, but in terms of the
9 septic part, I'm not too sure without a stronger
10 theoretical construct that I would make the company start
11 recording sepsis and proved sepsis and maybe sepsis and
12 sepsis syndrome and hemodynamic over-reactivity and
13 whatever.

14 DR. SESSLER: I would make it simple and do
15 bacteremia. In adults we know that only 30 or 40 percent
16 of septic patients have bacteremia, but if bacteremia is
17 the only hard definition that could be utilized, then that
18 would be better than nothing.

19 DR. LI: Dr. Jenkins.

20 DR. JENKINS: Assuming the drug is approved,
21 it's very likely that it will become standard of care even
22 more so than it is now. So, some of these questions that
23 you're suggesting about follow-up issues on NEC and sepsis
24 -- I'd be interested if you have any ideas how those

1 studies would be conducted. In other words, what would the
2 control groups be if nearly all of the patients with this
3 disease were receiving caffeine citrate? Would we limit
4 ourselves to historical controls, or how would you get some
5 handle on whether the incidence of NEC is higher? What
6 would your control group be?

7 DR. LI: Dr. Rothstein has the answer.

8 (Laughter.)

9 DR. ROTHSTEIN: We've heard that in some units
10 this drug is started while children are still being
11 ventilated in preparation for discontinuation of mechanical
12 ventilation. You can very easily double-arm that. So,
13 some kids are not started on it until mechanical
14 ventilation is discontinued, and they demonstrate disorders
15 of respiratory control. The practice already is
16 established of starting it earlier. So, you have a way of
17 perhaps getting a double-arm study there.

18 DR. LI: Molly?

19 DR. OSBORNE: I think it depends a lot on what
20 kind of database is available. If there's a database
21 through the NICHD that would have enough information,
22 certainly one simple way to do it would be to identify NEC
23 which, first of all, is going to need a longer study than
24 this anyway. The articles suggest 25 percent occur 30 days

1 after birth. So, we're missing a lot of them perhaps in
2 the study. And look at dose response. I mean, at least
3 dose response so you can get some information on dose, some
4 information on weight, and get some information, but doing
5 it that way without having to get a placebo group, although
6 controls would be great.

7 DR. SZEFLER: Correct me if I'm wrong, but I
8 would think NEC is a complication that you monitor in a
9 unit, and so good units that have good data would be places
10 to go to see what happens to the incidence before and after
11 approval. So, I think historical controls in a controlled
12 setting would be a good place to start in terms of looking
13 at changing incidence.

14 DR. JOBE: I think again the NICHD Neonatal
15 Network database and the Vermont Oxford databases are
16 published every year or two with incidences versus birth
17 weight for NEC, IVH, all the alphabet soup of neonatology.
18 One can at least get that sort of epidemiologic data with
19 the introduction of a drug. That was done very effectively
20 for surfactant and its introduction.

21 DR. CRIM: Who reports to those databases? Is
22 it just major university centers or is it even community
23 hospitals that have a pediatric --

24 DR. JOBE: There are two different databases.

1 The NICHD network is 14 university centers. The Vermont
2 Oxford is about 100 non-university centers by and large.
3 So, they have different flavors to them.

4 DR. CRIM: Yes, that's what I was wondering
5 because if you have a sicker population in the university
6 setting, then the incidence may be higher than, let's say,
7 some pediatric hospital out in the communities.

8 DR. LI: Dr. Goldsmith, did you have an
9 additional comment?

10 DR. GOLDSMITH: Maybe Alan can comment on this
11 in terms of what the NICHD did, but obviously the same
12 problems that you have with sepsis, we have in NEC. There
13 are stages, the Bell's modified criteria, and what level
14 does it have to rise to, to what stage in the Bell's
15 criteria before NICHD listed it as a complication of NEC?
16 Do you have information on that?

17 DR. JOBE: I don't know the definitions being
18 used right now.

19 DR. GOLDSMITH: We have similar kinds of issues
20 in terms of sepsis, and that obviously has to be looked at
21 carefully.

22 DR. LI: So, do I sort of hear, as a summary of
23 what was recommended, that a safety post-marketing study be
24 conducted primarily again looking at NEC and perhaps sepsis

1 too as a follow-up of safety and that this recommendation
2 would be required as a condition for approval? I see Dr.
3 Goldsmith nodding.

4 Curt, what's your feeling about the requirement
5 of this type of study for safety?

6 DR. SESSLER: Just as you stated it.

7 DR. LI: Is there anyone in disagreement?

8 DR. JENNE: I don't understand the definitions
9 here. You say a post-marketing study. In other words, it
10 would be marketed.

11 DR. LI: Yes.

12 DR. JENNE: And this would be a requirement for
13 the company to continue studying along certain lines.

14 DR. LI: Yes, as opposed to optional.

15 DR. JENNE: I would put a dose-response in the
16 same category frankly. Whether the company should do it or
17 somebody else be commissioned to do it, I think there could
18 be some ingenious ways of finding this information out.

19 DR. LI: So, I think the first issue is that
20 there was agreement I believe on our recommendation for a
21 post-marketing safety study looking, in particular, at NEC.

22 And the second issue that Dr. Jenne brought up
23 and which we discussed is studies regarding dose ranging
24 studies or concentration effects.

1 John, is it your opinion that you would
2 recommend that this be a required activity that would be a
3 condition for approval?

4 DR. JENNE: Yes, I think it should be done by
5 reputable investigators. It doesn't take a large group to
6 do this. It doesn't take controls necessarily to do a
7 dose-response study. But I think the company should have
8 the first chance to do this.

9 DR. LI: Dr. Kelly, I see you nodding. Does
10 that mean you're in agreement?

11 DR. KELLY: I agree and I think there are ways
12 to analyze sparse data now where you don't have to get
13 large amounts of blood samples and stuff from the patients
14 to do it. So, I don't think it's that difficult to do.

15 DR. LI: Any other comments from the group,
16 either agreement or disagreement?

17 (No response.)

18 DR. LI: Okay, thank you.

19 That really concludes the six questions that we
20 were asked to address. Let me ask Dr. Jenkins if he would
21 like to make some comments before we adjourn for the day.

22 DR. JENKINS: I would just like to thank the
23 committee. I think you've done an outstanding job of
24 reviewing the data and really have a very good discussion

1 today. Particularly I'd like to thank the neonatology
2 consultants who joined us today: Dr. Goldsmith, Dr.
3 Rothstein, and Dr. Jobe. I think they really added a lot
4 to the discussion and brought a lot of information that
5 maybe most of us who are not neonatologists don't have a
6 very good feel for. I think it was a very productive and
7 useful session, and we'll certainly take your
8 recommendations under consideration very strongly.

9 DR. LI: Yes, Peter.

10 DR. ROTHSTEIN: Since the transcripts are
11 available of this hearing, is the data that was presented
12 here now in the public forum?

13 MR. MADOO: It has to go through FOI. We'll
14 process it through FOI and then you can make a request for
15 it.

16 DR. LI: Yes, Stan.

17 DR. SZEFLER: If I could make one other
18 suggestion. I don't know if it comes under here, but I
19 would encourage a full publication of the study. I don't
20 know if you can make that a requirement. At least you have
21 some reference in terms of public access.

22 DR. ROTHSTEIN: That depends on the journals.

23 DR. SZEFLER: Yes, but I mean, I would
24 encourage a smaller detailed summary.

1 DR. JENKINS: One thing I can say to that, if
2 the drug is approved by the agency, the agency's reviews of
3 the NDA become available to the public under the Freedom of
4 Information Act. Those may be partially redacted to
5 protect any proprietary information, but the FDA reviews
6 are available. In fact, they're now available
7 electronically on the World Wide Web very quickly after the
8 approval. So, the medical officer review that you have,
9 once it's finalized, if the application is approved, as
10 well as the other discipline reviews, are available under
11 the Freedom of Information Act which, if the drug is
12 approved along its current time frame, might occur before
13 publication could be out there also.

14 DR. LI: Dr. Osborne?

15 DR. OSBORNE: Is it also possible it would come
16 out in the Medical Letter?

17 DR. JENKINS: The Medical Letter generally does
18 review newly approved therapies, and the FDA does receive
19 pre-publication copies of those documents for review and
20 comment. But I can't speculate on whether the Medical
21 Letter will consider this to be a substantive enough
22 approval that they'll put it in their publication, which is
23 very widely distributed and not just to neonatologists.
24 This is a pretty focused area of indication.

1 DR. LI: Okay. Thanks to the panelists.
2 Thanks very much to Dr. Jenkins, Dr. Pina, the FDA. Thank
3 you to the sponsor.

4 The meeting is adjourned.

5 (Whereupon, at 3:47 p.m., the committee was
6 adjourned.)

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