FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (GIDAC) AND THE PEDIATRIC ADVISORY COMMITTEE (PAC)

Thursday, May 3, 2018

8:00 a.m. to 4:08 p.m.

DoubleTree by Hilton Hotel Bethesda

The Grand Ballroom

8120 Wisconsin Avenue

Bethesda, Maryland

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P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. COLE: Good morning. I'd like first to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so.

I would also like to identify the FDA press contact, Theresa Eisenmann. If you are present, please stand. There she is back there. Everybody see her waving her hands back there?

Next, I'd like to ask all members, consultants, FDA panel, and our designated federal officer to go around the table and state their names into the record. Let's begin with Dr. Levine.

DR. LEVINE: Good morning, Doug Levine, industry representative for GIDAC.

DR. PORTMAN: Ron Portman, industry representative for the Pediatric Advisory Committee.

DR. HUNSBERGER: Sally Hunsberger,

biostatistician.

DR. SMITH: Brian Smith, temporary member for the Pediatric Advisory Committee.

DR. NEWMAN: Tom Newman from UCSF in epidemiology and pediatrics.

DR. ADAMS: Heather Adams, neuropsychologist, University of Rochester.

DR. GUILLORY: Charleta Guillory, neonatologist, Texas Children's Hospital and Baylor College of Medicine.

DR. CATALETTO: Mary Cataletto, pediatric pulmonology, NYU Winthrop. And I'm here for the Pediatric Advisory Committee.

DR. HOEHN: Sarah Hoehn, pediatric ICU and pediatric palliative care from the University of Chicago Comer Children's Hospital and I'm here as part of the Pediatric Advisory Committee.

DR. HAVENS: Peter Havens, pediatric infectious diseases, Medical College of Wisconsin in Milwaukee, Wisconsin, member of the Pediatric Advisory Committee.

DR. FEAGINS: Linda Feagins,

gastroenterology, Dallas, Texas.

DR. DRACKER: Bob Dracker, pediatrics, hematology, transfusion, medicine, Syracuse, New York, member of the PAC.

MS. ELLIS: Annie Ellis, patient representative, temporary member of GIDAC.

MS. BOYCE: Danielle Boyce, research data analyst and statistician at Johns Hopkins, Division of Pulmonary and Critical Care, and patient representative for the Pediatric Advisory Committee.

DR. MCVEY HUGICK: Good morning, I'm Joy McVey Hugick from Atlanta, Georgia and I'm the consumer representative on the Gastrointestinal Drugs Advisory Committee.

DR. RAUFMAN: Jean-Pierre Raufman, chair of the Gastrointestinal Drugs Advisory Committee. I'm a gastroenterologist at the University of Maryland in Baltimore.

DR. COLE: Sessions Cole. I am a neonatologist from Washington University in St. Louis.

DR. FAJICULAY: Jay Fajiculay, designated federal officer for the Gastrointestinal Drugs Advisory Committee, FDA.

DR. ASSIS: David Assis, adult hepatologist at Yale University School of Medicine, member of the GI Advisory Committee.

DR. ROSEN: Rachel Rosen, pediatric gastroenterologist, Boston Children's Hospital.

DR. CALLAHAN: David Callahan, child neurologist, Washington University Physicians in St. Louis.

DR. KHURANA: Sandeep Khurana, hepatologist, Geisinger Clinic, member GIDAC.

DR. WADE: Kelly Wade, neonatologist, Children's Hospital of Philadelphia, member of PAC.

DR. STRATE: Lisa Strate, gastroenterologist at the University of Washington in Seattle and I'm a member of GIDAC.

DR. SAYEJ: Wael Sayej, pediatric gastroenterologist, Connecticut Children's Medical Center in the University of Connecticut School of Medicine. I am a member of the Pediatric Advisory

Committee.

DR. WHITE: Michael White, pediatric cardiology from Ochsner Children's Hospital in Ochsner Clinical School, New Orleans, Louisiana, member of the PAC.

DR. WILKINS-PARKER: Jamie Wilkins-Parker, deputy director, Division of Risk Management, Office of Surveillance and Epidemiology, FDA.

DR. BAER: Gerri Baer, medical officer and neonatologist in the Office of Pediatric Therapeutics, FDA.

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DR. OMOKARO: Stephanie Omokaro, lead medical officer, Division of Gastroenterology and Inborn Error Products.

DR. LEE: Jessica Lee, associate director, Division of Gastroenterology and Inborn Errors Products, FDA.

DR. BEITZ: Julie Beitz, director, Office of Drug Evaluation III, CDER, FDA.

DR. COLE: Thank you very much. For topics

such as those being discussed at today's meeting, there are often many varied opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now, I'll pass it on to Dr. Jay Fajiculay, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today for the joint meeting of the Gastrointestinal Drugs Advisory Committee and Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and

temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions at today's meetings, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses and minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves supplemental new drug application 209904 for stannsoporfin injection for intramuscular use, submitted by InfaCare Pharmaceutical Corporation, proposed for the treatment of neonates greater than or equal to 35 weeks of gestational age with indicators of hemolysis or are at risk of developing severe hyperbilirubinemia.

This is a particular matters meeting during which specific matters related to InfaCare Pharmaceutical's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they

have made concerning the product at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Douglas Levine and Dr. Ronald Portman are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Dr. Levine and Dr. Portman's roles at this meeting are to represent industry in general and not any particular company. Dr. Levine is an independent pharmaceutical consultant and Dr. Portman is employed by Novartis.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank

you.

DR. COLE: We will proceed with opening remarks from Dr. Stephanie Omokaro.

FDA Introductory Remarks

DR. OMOKARO: Good morning, everyone. I would like to welcome you to the joint meeting of the Gastrointestinal Drugs Advisory Committee and the Pediatric Advisory Committee for the new drug application for stannsoporfin, a new molecular entity.

My name is Stephanie Omokaro and I'm a clinical team leader in the Division of Gastroenterology and Inborn Errors Products. Before we begin, I would like to thank the chair, Dr. Cole, and members of the advisory committee for taking the time out of your very busy schedules to consider various aspects of this application and provide your expert opinions.

I would also like to acknowledge and thank the attendance in the room and remote participants, which is indicative of the importance of this meeting. Finally and most importantly, thank you

to everyone in the patient community who has been impacted by neonatal hyperbilirubinemia and endured the complications from its severe forms.

Listed here is an overview of my discussion today, which will present the focus of the meeting, the backgrounds of condition, and the agenda for today's meeting.

FDA is seeking advisory committee input on the adequacy of a single study to establish substantial evidence of effectiveness, the clinical meaning of total serum bilirubin reduction, dose selection, the adequacy of the short-term and long-term safety database, and the need for any post-marketing activities if approved.

In the following slides, I will present an overview of neonatal hyperbilirubinemia and its severe form. Please note that I will use the abbreviated term hyperbili interchangeably with hyperbilirubinemia and TSB interchangeably with total serum bilirubin.

Neonatal hyperbili is an elevation of serum bilirubin concentration that occurs in up to 84

percent of newborns and is frequently self-limited. The cause is a higher rate of bilirubin production and limited ability of neonates to conjugate and excrete bilirubin due to their immature liver.

The severe form is defined as severe or extreme hyperbili associated with TSB levels greater than or equal to 25 or 30 milligrams per deciliter. This affects 7 to 40 newborns per 100,000 live births.

Predisposing factors include hemolytic disease, jaundice in the first 24 hours, premature birth, and elevated pre-discharge bilirubin levels. Severe hyperbili can lead to bilirubin-induced neurologic dysfunction, which can result in significant long-term neurologic morbidity and mortality.

The primary goal of treatment is to prevent bilirubin neurotoxicity through early recognition and phototherapy treatment, which are the mainstays of clinical management. Although rare with current clinical management, kernicterus can still occur. Thus, an unmet medical need exists for additional

therapies in these infants at high risk.

No specific single TSB threshold coincides with the onset of acute bilirubin encephalopathy or its chronic form, kernicterus. Risk factors such as premature birth, postnatal age, and co-morbidities contribute to the risk of developing complications from severe hyperbilirubinemia.

Stannsoporfin is a new molecular entity containing tin. Its mechanism of action is through heme-oxygenase inhibition, resulting in inhibition of bilirubin production. The applicant has proposed the indication of treatment of neonates greater than or equal to 35 weeks of gestational age with indicators of hemolysis who are at risk of developing severe hyperbili with a proposed dose of 4.5 milligrams per kilogram of body weight via a single intramuscular injection.

I will now highlight some of the important milestones in the applicant's commitment to the development of stannsoporfin and the associated regulatory history.

Within the first decade and a half of

development, two INDs were submitted to the FDA and only the second was consistent and compliant with good clinical practice standards. Two prior advisory committee meetings have been convened, the first of which discussed the drug development path for stannsoporfin and recommended development for a treatment indication and not a prevention indication.

The second AC meeting discussed the appropriate target population and the need for long-term follow-up data. This AC voted that stannsoporfin should be developed as an adjunct to phototherapy.

A complete new drug application was submitted December of 2017 and priority review was granted earlier this year.

Of note is that FDA granted a fast-track designation for an indication different from what the applicant has proposed. The designation was for the indication of adjunct therapy to phototherapy in neonates of 35 or more weeks gestational age, with laboratory evidence of

hemolysis and hyperbilirubinemia, meeting the American Academy of Pediatrics criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia.

In FDA's consideration of a new drug application, generally two or more adequate and well-controlled trials, each convincing on its own, are required to establish effectiveness. A single highly persuasive trial combined with confirmatory evidence that substantiates efficacy can also support approval if data is from a large multicenter study, there is internal consistency across study subsets, there is evidence of an effect on multiple endpoints evaluating different events or there is statistically very persuasive findings.

In terms of safety, an adequate number and duration of patient exposures is needed to characterize the safety risks of a drug. Less safety data may be required at the time of approval if the drug provides an important clinical benefit

to address an unmet need.

A risk management plan that uses risk minimization strategies beyond the professional labeling may be needed for certain drug products to ensure the benefits outweigh the risks. Post-approval studies or clinical trials may also be required to assess serious risks related to the drug.

I will now provide an overview of the available information to support efficacy. To date, the metabolism of stannsoporfin is not well characterized in humans. The terminal half-life is approximately 10 to 11 hours for both the 3- and 4.5-milligrams per kilogram doses in neonates. There is a shallow inverse relationship between increasing systemic exposure and dose-dependent attenuation of TSB rise.

One pivotal study of 91 neonates was submitted to establish the safety and efficacy of stannsoporfin. The primary endpoints of percent change from baseline in TSB at 48 hours post-treatment was statistically significant for both

3.- and 4.5-milligrams per kilogram doses compared to placebo.

One secondary endpoint, time in hours, at which TSB crossed at or below the phototherapy threshold for discontinuing phototherapy was achieved for the 4.5 milligrams per kilogram dose.

To provide more in-depth clinical context to the submitted efficacy information, I will discuss the published information on the clinical management of neonatal hyperbili based on expert consensus guidelines.

Clinicians treat hyperbilirubinemia in term and late pre-term neonates based on clinical practice guidelines. The AAP guidelines, updated most recently in 2004, is considered standard practice for neonatal care providers in the U.S. for management of neonates of at least 35 weeks' gestation at birth.

Its stated aims are to prevent severe neonatal hyperbili and bilirubin encephalopathy while minimizing unintended harm and unnecessary treatment. Nomograms designating risk for severe

hyperbili, thresholds for phototherapy treatment, and thresholds for exchange transfusion were developed, incorporating data from decades of clinical investigation.

These three nomograms are key figures in the AAP clinical practice guideline. Because some of you may not be familiar with the guidelines and the nomograms, which are central to treating neonatal hyperbili, we will spend a few minutes going over them as background.

The first nomogram was derived from a population of 2,840 healthy newborns using a pre-discharge total serum bilirubin to predict which patients were most at risk for clinically significant hyperbili defined as TSB greater than or equal to the 95th percentile for age in hours.

This nomogram is used clinically to predict which patients require earlier post-discharge follow-up for neonatal hyperbili. In order to determine which patients require earlier outpatient follow-up, the AAP clinical practice guideline recommends either a screening bilirubin prior to

discharge for all neonates or an assessment of risk factors for development of severe hyperbili.

The most important risk factors noted in the guidelines are jaundice noted before discharge, breast feeding, gestation less than 38 weeks, and significant jaundice in a sibling.

Additional risk factors include bruising and blood group incompatibility. The second nomogram guides clinical decision making and allows healthcare providers to determine for a given patient what TSB level necessitates treatment with phototherapy.

The AAP recommendations for treatment are based on both TSB level and clinical risk factors that increase the risk of bilirubin encephalopathy. The top line represents neonates considered to be at lower risk and are those who are greater than or equal to 38 weeks' gestation and without risk factors.

Those at medium risk, the middle line, are patients greater than or equal to 38 weeks' gestation with risk factors or those born at less

than 38 weeks of gestation, but are clinically well. The bottom line represents those at higher risk and are neonates born less than 38 weeks' gestation and have risk factors.

Risk factors for complications include isoimmune hemolytic disease, G-6-PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or serum albumin less than 3 grams per deciliter.

Clinicians use this nomogram to guide both the initiation and discontinuation of phototherapy.

The third nomogram guides clinicians as to which neonates should have a double volume exchange transfusion to prevent bilirubin encephalopathy. Clinically, immediate exchange transfusion is recommended if the infant shows signs of acute bilirubin encephalopathy, including hypertonia, arching, high-pitched cry, opisthotonos, or fever.

This nomogram uses the same risk strata and recommends at what TSB level and hour of life exchange transfusion should be performed. Again, the lower line represents at high risk in this case

for exchange transfusion; the middle line, medium risk; and the top line, those at low risk.

During the hospitalization immediately following birth, exchange transfusion should be considered if the TSB rises to these levels despite intensive phototherapy. If the patient is re-admitted, intensive phototherapy should be initiated and an exchange transfusion is considered within 6 hours if the TSB remains above the threshold for exchange transfusion.

Because screening with timely follow-up and treatment according to the previous phototherapy nomogram have been essentially universally adopted in the United States, exchange transfusions are rarely required.

Before we leave these nomograms, this is a side-by-side comparison of the relationship between the first two nomograms I showed you. The first on the left, again, is used to assess the need for early follow-up after hospital discharge.

Here, a healthy 48-hour-old term newborn, represented by the blue asterisk with a bilirubin

of 10, would fall into the low intermediate risk zone and could have routine follow-up at the pediatrician's office. According to the data used to develop this curve, 12 percent of newborns in this zone will develop a TSB greater than the 95th percentile.

On the right side is the phototherapy curve. As you would expect, the same lower risk newborn would not be a candidate for treatment. In fact, her treatment level would be a total serum bilirubin of 15. However, if she were late pre-term and less than 38 weeks' gestation or has risk factors such as hemolytic disease, infection, or acidosis, or was both late pre-term and had risk factors, according to the AAP guideline, the bilirubin level at which she should be treated decreases. In conclusion, predicting which neonates need early follow-up and those who need treatment while related matters in fact require two different nomograms.

The reason for this is that there are many other factors such as gestational age, hour of

life, and co-morbidities that contribute to the risk of developing complications from severe hyperbilirubinemia.

Therefore, the clinical meaning of a reduction in TSB or time to a particular TSB level is unknown. The major safety concerns of this application were phototoxicity, thrombocytopenia, and the potential for adverse neurodevelopmental outcomes.

The long-term neurodevelopmental database is small. Preliminary data from the pooled long-term extension studies showed a numerically higher rate of both speech and hearing adverse events in stannsoporfin-treated pediatric patients compared to those treated with placebo.

The benefit of stannsoporfin treatment must be weighed carefully against the seriousness of the potential risk associated with use, including the risk of long-term neurodevelopmental toxicity.

FDA has the authority to require a risk evaluation mitigation strategy if additional measures beyond labeling are necessary to ensure

the benefits of a drug outweigh the risk. FDA has proposed a potential REMS consisting of restricted distribution, healthcare setting certification, safe use conditions, and a registry if stannsoporfin were to be approved.

If approved, post-marketing requirements may also be needed to obtain additional long-term safety data, including potentially implementing an observational study and completing ongoing long-term extension studies.

Displayed is today's agenda. For the FDA presentations, Dr. Steven Li will describe the submitted pharmacology data; Dr. Feiran Jiao, the efficacy data; Dr. David Joseph, the non-clinical findings; Dr. Veronica Pei, the available safety data; and Dr. Charlotte Jones, the potential post-marketing activities if approved.

I will now summarize the questions to be discussed today. Question 1 relates to the clinical meaningfulness of the primary endpoint. In question 2, the committee will discuss their recommendations for the 3- or 4.5-milligrams

per kilogram dose. Question 3 relates to whether the applicant has provided substantial and persuasive evidence for stannsoporfin as an adjunct to phototherapy in those neonates at risk for developing complications associated with severe hyperbilirubinemia.

Question 4 relates to the adequacy of the long-term safety assessments to characterize the potential for adverse neurodevelopmental outcomes. The long-term and short-term safety profile is addressed by question 5. In question 6, the committee will opine on the potential risk evaluation and mitigation strategy and its design elements if stannsoporfin is approved.

For question 7, the committee will vote on whether the risk-benefit profile supports approval and, if so, with or without a REMS. Finally, the committee will discuss in question 8 the need for additional studies to assess the potential for adverse neurodevelopmental outcomes.

Thank you again for your time and we look forward to your discussion.

DR. COLE: Thank you. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from

speaking. We will now proceed with the applicant's presentations, I believe, Dr. Steven. Is that right? Yes.

Applicant Presentation – Lawrence Hill

DR. HILL: Good morning, everyone. I'm Lawrence Hill, vice president of clinical development at Mallinckrodt Pharmaceuticals, the parent owner of InfaCare. We're extremely pleased to present data today supporting approval of stannsoporfin for the treatment of neonates at risk for developing severe hyperbilirubinemia.

We're grateful for the hundreds of individuals who have worked to bring this therapy to neonates who will benefit from an additional option for treating hyperbilirubinemia, the first new intervention for this condition in 50 years.

Briefly, neonatal hyperbilirubinemia is a clinical condition of excess bilirubin in newborns. It occurs when there's an imbalance between a neonate's production of bilirubin and the body's capacity to clear it.

Unconjugated bilirubin is produced when red

blood cells break down, a process known as hemolysis. Currently, hyperbilirubinemia is most commonly treated with blue-light phototherapy. The first goal of treating hyperbilirubinemia is of course to lower bilirubin in order to prevent the need for more invasive interventions such as exchange transfusion, but ultimately to prevent the serious neurodevelopmental complications that can result from high bilirubin.

Stannsoporfin is the 1st pharmacotherapy that effectively treats neonatal hyperbilirubinemia. It's been studied with and without phototherapy. Its mechanism of action does not require phototherapy at all to provide benefit.

Stannsoporfin is different from phototherapy in that it inhibits bilirubin production at its source, resulting in a more rapid and sustained reduction in total serum bilirubin.

Stannsoporfin inhibits heme-oxygenase, the enzyme responsible for the rate-limiting step in bilirubin production. Regardless of the cause of overproduction of bilirubin, stannsoporfin works

and its mechanism is especially relevant for babies with hemolytic disease, our target population for use.

Phototherapy on the other hand targets the elimination of bilirubin that has already accumulated in the blood, has no effect on bilirubin production.

Now, I'm also going to present a brief review of our regulatory history. Stannsoporfin has been studied under two investigational new drug applications. First, an investigator IND was initiated in 1987 by Rockefeller University. This organization conducted 9 studies. These investigations confirmed the initial efficacy and safety of stannsoporfin and were relied upon to design the InfaCare development program.

InfaCare then submitted another IND in 2002 that included 10 additional studies. I'm also going to highlight that, in 2012, the Gastrointestinal Drugs Advisory Committee met to discuss appropriate target populations, objectives, and trial designs to evaluate treatments for

neonatal hyperbilirubinemia.

I include this milestone here because expert guidance from this ad com helped us to finalize the appropriate patient population for our pivotal trial, 204, that we completed in 2016. Finally, in 2017, we filed an NDA based on the totality of data from both INDs.

All total, more than 1,400 neonates have been studied in clinical trials, of which 890 have been exposed to stannsoporfin. As mentioned, FDA granted fast-track designation based on the proposed stannsoporfin development program, investigating an adjunct therapy to phototherapy in neonates greater than 35 weeks' gestational age and meeting the inclusion criteria for the pivotal study.

FDA also granted priority reviews since stannsoporfin treats a serious condition and, if approved, is expected to provide a significant improvement in safety or effectiveness when compared to available therapies.

I'm now going to provide a little detail

about the non-clinical and clinical programs. Stannsoporfin has been extensively studied in pre-clinical investigations; 6 radiolabeled ADME studies, 12 safety pharmacology studies, and 27 toxicology studies.

The key results from the pre-clinical program support a favorable risk profile in humans for the proposed indication. I'm going to highlight just a few points here in response to some of the comments in the agency's briefing book.

First, stannsoporfin, also known as tin mesoporphyrin, is a large molecule, 754-Daltons. Due to its large size, stannsoporfin does not readily cross the blood-brain barrier. In fact, there was no significant distribution into the brain tissue of the animals studied.

Next, it was also learned that stannsoporfin is over 96 percent protein bound, so very little free molecule circulates. Finally, no major metabolites have been discovered. It's hardly metabolized at all. It's not a substrate for major enzyme systems and is almost exclusively excreted

intact in the urine and bile.

These characteristics support the findings of no evidence of neuropathology in any toxicology study, no effects seen in the rat developmental study, and no mechanistic basis for a theoretical long-term risk.

Now, here's a summary of the clinical program. Of the 9 Rockefeller studies, data from 6 had relevant patient populations to our proposed indication. We acknowledge the limitations of these studies as mentioned by the FDA, but they still provide important supporting evidence that stannsoporfin has a large effect on TSB.

Also, the safety observations are valuable and align with the results from the InfaCare studies. All of these studies also collected valuable long-term data. Now, of the 10 InfaCare IND studies, 7 are relevant for our consideration today and these include 4 acute studies with 3 to 6 years of long-term follow-up data.

Study 204, the pivotal trial, was designed to show the improvement in phototherapy when

stannsoporfin is administered with light therapy. Study 202 was designed to show that, when stannsoporfin is administered before phototherapy, it could reduce the need for subsequent phototherapy.

Study 01 actually recruited healthy neonates who were at risk for neonatal jaundice. As you know, this population is quite different from the target population we are seeking approval for today, but we did include its safety data in the application.

Finally, study 06 was conducted in neonates at risk of exchange transfusion; again, not exactly the proposed indicated population, but we are still including its safety and efficacy data.

So today, we're going to focus on the data that demonstrates the efficacy and safety of the stannsoporfin 4.5-milligrams per kilogram dose administered as a single IM injection. We'll show that this dose produces a statistically significant and clinically meaningful reduction in TSB in hemolyzing neonates for whom phototherapy is

indicated.

The protocol for study 204 aligns precisely with the 2004 American Academy of Pediatrics criteria for using phototherapy. We're also going to review stannsoporfin's short- and long-term safety profile in this specific population as well as in the more general pooled population of all InfaCare studies.

Finally, we'll touch on results from the Rockefeller studies just to highlight the consistency in the results between the two INDs.

Our proposed indication is for the treatment of neonates greater than or equal to 35 weeks of gestational age with indicators of hemolysis at risk of developing severe hyperbilirubinemia.

To be clear, the proposed indication is for the populations specifically studied in Study 204; that is, hemolyzing babies who meet the AAP guidelines for receiving phototherapy.

One final note; Mallinckrodt is committed to adding considerably to the safety database through future studies. You saw in the FDA briefing

package their REMS proposal. Our approach for meeting the FDA's goal is somewhat different and we believe our proposal will meet their goals more rapidly. I'll describe why a little later in our presentation.

The risk management proposal we'll describe focuses on facilitating access to stannsoporfin to the patients outlined in our proposed indication, educating and informing prescribers and parents, and collecting and regularly reporting on long-term safety data.

We're looking forward to having a collaborative dialogue with the agency on the best way to build this plan. All right. Let me share the full agenda. First, Dr. Jeffrey Maisels from the Oakland University William Beaumont School of Medicine will provide an overview of the unmet need.

Then Dr. Nancy Ruiz will present the data supporting the clinical pharmacology, efficacy, and safety of stannsoporfin. Next, Dr. Dawn Phillips from Evidera will discuss the long-term

neurodevelopmental safety. I'll come back to the podium to present our proposal for risk management. And finally, Dr. Maisels will conclude our time with his clinical perspective and benefit-risk assessment.

I'd also like to mention that we have additional experts with us today, all of whom have been compensated for their time or travel for today's meeting with the exception of Dr. Bhutani (phonetic). Now. Dr. Maisels?

Applicant Presentation – Jeffrey Maisels

DR. MAISELS: Good morning. I'm Jeffrey Maisels and I'm honored to be here. I'm a professor of pediatrics at the Oakland University William Beaumont School of Medicine and director of academic affairs at the Beaumont Children's Hospital in southeastern Michigan.

I've been involved in pediatric research and clinical practice for 51 years and my entire research career has been devoted almost exclusively to the study of jaundiced newborns. I was the primary author of both the 2004 American Academy of

Pediatrics guidelines and the 2009 update of those guidelines for the treatment of neonatal hyperbilirubinemia.

I'm here today because I believe that we have a unique opportunity to improve the way we take care of jaundiced newborns. Let's begin with a review of newborn bilirubin metabolism.

Bilirubin is produced primarily by the normal breakdown of aging red blood cells. When this breakdown is excessive -- we call it hemolysis -- newborn infants have much higher hematocrits and therefore more red blood cells than adults. And these cells have a shorter lifespan.

As a result, the normal rate of bilirubin production in a newborn is at least twice as great as that of an adult when expressed per kilogram of body weight.

When the red blood cells are broken down, heme is converted into unconjugated bilirubin, which is carried to the liver, where it's conjugated so that it can be excreted into the gut. But newborns have two additional problems. They

have a decreased ability to clear the bilirubin through the liver and they re-absorb some bilirubin from the gut.

Because newborns produce more bilirubin, have a decreased ability to clear the bilirubin, and re-absorb bilirubin from the gut, eight out of 10 newborns are visibly jaundiced in the first week of their lives.

If bilirubin accumulates to excessive levels in the blood, it can cross the blood-brain barrier and cause brain damage. In short, an infant serum bilirubin level is simply a reflection of the rate of bilirubin production and its elimination.

When the rate of production exceeds the baby's ability to clear the serum bilirubin, the level rises like a faucet of bilirubin overflowing in a sink. Although the mechanisms that I have mentioned all contribute to the jaundice that babies experience in their first week, by far the most important of these is the fact that these babies produce too much bilirubin.

Nevertheless, bilirubin levels in the

majority of newborns only become a concern if the level increases to a point at which it is necessary to intervene.

We have used phototherapy to treat newborn hyperbilirubinemia for more than 60 years. Every year in the United States, about 7 percent of babies who are born at 35 weeks gestation or greater develop bilirubin levels that are high enough to require phototherapy.

About two-thirds of them get phototherapy before they are discharged from the hospital and most of those have some degree of hemolysis. The remaining third are discharged, but re-admitted for phototherapy. And in fact, jaundice is a leading cause of hospital readmissions.

We know that phototherapy works, but it does have some therapeutic limitations. First, it only removes excess bilirubin from the blood. It does not inhibit bilirubin production.

Second, for babies with hemolysis, phototherapy sometimes fails to prevent the bilirubin level from rising or it does not lower

the bilirubin level. As a result, prolonged phototherapy is needed and occasionally an exchange transfusion is necessary.

Third, even if the serum bilirubin level goes down, in about 5 percent of infants, when the lights are turned off, there is a rebound in the serum bilirubin level so that the infant requires a restart of phototherapy.

In addition to infants with documented hemolytic diseases, as many as 28 percent will have a rebound and require repeat phototherapy. In clinical practice, total serum bilirubin level or the TSB is the primarily laboratory measurement that guides clinical decisions.

For example, we use total serum bilirubin levels to tell us when to start, when to stop, or when to restart phototherapy, when to use off-label products such as intravenous immunoglobulin, when to do an exchange transfusion, when to discharge the baby from the hospital, and when we might need to rehospitalize the baby for phototherapy.

The 2004 American Academy of Pediatric

guidelines for initiating treatment use total serum bilirubin gestational age and various risk factors for bilirubin toxicity to set the thresholds for using phototherapy.

This plot from the AAP guidelines shows the total serum bilirubin on the Y axis and the age in hours on the X axis. The yellow line is used for infants who are at least 38 weeks' gestation and well.

Because they are at a lower risk for bilirubin toxicity, we initiate phototherapy at higher bilirubin levels than those represented by the red line. The red line is used for infants who, in addition to being of lower gestational age, are also sick or suffering from hemolysis and therefore at a greater risk for developing bilirubin toxicity.

Let me just give you an example. At age 36 hours, we would start phototherapy at the bilirubin level of about 9.5 milligrams per deciliter in a 35- to 37-week infant with indicators of hemolysis, while in a 40-week infant

with no risk factors, we would only initiate phototherapy at the bilirubin level of about 14.

Let's now review some of the limitations associated with phototherapy. As I mentioned before, phototherapy does not directly affect the root cause of hyperbilirubinemia, which is excessive production of bilirubin.

If phototherapy does not lower the bilirubin level, the level can increase. This can extend the time that the baby is exposed to phototherapy and the time that the mother and newborn have to spend in the hospital. Finally and if this doesn't work, we might need to do an exchange transfusion.

Phototherapy separates the baby from the mother. Once phototherapy begins, the babies are placed in a bassinet or incubator under intensive blue light, wearing only a diaper and eye protection. They're usually kept under lights continuously and are only removed for short periods for feeding.

This separation can disrupt the mother's ability to successfully breastfeed and bond with

the infant. Both outcomes, we try hard to avoid. The benefits of breastfeeding are well established and the longer the need for phototherapy, the longer the separation between mother and baby.

Case reports and published structured interviews document that mothers whose babies were on phototherapy felt that they were robbed of bonding time with their infant and, among other stressors, they worried about their ability to touch and breastfeed their infants, particularly if they were discharged before the infant was allowed to go home.

Covering the baby's eyes to protect the retina interferes with one of the most important interactions between mothers and babies, face-to-face or on first contact with mutual recognition of facial expressions and responsiveness of both the mother and the baby.

So the sooner we can get the bilirubin down, the sooner the infant and mother can get back together where they belong.

In summary, it is time to advance treatment

options for neonates with hyperbilirubinemia. We have no pharmacologic options that inhibit bilirubin production currently. What we need is a therapy with a favorable safety profile that addresses this problem.

Ideally, this therapy will reduce the duration of intensive phototherapy, reduce the need for restarts of phototherapy and rehospitalization for hyperbilirubinemia, decrease the rate of phototherapy failures, and support mother-infant bonding and breastfeeding.

All of these outcomes would represent a meaningful addition to the currently available therapies for neonatal hyperbilirubinemia in the United States. Thank you. Dr. Nancy Ruiz will now present the stannsoporfin study results.

Applicant Presentation – Nancy Ruiz

DR. RUIZ: Thank you, Dr. Maisels. Good morning. I'm Nancy Ruiz, senior medical and clinical advisor at InfaCare. Today, I will present the efficacy and safety data demonstrating that stannsoporfin inhibits bilirubin production

and ultimately results in a clinically meaningful reduction in total serum bilirubin.

Let me very briefly review the clinical pharmacokinetics. Here, we see the PK parameters in neonates from study 202. All doses of stannsoporfin were rapidly and well absorbed. The peak concentrations of stannsoporfin were observed in 1 to 2 hours and the terminal elimination half-life was about 10 hours.

There was a dose proportional increase in Cmax over the 1.5 to 4.5 milligrams per kilogram and a slightly more than dose proportional increase in the AUC of about 20 to 25 percent from the 3.0- to the 4.5-milligramsdose range.

Let's move on to the clinical development program. During today's presentation, I will show results from studies that evaluated the efficacy and safety of stannsoporfin. Efficacy data comes from two randomized placebo-controlled trials, pivotal study 204 and study 202.

Both studies evaluated similar patient populations and characteristics. The difference

was the point to initiate phototherapy. In pivotal study 204, we learned that stannsoporfin 4.5 milligrams per kilogram used with phototherapy was statistically superior to phototherapy used alone.

Study 202 evaluated stannsoporfin to reduce the need for phototherapy and provide supportive efficacy data. Study 06 was an open-label evaluation of two lower doses and enrolled neonates at risk for exchange transfusion.

The data provide evidence of efficacy and can be found in your briefing books. Additionally, the large body of data in the Rockefeller IND provides a foundation for the InfaCare IND and adds significant support for stannsoporfin. The totality of evidence across both INDs demonstrate the consistent efficacy of stannsoporfin.

I'll first review our pivotal trial study, 204, which was a double-blind, randomized, placebo-controlled, parallel group study of two dose levels of stannsoporfin. The study was designed to randomize patients in a 1:1:1 ratio to receive a

single intramuscular injection of stannsoporfin or placebo when the TSB level reached or crossed the age-specific threshold for initiating phototherapy.

The doses studied were 3.0 and 4.5 milligrams per kilogram. All patients had rapid rises in TSB and a qualifying TSB within the first 48 hours of life. Neonates received study drug or placebo and all started phototherapy as soon as it was practical, but within a window of 30 minutes from each other.

TSB levels were measured every 6 hours and at 48 hours for the primary endpoint. We also conducted follow-up visits on day 7 and day 30. The parents or guardians of all patients who received study drug were asked to participate in a 4-year follow-up safety study.

Study 204 enrolled term and late pre-term patients who were at or above the threshold for phototherapy according to the AAP guidelines. Patients had ABO and Rh incompatibility and indicators of hemolysis including a rapidly rising bilirubin and a positive Coombs test or a negative

Coombs test with a reticulocyte count greater than 6 percent.

The primary endpoint was the percent change from baseline in total serum bilirubin at 48 hours post-treatment. Change in TSB is the primary clinical measurement driving treatment of neonates with hyperbilirubinemia and represents a clinically meaningful endpoint.

Additionally, reductions in TSB allow for other clinically meaningful outcomes, some of which have been captured in our secondary endpoints. We pre-specified three key secondary endpoints that were tested in a hierarchical order.

The first was time at which total serum bilirubin first crossed at or below the defined threshold for discontinuation of phototherapy. The second was phototherapy failure defined as restarting phototherapy after six hours of stopping, hospital readmission for hyperbilirubinemia, use of intravenous immunoglobulin, or needing exchange transfusion.

The third was rebound hyperbilirubinemia

requiring a restart of phototherapy within 54 hours after discontinuation. 91 percent of patients completed the study and disposition was similar across treatment groups.

Ninety-one patients were randomized overall. 8 patients withdrew. Of these, 6 were lost to follow-up and 2 were voluntarily withdrawn by the parent or guardian. 6 of the 8 patients had a 48-hour TSB sample prior to withdrawal. And no patient was withdrawn because of an adverse event in any group.

This defines our intent-to-treat or ITT population. As pre-specified, we will present data for this population. Demographics and other baseline characteristics were balanced. The mean gestational age was about 39 weeks. More than 90 percent had a positive direct Coombs test.

The mean H time of dosing was around 24 hours. And the mean bilirubin at baseline was around 9.9 milligrams per deciliter.

All patients had a rapid rise in bilirubin level after birth and entered the study within the

first 48 hours of life. In fact, 65 percent of babies in the 4.5-milligrams per kilogram arm entered within the first 24 hours of life.

Using the Bhutani nomogram, we can illustrate the risk level for developing severe hyperbilirubinemia. The Bhutani nomogram is based on time-specific serum bilirubin values and is different, as was mentioned, than the AAP guidelines for phototherapy that Dr. Maisels presented.

On the Bhutani nomogram, the zone for a total bilirubin value predicts the likelihood that it will rise to a subsequent bilirubin level exceeding the high-risk zone for hyperbilirubinemia.

When we overlay study 204 patients, we see that all patients were above the high intermediate risk threshold for developing a severe hyperbilirubinemia, shown by the blue dotted line.

The vast majority were at or above the high risk, shown by the black dotted line. The objective of treatment is to decrease the risk of

developing severe hyperbilirubinemia, shifting the severity of risk from a high zone to a lower zone.

Let's review the results. The study demonstrated that stannsoporfin was superior to placebo in decreasing total serum bilirubin from baseline to 48 hours. The LS mean difference was highly statistically significant for both the 3.0 milligrams per kilogram and the 4.5 milligrams per kilogram stannsoporfin groups compared to the difference in the placebo group with p values less than 0.0001.

Several sensitivity analyses verified the results of our primary endpoint. The significant primary endpoint results allowed us to analyze the pre-specified key secondary endpoints.

Starting with time to crossing the TSB threshold for discontinuing phototherapy, stannsoporfin, 4.5 milligrams per kilograms, crossed the threshold approximately 10 hours sooner than the placebo group with a p value of 0.003. This represents a potential for earlier discontinuation of phototherapy.

We can see from the error bars that there was much variability in the 3.0 milligrams per kilogram group and the endpoint was not met, ending the analysis hierarchy. Nevertheless, we will present the data for the other endpoints.

The next secondary endpoint was phototherapy failure. Stannsoporfin, 4.5 milligrams per kilogram, reduced the frequency of phototherapy failures compared to phototherapy alone. The phototherapy failure rate was nominally significant at 3 percent in the 4.5 milligrams per kilogram group and 27 percent in the placebo group.

Here, we see the reasons for phototherapy failure. Neonates could have more than one reason for failure and therefore could appear more than once in a column. There was 1 patient in the 4.5-milligrams per kilogram group who was re-hospitalized for restart of phototherapy.

This neonate was dosed within the first 6 hours of life. There were 8 placebo patients who restarted phototherapy. Of these, 3 were readmitted to the hospital and one was readmitted

and restarted twice.

The last sequential outcome was rebound hyperbilirubinemia occurring within 54 hours after dosing. There was no difference in rebound within 54 hours for either dose.

In summary, pivotal study 204 demonstrated that stannsoporfin 4.5 milligrams per kilogram was statistically superior to placebo and the dose that offered a clinically meaningful benefit. Although compared to placebo both doses were superior in achieving statistically significant decreases in TSB at 48 hours, only the 4.5-milligramsgroup achieved the clinically relevant secondary endpoint of reduced time to cross the AAP threshold; 4.5 also reduced phototherapy failures, including rehospitalizations and restarts of phototherapy.

To put these results into perspective, let's look again at the risk zones of the Bhutani nomogram. The difference between the zones is about 2 milligrams per deciliter, which defines a clinically meaningful change for a patient.

Here, you see where patients started at

baseline and where they landed at 48 hours, with a mean difference of 3 milligrams per deciliter between stannsoporfin 4.5 and placebo. 87 percent of patients who received stannsoporfin, 4.5 milligrams per kilogram, shifted from a high or high intermediate risk at baseline to low risk.

This compared to 40 percent of placebo who shifted to low risk, clearly demonstrating the clinical meaningfulness of change in TSB. Study 204 meets the regulatory characteristics of a highly persuasive single pivotal trial. The data were collected from a 22-site study and provide highly statistically persuasive evidence.

We see internal consistency across study subgroups and see an effect on multiple endpoints. Additionally, various sensitivity analyses corroborate the positive results. And finally, we had consistent findings in our supportive studies that I will review next.

Turning to supportive study 202, which was a blinded, randomized, placebo-controlled, dose-escalation study, the inclusion criteria in study

202 were nearly identical to study 204. Neonates were enrolled in sequential cohorts and randomized to 1 of 3 doses of stannsoporfin or placebo in a 3:1 ratio.

TSB was assessed every 6 hours to determine whether phototherapy was necessary. Follow-up visits occurred at 72 hours, 14 days, and 30 days. All patients and guardians were asked to enroll their patients into a long-term safety study for up to 4 years.

Study 202 was stopped early by the FDA to discuss the most appropriate TSB value to initiate stannsoporfin. At that point, the 4.5 milligrams per kilogram dose group was approximately 50 percent enrolled. There were no safety observations that drove this action. Full details about this study can be found in your briefing books.

The primary endpoint was a change in adjusted TSB from baseline to 48 hours after treatment. As we heard from Dr. Maisels, the AAP-recommended threshold for starting phototherapy

takes factors other than TSB into account, including gestational age and additional risk factors.

Therefore, since neonates entered the study when bilirubin was below the threshold for phototherapy, we used an adjustment calculation to indicate how far the TSB value was from the age-specific threshold.

Key secondary endpoints included the change from baseline in an actual TSB at 48 hours after treatment and the proportion of patients who required phototherapy or exchange transfusion. There was no adjustment for multiplicity.

Although the change from baseline in adjusted TSB was favorable for the stannsoporfin 4.5 milligrams per kilogram dose, compared to placebo the p value was 0.057. Recall the N is 8 for the 4.5 milligrams per kilogram group.

We also looked at actual TSB and found that the 4.5 milligrams per kilogram group had an earlier onset of effect compared to placebo. Between 6 and 12 hours, the 4.5 milligrams

per kilogram curve began to flatten with a steep decline beginning at 12 hours while the placebo group continued to rise despite 53.3 percent of patients continuing to receive phototherapy.

The 1.5 and 3.0 treatment groups were also efficacious, but we observed a clear dose response favoring the 4.5 milligrams per kilogram dose. Although the study was not powered to detect differences in the need for phototherapy, 50 percent fewer patients in the stannsoporfin 4.5 milligrams per kilogram group received phototherapy compared to placebo.

No patients in the study required exchange transfusion and there were no hospital readmissions in the stannsoporfin-treated group versus 2 patients in the placebo group.

In summary, study 202 provides supportive efficacy data demonstrating stannsoporfin's consistent reduction of TSB. The study also confirmed a dose selection of 4.5 milligrams per kilogram from the Rockefeller studies. Additionally, the secondary endpoints provide

support for the clinical meaningful secondary endpoints in study 204.

Finally, the Rockefeller IND studies showed consistency, efficacy, including a strong effect on TSB along with other benefits to support the InfaCare development program.

For example, let me show you how they support duration of phototherapy. Studies 04 and 08 on the right were conducted in premature infants, but the magnitude of difference between the two arms is similar and supports the observations in study 202 and 204 in the InfaCare IND.

The duration of phototherapy was lower in patients who received stannsoporfin in all four studies. More information about the Rockefeller IND studies can be found in your briefing books.

In conclusion, stannsoporfin, 4.5 milligrams per kilogram, effectively treats neonatal hyperbilirubinemia. Pivotal study 204 provides highly statistically persuasive evidence and internal consistency across subgroups and

clinically meaningful endpoints.

The populations across trials, including study 202 and the Rockefeller IND, varied slightly with respect to initiation of stannsoporfin treatment, but what we learned was that stannsoporfin, 4.5 milligrams per kilogram, consistently showed reductions in TSB.

The consistency of the data across both INDs confirms that stannsoporfin, 4.5 milligrams per kilogram, is an effective new treatment for neonatal hyperbilirubinemia and supports the proposed indication.

Now, let me share the stannsoporfin safety profile. The clinical development program demonstrates that a single injection of stannsoporfin is well tolerated in neonates with a favorable safety profile. Overall, more than 1,400 neonates participated in the stannsoporfin development across the Rockefeller and InfaCare IND in multiple patient populations.

Nearly 900 neonates received stannsoporfin in clinical trials, including 588 at the

4.5 milligrams per kilogram dose.

Our safety assessments of stannsoporfin is based on 4 data sources. First, I will present pivotal trial 204 alone, looking at the short-term of stannsoporfin with phototherapy in neonates. Next, I will show the three acute studies pooled to provide the broadest assessment of short-term safety in patients of similar gestational age.

The pooled dataset also includes study 204. Then we will cover the three long-term extensions of the acute pooled studies with outcomes from 2 to 6 years. Additionally, the 6 Rockefeller IND studies provide both acute and long-term safety data and are consistent with findings from the later studies.

We recognize that some safety events appear differently in the sponsor and the FDA briefing books.

After finalizing our briefing book, the FDA asked us to recode our events, which we agreed to do. The differences you see are due to this recoding, but do not change the interpretation of

the data. Let's start with pivotal study 204. Although both doses of stannsoporfin showed a favorable safety profile, the 4.5 milligrams per kilogram group had generally fewer AEs than the 3.0 milligrams per kilogram group.

AEs were similar between 4.5 milligrams per kilogram and placebo groups. The percentage of patients with SAEs was also similar in all treatment groups. There were no discontinuations due to AEs or deaths reporting during the study.

Let's look at treatment-emergent adverse events. Many of these are common among the neonate population and, importantly, most were mild in severity. Hematologic events were most commonly reported across treatment groups and erythema was more frequent in the stannsoporfin groups versus the placebo groups. I will discuss these events in more detail shortly.

Now, let's look at serious adverse events. Overall, the proportion of patients with serious treatment-emergent adverse events was similar among treatment groups. Serious TEAEs that occurred in

more than 1 patient were hyperbilirubinemia in the placebo group, sepsis in the stannsoporfin 4.5 milligrams group, and medical observation in the stannsoporfin 3.0 group.

Medical observation was for prolonged hospitalization, one for sepsis and one for supraventricular tachycardia in a neonate with a congenital heart defect. No serious TEAEs led to study discontinuation.

Next, let's look at the pooled blinded placebo-controlled studies. Overall, once pooled, the 4.5 milligrams per kilogram treatment arm provides the greatest amount of data in neonates on stannsoporfin.

As seen in study 204, the proportion of patients with TEAEs and SAEs was also similar in the stannsoporfin 4.5 milligrams per kilogram and placebo groups. None of the AEs led to discontinuation. Once again, the treatment-emergent adverse events were mild and the overall incidence of adverse events in the 4.5 milligrams per kilogram group was almost always similar to

placebo.

Erythema was an adverse event of interest and was seen more frequently in the treatment groups than in placebo. I have always included thrombocytopenia here, which does not make the cut-off more than 5 percent, but FDA made a comment upon this finding and so I'm going to talk about this event shortly as well.

Dermatologic TEAEs were the most commonly reported across all treatment groups. Overall, skin-related events had a similar incidence in neonates treated with stannsoporfin, 4.5 milligrams per kilogram or placebo.

More patients in the stannsoporfin group experienced erythema. These events were transient, mild to moderate, and resolved without major intervention. No dermatologic event was severe.

Because photosensitivity may be associated with stannsoporfin, the label and educational materials will include guidance to protect neonates from direct sunlight for 10 days. Also, we will include instructions to use special filters for

patients undergoing surgery.

Let's look at thrombocytopenia. We carefully reviewed all of the 33 cases of babies with platelets below the reference range of 150,000 mentioned in the FDA briefing book. Of these, we counted 8 that were below a clinically meaningful level, defined as 100,000. This slide represents those cases. As you can see, there are concomitant factors in most patients that could contribute to the observation of low platelets in the stannsoporfin cases such as possible sepsis, meningitis, and exchange transfusion. There were no confounding factors in the placebo group.

Because of the number of confounding factors in these cases, it is difficult to draw any conclusions at this point. However, what we can say is that there was no indication of blood-clotting abnormalities in the pre-clinical studies and, importantly, there were no bleeding episodes associated to low platelets in the clinical program.

Moving on to serious treatment-emergent

adverse events, the proportion of patients with serious TEAEs in the pooled acute studies was similar between groups. Most serious AEs were reported in no more than 1 patient.

Now, let's turn to the three long-term extension of the acute pooled studies. Overall, the long-term safety profile was generally similar between stannsoporfin and placebo groups. There was 1 death from sudden infant death syndrome at 4 months of age in a patient who received stannsoporfin, 4.5 milligrams per kilogram.

In general, AEs were comparable in both stannsoporfin groups and placebo. We thoroughly examined the neurocognitive events of interest to investigate any potential imbalances. In the ear and labyrinth disorder system organ class, 5 to 7 percent or 7 patients total in the stannsoporfin treatment groups had an adverse event compared to 0 in the placebo group.

We also thoroughly examined the nervous disorder system organ class and found that speech disorders were seen in 3 to 14 percent of patients

who received stannsoporfin and in 5 percent of those who received placebo.

Because of these events of interest, we initiated an independent expert review with Dr. Dawn Phillips to assess the long-term safety data, looking for any neurodevelopmental signal. Dr. Phillips will present her findings shortly.

Finally, I would like to summarize the safety data from our Rockefeller IND studies. As you have seen in your briefing book, the Rockefeller IND safety profiling included more than 1,000 patients and the safety observations were consistent with those in the InfaCare IND.

Across studies in both INDs, there was a similar rate of adverse events compared to the various control arms.

In summary, stannsoporfin 4.5 milligrams per kilogram was well tolerated with a favorable safety profile. Across the acute studies, transient erythema was more common in neonates treated with stannsoporfin. The events were mild to moderate and resolved without major intervention.

This potential risk is manageable and will be addressed in the label and educational materials. In the long-term study, the safety of stannsoporfin, 4.5 milligrams per kilogram, was generally consistent with the exception of the observation in study 01, which I have noted. I will now invite Dr. Phillips to provide her independent assessment of long-term neurodevelopmental safety. Thank you.

Applicant Presentation – Dawn Phillips

DR. PHILLIPS: Good morning. My name is Dawn Phillips and I am a research scientist in the patient-centered research unit of Evidera. I have been a clinician and a researcher for 30 years with a specialization in neurodevelopmental evaluation and treatment of infants and children at risk of developmental disability. I have worked extensively in clinical trials to analyze neurodevelopmental data and train sites around the world on the administration of neurodevelopmental assessments.

My independent review of the stannsoporfin development program focused on two types of data,

clinical judgments of site investigators, and neurodevelopmental test scores. I used a framework of factors to determine if a safety signal exists in the long-term stannsoporfin studies.

These factors include whether there is consistency in adverse events across studies, the severity of adverse events, the plausibility of alternative explanations for adverse events, the persistence of these events, whether there is evidence that standardized neurodevelopmental outcomes are comparable to those of typically developing children and consistent across studies and a hierarchy of evidence.

Today, I will walk you through the most clinically relevant data and apply this framework to draw conclusions. In examining the long-term studies, I found that blinded assessors used well-known and validated age-appropriate psychometric instruments that represent the standard of care in early intervention and neonatal follow-up clinics.

These tests provide scores for a comprehensive assessment of general development and

specific domain scores for cognition or IQ, language development and motor skills, and general behavior, and psychological status.

The stannsoporfin development program includes follow-up of children as old as 6 years. The long-term program includes extensions of controlled studies 01, 202, and 204. This slide shows the numbers of children who contributed data at each follow-up time point in each study.

In general, there were more patients in the stannsoporfin groups than in the control groups. Study 01 extension was a 6-year study in which 87 patients contributed data to at least 1 long-term visit, while study 203 followed patients for up to 4 years with 42 patients contributing data.

Study 205 is ongoing and will follow children to 4 years of age. Since study 204 ended in 2016, few children have reached their 2-year follow-up visit. First, I evaluated the speech disorder AEs identified by site investigators.

As you heard from Dr. Ruiz, there was an imbalance in speech disorder adverse events in

study 01 extension. The term speech disorder includes a range of descriptors such as expressive language delay, articulation, and speech language delay.

Speech disorder AEs were more frequent in the stannsoporfin arm with 9 patients in the 4.5 milligrams per kilogram group versus 3 speech and language events in the placebo group.

Investigators did not determine any speech disorders to be severe. I am unable to draw any conclusions regarding persistence due to loss to follow up. However, I reviewed individual records of these children and found many had multiple risk factors for neurodevelopmental events.

These included young maternal age with 7 of the 9 mothers in the stannsoporfin group with an age of 21 years or younger, recurrent otitis media, head trauma, malnutrition, and child neglect. This makes it difficult to attribute a child's speech related difficulties to a single factor.

Next, I looked at extension 203 to determine if the AEs were consistent across studies. A total

of 4 speech disorders were reported with two events in each group. All events were mild and all resolved.

Even though the stannsoporfin group had more than double the patients than placebo, each group had 2 events. Again, there were confounding factors.

Next, I looked at the ongoing extension study 205 and found that 1 patient from the 3 milligrams per kilogram group presented with speech disorder. The final status is not yet known.

Let's now discuss the hearing impairment seen in the program. The FDA briefing book reported 7 patients with deafness compared to the prevalence seen in sensory neural hearing loss in newborns.

However, the hearing loss seen is conductive hearing loss, which is common in children and often due to otitis media or other infections. It is often transient and improves with treatment. All but one hearing impairment event resolved and the

unresolved event was just reported at the 6-year visit in a child with an upper respiratory and ear infection.

No AEs were labeled as serious. The hearing impairments all appeared at least 8 months after the stannsoporfin dosing and all of these patients had previously passed their hearing screenings. Therefore, I do not think a hearing loss signal is present.

Finally, I looked at the Rockefeller studies. These six studies provided a considerable amount of long-term safety data with 459 children who received a 4.5 milligrams per kilogram dose. This table shows overall frequencies of adverse neurodevelopmental events through 18 months.

There is no dose relationship and there is a comparable rate of neurodevelopmental AEs in the 4.5 milligrams per kilogram dose group and controls.

We also looked at rates of speech disorder events. They were similar in the stannsoporfin and control groups. As with any clinical program, it's

difficult to fully exclude the possibility of a very low frequency AE.

So I looked to the neurodevelopmental test scores to determine if evidence existed to support a neurodevelopmental signal. Since these observations come from our best validated instruments used by trained professionals, I weighed these data somewhat higher than adverse events captured through a less systematic or standardized method.

First, I would like to address a comment in the FDA briefing book that questioned the use of different neurodevelopmental assessments across different trials. It's important to note that development varies greatly by age and a single instrument is not available to capture development across multiple domains from birth to 6 years of age.

Instruments must have the sensitivity to detect issues at a particular stage of development. Therefore, multiple age-specific instruments are typically used in clinical practice and clinical

research. And longitudinal studies often require transitions between instruments.

In the stannsoporfin program, global measures of development such as the Mullen Scale of Early Learning and the Bayley Scales of Infant and Toddler Development were used with younger children. Then the Wechsler Preschool and Primary Scale of Intelligence or the WPPSI was used as the children aged since it provides a more specific measure of cognition through 7 years.

Supplemental domain-specific measures were also completed such as the Receptive-Expressive Emergent Language test and the Child Behavior Checklist.

Let's first take a look at the 01 Bayley results. The Bayley provides a global measure of development, yielding a mental and psychomotor developmental index. The red line represents the lower bound of the normal range. The data are presented as box and whisker plots. This type of plot is especially suited to evaluate safety because it shows the range of observations and the

outliers are shown as Xs.

The MDI scores of the stannsoporfin and placebo groups did not differ significantly, but the PBI scores did, favoring the placebo group. Because the Bayley was also administered at 18 months in 5 of the Rockefeller studies, we looked to see whether the finding was replicated. It was not.

In some studies, the stannsoporfin group was higher. In others, the placebo was higher. There was no consistent signal.

Next, I review domain-specific measures at 18 months. The REEL is a parent-completed questionnaire designed for use in children age 0 to 3 to determine a delay in receptive or expressive processes of emergent language.

The T-score represents a standard distribution analysis to allow comparisons to age-level peers and has a mean of 50 and a standard deviation of 10. The findings show no significant differences between the stannsoporfin and placebo groups at 18 months in either receptive or

expressive language.

These data fall within an expected range for typical development. Normative data is not available for the REEL beyond 36 months and the Bayley beyond 42 months. For that, you must transition to other assessment tools. The WPPSI is the most widely used assessment of intelligence in preschoolers and represents a common transition from the Bayley.

The WPPSI and the Bayley have strong concurrent validity and low Bayley scores at 18 months have predictability in identifying low scores on the WPPSI at 60 months.

This slide will show the data for the WPPSI, specifically the percentile ranks along the vertical axis for the stannsoporfin and placebo groups at each age for the full-scale IQ and verbal IQ. For both scales, a higher score is better.

The red line shows the lower bound of the average or normal range, the 8th percentile, that would correspond to an IQ score of 79, which is considered the threshold for clinical concern. I

draw two conclusions from these data. First, at all ages, the medians in the stannsoporfin group ranged between the 34th and the 45th percentile. For children in the placebo group, the ranges at all ages were similar between the 28th and the 47th percentile.

Second and more important from the standpoint of safety, similar numbers of children fell below the threshold of concern for both the full IQ and the verbal IQ at year 6.

I wanted to know if there was a correlation between those with a speech disorder event in 01 extension and an abnormal WPPSI score. And I found no consistent relationship. Only 2 of those in the 4.5 milligrams per kilogram group scored below the 8th percentile or threshold for clinical concern.

The verbal IQ WPPSI scores in percentile rank are recorded in the last column. 2 patients did not have a WPPSI recorded. The child with the score in the 6th percentile had many confounding variables.

In the placebo group, there was one patient that approached the threshold for concern. The Child Behavior Checklist is a parent-reported questionnaire that assesses internalizing behavior reflecting problems such as anxiety and externalizing behavior reflecting problems such as hyperactivity.

In contrast to the WPPSI, a higher norm-based Z-score indicates more problematic behavior. A score more than 1.5 Z-units above the population mean, shown by the red dotted line, is considered to be clinically significant.

The mean scores of the stannsoporfin group were very close to normative values with the differences being less than 10 percent of a standard deviation for both scales at all 3 ages. Also, as would be expected, a small number of children in both groups had scores above the threshold of clinical concern at some point.

So putting this all together, I'll return to the framework to assess if a neurodevelopmental or speech language safety signal is present. First, I

found no consistent presentation of speech disorder AEs across studies. In addition, the findings in 01 were not replicated in any other study and not consistent with the totality of the data.

Second, the adverse events were not considered to be severe. Third, there were plausible alternative explanations for the occurrence of adverse events. Fourth, with regard to persistence, we can't draw a conclusion either way because of the loss to follow-up.

Fifth, the values of neurodevelopmental assessments fell within the normal range and were consistent across studies. Finally, when there is a discrepancy by data source, we take into account the highest level of evidence. In this case, it is standardized assessments administered by trained professionals. Collectively, I conclude that the data show no consistent signal of a safety concern among children who receive stannsoporfin.

The preponderance and consistency of the long-term data lead me to conclude that the long-term safety profile of stannsoporfin is favorable.

Thank you. Dr. Hill will now present the sponsor's proposed risk management plan.

Applicant Presentation – Lawrence Hill

DR. HILL: Thank you, Dr. Phillips. As I previously mentioned, Mallinckrodt is committed to a robust risk management plan and I'll go into more details now.

We share common long-term goals with the FDA. We both seek to minimize potential risks by ensuring that stannsoporfin is used in term and near-term hemolyzing infants who meet the AAP guidelines for phototherapy. And we agree there is great value in collecting additional safety data that would confirm the long-term safety profile observed in pre-clinical and clinical trials.

Yet, there are important differences in Mallinckrodt's risk management proposal compared to FDA REMS. In the next few slides, I'll outline our proposal, which we believe will more completely and rapidly address any underlying questions.

Both the FDA's REMS and Mallinckrodt's risk management plan consist of similar elements;

access, prescriber education, parent or guardian education, and a registry. The Mallinckrodt plan addresses the first three points in a manner that is commensurate with our assessment of developmental risks and it will overcome potential unintended consequences in the FDA registry proposal; namely, reduced patient access, resulting in low data collection.

We also agree with FDA's proposal for some control of access. Our plan is to only make stannsoporfin available to hospitals with NICUs. These types of centers have healthcare providers who are able to care for neonates with hyperbilirubinemia.

Since these healthcare providers have considerable experience in identifying this specific neonate population and frequently administer IM drugs, a certification of the site as FDA proposes seems unnecessary.

Here are the healthcare providers who would be targeted and documentation of their training would be required before they could prescribe

stannsoporfin. Regarding education, Mallinckrodt supports the FDA's proposal to confirm healthcare providers are educated and trained on the appropriate use of stannsoporfin.

This education and training will be based on the material and the approved label. Finally, we'll develop a website for practitioners so they can revisit training and educational materials at any time and use these resources for hospital in-services.

In addition, parent brochures would be modeled after products such as vaccines. The brochure would be provided at time of stannsoporfin use in the same manner as when information is provided at the time of a childhood vaccination.

This brochure would inform the parents of potential risks as defined in the approved label. There would also be a patient-centered website housing all of these educational materials.

Now, a cardinal piece of our proposal is a prospective open-label study examining long-term development in the indicated population. We

propose a study for approximately 800 to 1,000 babies and would follow them out to 5 years of age. We wish to design a study to have very high assay sensitivity for detecting long-term events.

Let me show you some of the tests we're recommending. The list of tests is very similar to those completed in study 202 and 205, although we propose that they be used more frequently.

Additionally, we'll add audiometry testing, adaptive skills evaluations, and screenings by speech language pathologists. The combined testing would thoroughly evaluate children through 5 years of age and will establish an independent data safety monitoring board that will meet annually to review data.

We'll finalize the details of the study with the FDA in the future. Now, in order to understand the Mallinckrodt proposal for this registry, I should mention how the therapeutic setting influences willingness to enroll.

For parents of neonates with hyperbilirubinemia, their first priority is getting

treatment for the baby. It's not about discussing enrollment in a clinical trial. Therefore, our proposal separates the treatment decision from the enrollment decision so that parents are in a less distracted state of mind when deciding to participate.

We believe this approach will greatly facilitate enrollment, collecting data much more rapidly. So in conclusion, we're confident that Mallinckrodt's proposed risk management plan will assure use of stannsoporfin in the appropriate population as well as add significantly to the long-term safety database in an expeditious and timely manner.

Thank you. Dr. Maisels will now close out the presentation with his benefit-risk assessment.

Applicant Presentation – Jeffrey Maisels

DR. MAISELS: Thank you, Dr. Hill. I am pleased to provide my clinical perspective on the totality of data presented today that supports the indication for stannsoporfin as well as my assessment of the benefit-risk profile.

Based on my experience and years of researching jaundiced neonates, I'm confident that the benefits of stannsoporfin clearly outweigh the risks. Stannsoporfin is unique because it effectively and predictably reduces bilirubin by inhibiting its production at its source.

The mechanism of action of stannsoporfin is not tied to phototherapy. This is a first for the prevention of treatment of hyperbilirubinemia and an important addition to our armamentarium.

Stannsoporfin clearly provides clinically meaningful benefits. First, it reduces the duration of phototherapy and phototherapy failures. Stannsoporfin significantly reduces the likelihood of rebound and the need for rehospitalization for restarting phototherapy. This finding is consistent with all of the Rockefeller studies, that encompass a wide range of newborn infants, including those with documented hemolytic disease.

Reducing phototherapy failures means we can also reduce the need for exchange transfusion. And finally, stannsoporfin can potentially shorten the

separation of mothers from their babies. As clinicians, we use the Bhutani nomogram to predict the risk that an infant's next bilirubin level will be above the 95th percentile for their age or, in other words, that they will be at a higher risk for severe hyperbilirubinemia.

As Dr. Ruiz showed us earlier, in the pivotal trial, 87 percent of the patients who received stannsoporfin, 4.5 milligrams per kilogram, shifted from the high or high intermediate risk level to the low risk level at 48 hours, which is 47 percent more patients in the stannsoporfin group than neonates who received phototherapy alone.

This rapid shift in risk of severe hyperbilirubinemia is reassuring to me as a physician and, more important, clinically meaningful for babies and their families. Regarding safety, the extensive clinical trial data show that a signal injection of stannsoporfin is well tolerated in jaundiced neonates and has a favorable safety profile.

In controlled trials, when stannsoporfin was compared with placebo, mild to moderate photosensitivity was the only clinically meaningful acute adverse event related to the drug. Photosensitivity was self limiting, manageable, and resolved with minor intervention.

As my colleagues, Dr. Phillips, concluded, stannsoporfin isn't likely to cause long-term persistent neurodevelopmental problems. The sponsors' proposed long-term registry will provide even more data to confirm the established safety profile.

Considering all of the information, we see consistency in safety. In conclusion, based on the totality of data that demonstrate both the robust efficacy and a favorable safety profile, we can conclude that the benefits of stannsoporfin, 4.5 milligrams per kilogram, outweigh its risks.

Stannsoporfin provides us with a unique and meaningful addition to the option we have for treating babies at risk for developing severe hyperbilirubinemia. The benefits clearly outweigh

the risks for neonates, who are at least 35 weeks' gestational age and who are at risk for developing severe hyperbilirubinemia.

Thank you. Dr. Hill will now return to the lectern to take your questions.

DR. COLE: Before we start the questions, Dr. Aly, could you introduce yourself, since you've arrived since everyone else did?

DR. ALY: I'm sorry for that, being late for the traffic. I'm Hani Aly. I'm the chairman of the Department of Neonatology at the Cleveland Clinic Children's Hospital, professor of pediatrics at Case Western University.

Clarifying Questions

DR. COLE: Thank you. We'll now start clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Dracker?

DR. DRACKER: Bob Dracker in Syracuse. I had the good fortune of training under Frank Oski, who was a pretty well-known hematologist at his

time. And Frank did an article with Dr. Jon Watchko entitled, Vigintiphobia, A Fear of 20.

The reason I'm mentioning this is, Frank always taught us to consider all aspects of what happens naturally, one of which was his belief that bilirubin had significant value.

When you consider the treatment of jaundice, I always tell parents that jaundice is sometimes a good thing because it is a major antioxidant for babies. We know that there are oxidative stress-associated findings that you can have, especially in a long-term outcome, including as we've just reviewed neurodevelopmental issues, asthma, insulin-dependent diabetes, hypertension related to nitric oxide, coronary heart disease, and stroke.

To that end, I would like to submit some things I feel should be considered. I haven't heard any data regarding markers for oxidative stress, especially in infants who receive stannsoporfin, which I feel is very important.

I think, looking at those markers after the use of stannsoporfin would be critical in my mind.

And those markers could be such as nicotinamide phosphoribosyltransferase, oxidative LDL values, looking at MDA and lipid hydroperoxidase (phonetic), and also looking at total oxidative stress indices, which I have not heard referenced.

I think those things are very important when you consider use of this drug for hyperbilirubinemia. The other thing I wanted to mention is that there are natural antioxidants which are deficient in newborns such as alpha tocopherol, which again Frank had done a number of studies looking at red cell survival related to decrease alpha tocopherol levels in newborns.

So one consideration which is for therapeutic modality currently used in certain infants is whether the consideration of using alpha tocopherol therapy along with stannsoporfin has ever been considered to avoid the oxidative stress that might occur.

I'm sorry for the long questions, but thank you.

DR. COLE: Thank you. Dr. Hill?

DR. HILL: I don't know if I heard a question there, but I heard two recommendations. Is that correct?

DR. DRACKER: Yes. That's correct, long winded, I'm sorry, but yes.

DR. HILL: I think those are excellent suggestions. The oxidative assays you cited were not performed in the program. However, there is an opportunity to include some of that in the registry that we've proposed and we'll take that under consideration.

DR. COLE: Thank you. Dr. White?

DR. WHITE: Michael White, New Orleans. I had several questions from someone who's not a hematologist. First of all, the metabolism of heme to bilirubin; what we're trying to do is block the metabolism of heme to bilirubin.

In all your presentations and the information you provided, there is very little discussion of what happens when the heme gets backed up because you're not converting to bilirubin. I didn't see a whole lot telling me

what, other than it's going into the bile and being excreted, and that would be helpful in me making my considerations.

The second is, it looks like your dosing schema of using a single dose relies on 4.5 to have a larger area under the curve so that the effective range extends out further. Why did we focus on a single dose and not two smaller doses to extend a more steady-state level in order to possibly prevent some of the bouncebacks that you're going to see, not many in the data presented? But there were some that came back. One child in the 4.5 group came back, I think, for phototherapy after discharge.

That's a question for you. And then finally, in the developmental data in your REMS book; well, not your REMS, your follow-up program; is only going to 5 years, which I think is good and I know it's difficult to have these long-term studies, but many, many developmental problems don't show up until the first, second, and third grade, behavioral problems and learning

disabilities that show up once children are enrolled into first, second, and third grade and start having to undergo a formal education.

Those are much more subtle and much more difficult to pick up, I think, if you'll ask our developmental person who is our consultant. I think that some of those things are much too subtle to show up under the tests that we're using and I think could be significant and possibly you would want to extend beyond that 5-year.

That's plenty of questions. Thank you.

DR. HILL: Two questions and a recommendation. So your first question was about the heme-oxygenase and what could possibly be the result of inhibiting heme-oxygenase. I would want to point out that stannsoporfin is not a complete inhibitor of the enzyme. So it's about 60, 70 percent.

So there is still some metabolism of the heme and the adverse effect profile does not suggest that there is any result from heme build-up. Your second question was about the dose, why

the sponsor hadn't considered two doses.

First, I would say, with the type of efficacy and the effect we see on a single dose, it doesn't seem too necessary to provide a second dose. Keep in mind that a second dose would probably be administered possibly 3 days later. And that would be a time at which many babies have completed their phototherapy.

DR. WHITE: Your half-life is 10 hours.

DR. HILL: Yes.

DR. WHITE: So it's gone after 5. So basically, you're well below a useful threshold at 5 half-lives. So 50 hours of phototherapy is only 2 days.

DR. HILL: Right. Well, when we look at the effect on an endpoint that's representing efficacy later than the 48-hour endpoints such as phototherapy failures, stannsoporfin in the 204 study only had 1 case versus 8 in the placebo.

So there still appears to be plenty of power there with the single dose. That said, that's a reasonable suggestion and could be considered.

Now, your third point, I think, was a suggestion more than a question. Yes. And we will consider that. That's useful advice. Thank you.

DR. COLE: Dr. Rosen?

DR. ROSEN: So I also have two questions. I'm sorry about that. The first also relates to the pharmacokinetics and the hematology. And again, I'm a GI, not a hematologist, but what I'm having a hard time understanding is that the half-life seems relatively short, but looking at your curves, the bilirubin level seems sustained over a longer period of time, well past when the half-life would be.

Is there a chance that this drug is living somewhere else or getting deposited somewhere else, that the half-life isn't representing? And is there a chance that we're going to see a spike in bilirubin past the time where these kids were followed, so a secondary peak of hyperbilirubinemia past when they were followed in the study?

Then the second question was that one of the things babies do is feed. Right? And I didn't see

any data on feeding, or growth parameters, or head circumference over the course of the immediate time and then long-term follow-up.

So do you have any height, weight, and head circumference parameters that you can share with us, especially because speech and language go along with feeding issues?

DR. HILL: So let me take your first question first. You are exactly right. The pharmacodynamic effect seems more sustained than the apparent plasma concentrations.

In fact, what we observe in pre-clinical study is some sequestering in organs such as the spleen and the liver and that is what we believe is contributing to that sustained effect, another reason, Dr. White, that a second dose may not add too much more benefit.

Now, you asked if some of the developmental measurements had been performed. I'll have to ask Dr. Nancy Ruiz, who ran those studies, if those data are available.

DR. RUIZ: Yes, those data are available.

And we did laboratory vital signs, physician examinations, measuring weights, head circumferences, and there was no safety signals in 4 years of long-term follow-up.

DR. COLE: Dr. Callahan?

DR. CALLAHAN: David Callahan, child neurologist. I have a question, if Dr. Maisels or Dr. Ruiz have anymore information about inhibiting the heme-oxygenase. Is that reversible or irreversible effect on that enzyme, and if they have anymore information on how high the heme levels rise? And is there information on the toxicity of heme or is there just no information available?

DR. HILL: Stannsoporfin is a competitive inhibitor and it's reversible. What type of heme toxicity would you be interested in knowing?

DR. CALLAHAN: Any toxicity, whether it's to the brain or other organs.

DR. HILL: From a clinical perspective, we've shown the AE profile that was associated with its use. And that's not answering your concern or

addressing your concern?

DR. CALLAHAN: Right. So I didn't know if there was any toxicology data on high levels of heme.

DR. HILL: Dr. Randall, would you like to address his question?

DR. RANDALL: Yes, Joseph Randall, Mallinckrodt. So stannsoporfin causes a transient partial inhibition of heme-oxygenase and elevation of heme levels. And it also induces its own metabolism and induces heme-oxygenase itself in the liver.

So there's two mechanisms for returning heme levels to normal. One is elimination directly in the bile. The other is uptake of induction of heme-oxygenase in the liver. So we don't have any direct evidence or limited information related to administration of heme, but we do know that heme is used and approved in Europe for the treatment of acute porphyria in patients that have developed motor neuropathy and that the use of exogenous heme at a dose of 3 milligrams per kilogram IV for up to

3 months is effective for ameliorating the motor neuropathy in patients with acute porphyria.

So that's the information that we have. And we don't understand, so intravenous heme arginate is used in these patients and it increases heme-oxygenase levels by four to fivefold and fifteenfold in peripheral blood mononuclear cells and volunteers.

The mechanism for heme neuroprotection is unknown, but stannsoporfin also transiently increases heme and induces heme-oxygenase in a manner that's consistent with exogenous heme.

DR. COLE: Follow up, David?

DR. CALLAHAN: Thank you. And another question is, if this is a safe and effective treatment, why limit it to NICU or how do you define NICU? Aren't there different levels of nurseries and NICUs?

DR. HILL: That was our proposal in response to the FDA's proposal for certification. We are suggesting that it be used in centers that are capable of dealing with patients who have high risk

for severe hyperbilirubinemia as opposed to centers that could not deal with cases with those kinds of risks.

DR. CALLAHAN: But then aren't you concerned that, that would result in unnecessary transfer of infants so that they could get this treatment?

DR. HILL: That could possibly be a consequence, but that would be support for no certification or no restricted access. Right?

DR. COLE: Dr. Adams?

DR. ADAMS: Thank you. My questions are for Dr. Ruiz and Dr. Phillips, who I think are behind me, so I'm sorry that I'm asking these questions with my back to you, but I'm not sure I can bring this microphone around.

I'm a neuropsychologist. I have actually a number of rather granular questions that have to do with the management or the sort of evaluation of the data from the neurodevelopmental follow-up, so I don't know if we'll have time to get through all of them, but let me just start by asking a few.

I realize these are very granular, but they

will help us, I think, to understand how best to interpret these data. One question I had was with regard to the REEL, which is the Receptive-Expressive Emergent Language test. I was interested in the choice of a parent rating form for assessment of language rather than a performance-based measure like the Preschool Language Scales or something else that could be used at a young age developmentally.

Then I also noticed just in the briefing materials that were provided that you had analyzed the age equivalent scores as well as the T-scores for the REEL. And I just was curious about the analysis of the age-equivalent scores because my understanding is that age-equivalent scores are really just sort of scores that describe the median of performance for a particular age.

They don't have the properties that would allow them to be averaged and analyzed in that way. So I don't think that they are ratio or interval data. I'm not sure that you can calculate an average from them.

So if we're going, it's a very granular question, but if we're going to look at that data, we have to understand whether we can actually do that with that type of value. And then a similar question is with the Child Behavior Checklist, which is a gold standard assessment, omnibus assessment of child behavior.

I was curious about, first, the switch from the Conners to the CBCL because the CBCL goes down to 18 months, so I was curious why there was a different assessment for behavior at a younger age and then switching to the CBCL later on for the follow-ups.

Then secondly, I noticed that, on a table, I think it was page 117 that the CBCL data were expressed as Z-scores for the syndrome scales. And I noticed that a number of those Z-scores went below 0, but when I think about the CBCL, normally those data are expressed as T-scores and those syndrome scales are truncated at a T of 50. They don't go below that. You can't calculate a T below 50.

So if you were going to convert that to a Z, I wouldn't see that you would have a negative value for your Z-scores. So I'm just trying to have an understanding about how these data were evaluated and managed at that level. So I have lots of other questions, but we'll start with those two.

DR. HILL: Dr. Adams, I'm not sure I understood your question, but perhaps Dr. Phillips did. Dr. Phillips, can you address that?

DR. PHILLIPS: Dawn Phillips, Evidera. That was a lot of questions. So as an independent reviewer, I can't speak specifically to the decisions that were made early on related to all the tests.

I will say, as an evaluator, though, I think it's very important that we did have an opportunity to capture the parent perspective in order to not just see what we see in the clinical environment, but to represent what happens outside of the clinical environment in both the behavior checklist and in speech and language evaluation.

Related to your question on the age-

equivalent scores, I completely agree with you that we know that age-equivalent scores are not an equal interval scale. And so that's why the scores were first represented as standard scores.

Then in order to add clarity for people that are maybe not as familiar with seeing data in that format. We show the age-equivalent scores to show that they align generally with the age of the children at the time frame.

It gives you a little bit more information in order to be able to interpret it.

DR. ADAMS: So thank you for those comments. I think it is important to have the parent perspective on the child's function day to day, but just thinking about the levels of evidence review that you walked us through, I would also argue that, while it's interesting and important to have, it's not going to be the be-all and end-all to give us really standardized data from child to child to child on language development over time.

I had some other questions. I'm aware of the time that we're scheduled for break now, so --

DR. COLE: Could we hold those questions?

DR. ADAMS: Yes.

DR. COLE: We have three more potential questions here and then we're going to take a break. Dr. Havens?

DR. HAVENS: Thank you very much. One of the early slides suggested that there was intact excretion and urine in bile. But in the backgrounder, we note that the liver color was abnormal in animal models for, I think, 6 months. So how much of the agent is actually excreted? What percentage of the total agent is ever excreted?

DR. HILL: Dr. Randall, can you comment specifically on the recovery of the parent molecule?

DR. RANDALL: Yes, Joseph Randall, Mallinckrodt. So we've done 6 different ADME studies as we mentioned and we looked at mass balance and at the recovery. And we see incomplete recovery. The recovery varies by species and varies from 50 to 65 percent in rat and dog. And

the rest of the material is slowly eliminated from the liver.

Here's the data. So in dogs, the overall recovery is 44 to 49 percent with 15 to 19.8 percent of the urine and 24 to 33 percent in the feces. The low recovery is due to tissue retention and the kidney, liver, and spleen.

In the rat, we see recovery, overall recovery of 66 percent, 64.3 percent after IV and IM administration, with 11 percent in the urine and 51 percent in the feces, with most elimination occurring within 72 hours. And the low recovery, again, is due to incomplete elimination and slow clearance from the liver, kidney, and spleen.

DR. HAVENS: What's the time course in the dog? It says 72 hours in the rat, but it doesn't give the time course in the dog.

DR. RANDALL: The time course in the dog is much longer. The clearance from the kidney, liver, and spleen, the half-life, terminal half-life ranges from 25 to 35 days.

DR. HAVENS: So the half-life is 35 days.

And in the animal model, where there was liver staining, how far out were those studies taken to identify the agent in the liver? Was it 6 months?

DR. RANDALL: The liver staining was taken to the end of the toxicology and metabolism studies, so it varies by study, but up to 6 months in the neonatal dog study, we saw pigment accumulation in the liver that was not associated with liver pathology or elevated liver enzymes.

This was due to the slow clearance of the drug from these organs. And so this discoloration of the liver was attributed to accumulation of the test article and slow clearance from -- this is the biodistribution data looking at the levels in the kidney, liver, and spleen. This is nanogram equivalence per gram of tissue over time and the X axis is time and hours post-dose.

You can see the top graph is the amount of material in the liver in the blue triangles. The green triangles is amount in the kidney and the spleen is the purple squares, so there's slow elimination from organs of clearance.

DR. HAVENS: Is there going to be time later for more questions? I'm glad to cede, because this is a --

DR. COLE: Yes, there'll be discussion further. I also think we'll need to discuss the specifics about the tin excretion as well as the drug excretion because we'll need to cover both of those. Dr. Aly?

DR. ALY: I would first would like to really mention that we have been waiting a long time for a trial like this to come because you do need to see more than one baby with bad cerebral palsy kernicterus to really see the disaster that is facing babies with hyperbilirubinemia. But also, in the meanwhile, I would like to mention that bilirubin is present only in mammals and other non-mammalians who have blood, but the blood doesn't go to bilirubin. So there is always thinking that bilirubin is protective.

Therefore, in evaluating a drug like this, I would like to focus on the very low bilirubin babies, babies who receive the drug and have how

low did it go. I see that one study showed 6 percent instance of sepsis and another study had 1 baby with meningitis.

What was the bilirubin level? How low did it go in these babies? The same thing for the neurodevelopmental outcomes. We see the number of babies are a few, but I would like to stratify it by bilirubin level. The ones that has the lowest bilirubin; did they do worse in neurodevelopmental outcome or did they have similar or was it high?

The heme molecule; of course this will be the first drug to give to babies to of course increase the heme molecule. And with all this hemolysis, you can have renal failure. So do we have any data on kidney functions for babies who received this drug?

My last question is the drug we are discussing in the setting of hemolysis. However, I will say, on the day-to-day management, Mom, who wants to go home and the baby who's having a bilirubin borderline, so instead of keeping the baby in the hospital for a day or two, give him a

chance of a drug and send the baby home.

So do we have clear criteria in these studies or in the proposed indication that the baby will not receive this drug unless this specific criteria for hemolysis exists. Otherwise, we'll have a quarter-million babies every year who receive phototherapy for high bilirubin and now you can send the baby home very early.

Needless to say, phototherapy does have side effects. It can cause DNA damage. But for the sake of the setting today, we are really proposing it only for hemolysis. Then we need to have very clear criteria, what do you mean by hemolysis before giving it? Thank you.

DR. HILL: May I have slide CO-33, please? These are the inclusion criteria for study 204, which we believe represents the appropriate population for stannsoporfin's use. There is a gestational age factor. There is the requirement to be at the American Academy of Pediatrics threshold for initiation of phototherapy, then evidence of isoimmune hemolytic disease, and

Coombs-positive or a Coombs-negative with an elevated reticulocyte count.

This is the population of 204 and we believe it represents the population, I think, that you're describing at risk for severe hyperbilirubinemia.

DR. COLE: Thank you. Dr. Newman?

DR. NEWMAN: Thank you. Tom Newman. I have worked with Jeffrey on and off for almost 30 years on jaundice and I worked on the AAP guidelines. And I guess it's a question for you. There seems to be a discrepancy between your clinical picture of the need for this drug. It seemed like you were presenting it could shorten the duration of phototherapy. It looks like it shortens the duration of phototherapy by about 10 hours, but the indication that is being requested is for neonates at risk of developing severe hyperbilirubinemia.

Those seem kind of different and I guess the question is, if I were going to try to help a parent make an informed decision about this drug with sort of still not, well-documented safety to quantify what the benefit was, I think a parent

would be able to understand, yes, you can stop phototherapy on the average of 10 hours sooner, but in terms of how high the risk of developing severe hyperbilirubinemia would need to be and how many babies I would need to treat with this drug to prevent one from, for example, reaching an exchange level?

None of the babies in the study came anywhere near exchange levels. So the question is, what would be the estimated number needed to treat to prevent an outcome like that, either exceeding the exchange level. It's, I think, to, say prevent one case of kernicterus, forget it, but even just exceeding exchange levels -- and that could even be -- as you know, we're considering raising the exchange levels in the next AAP guidelines.

So would you have any estimate of that to help a parent make an informed decision?

DR. HILL: Dr. Maisels, this is right in your territory. Would you please address that?

DR. MAISELS: Yes. As Dr. Newman has shown us, the number of babies that we need to treat with

phototherapy to avoid one exchange transfusion varies dramatically depending on when the phototherapy was needed, the baby's gestational age, and so on and so forth.

We have not done that kind of analysis for this drug and clearly it needs to be done. So yes. I agree with you that we would end up treating a fairly large number of babies in order to prevent one exchange transfusion. It would be perhaps slightly more efficient than exchange transfusion because it lowers the bilirubin level more rapidly and so the number needed to treat should be less than we needed to treat with phototherapy.

But that's all I can say for it at the moment.

DR. NEWMAN: We're already treating with phototherapy, so it would be in addition. Right?

DR. MAISELS: I'm sorry. Well, then, yes, in addition to phototherapy, yes, like I said, than phototherapy alone.

DR. COLE: Dr. Guillory?

DR. GUILLORY: Charleta Guillory, Baylor

College of Medicine, Texas Children's Hospital, and I'm a neonatologist. The first thing I want to say is that we have almost approximately 4 million children that are born each year.

Out of that 4 million, if you divide it with what was said previously, that extreme hyperbilirubinemia occurs in 7 to 40 babies per 100,000 deliveries. That means we would expect about 1,600 babies to have severe hyperbilirubinemia.

In all the discussions that I've heard, I've not heard anyone tell me about what is the risk presently of severe bilirubin encephalopathy or kernicterus. So that's my first question; what is that number? It will certainly help us as we go on with trying to determine the effectiveness of this drug.

The second thing I want to mention is, in Texas, we are working on designations of levels of care. So I can see the use of this drug not only in level 3 and 4 babies, but we have a lot of level 2 babies because our bilirubin problems are

so common that, how do you prevent it from being used in newborn nursery or in level 2 units as well as 3 and 4.

The final thing; I just have to understand, since we are talking about using this drug in babies that had ABO incompatibility, I still see the antibodies being present so that you continue to have hemolysis a month or 6 weeks after the baby's born. How do we address that issue? Does it mean that you'll continue to have it if the drug's effectiveness is not that long? Thank you.

DR. HILL: So I think I heard three questions there. Dr. Maisels, would you like to address the first one?

DR. MAISELS: I can answer a couple. We don't have national data on the incidence of kernicterus in the United States, but taking into account the most recent data, both from the California population, from the Danish population, from other studies in Europe, we can say that the incidence of chronic bilirubin encephalopathy is somewhere between 1 and 2 per 200,000 babies.

There's a potential .5 to 2 per 100,000 babies would be the range of documented chronic bilirubin encephalopathy. With regard to the ABO positive Coombs-test infants, those were the infants that we studied in 204. They had positive Coombs tests and most of them were ABO incompatible. They have also been studied by the Rockefeller group that showed clearly that the drug worked in spite of the fact that there might still be antibodies present and are not removed by an exchange transfusion, which is what an exchange transfusion does.

It still worked. The drug still worked to keep the bilirubin level down.

DR. COLE: Thank you. Dr. Wade?

DR. WADE: Thank you. I wondered if you could review the number of gestational age 35- and 36-week babies in 204 because, with an indication that goes down to 35 weeks, it looked to me like there were very, very few 35- and 36-week gestational age infants.

My second comment really in follow-up to

Dr. Guillory is that there are a variety of levels of care in neonatology and phototherapy is even administered in the well nursery in some institutions.

So just having that NICU designation to me did not feel thorough enough when discussing the potential long-term side effects because phototherapy and just being in NICU is very broadly defined and level 2, levels of care would not typically be able to provide an exchange transfusion or even potentially IVIG for babies with aggressive hemolytic disease.

Then my third comment was just, it was interesting in the animal data this color of the urine. And I'm wondering if any of the babies had differences in the color of their urine that may have unblinded the study.

DR. HILL: So you had two questions and a suggestion. The first question was the age categories. What was the distribution of age in study 204? We divided the categories of age from 35 to less than 38 and greater than 38 and, for the

stannsoporfin 4.5-milligram dose, the vast majority, 28 out of 31 were in the greater than 38, and for the placebo, 25 out of 30, the same pattern. So most of them are greater than 38.

Now, in animal species, there is an indication of color in the urine, but it is not seen in humans. So there was no possibility for unblinding in humans, in clinical data.

DR. COLE: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. Dr. Newman asked the question I had about what was the intent to treat for the really severe babies, and it sounds like we don't have the answer.

DR. COLE: Thank you. So we'll now take a 10-minute break. We need to be back here promptly at 10:30. Thank you.

(Whereupon, at 10:22 a.m., a recess was taken.)

DR. COLE: Please take your seats and we'll start with the FDA presentations. I'd like to thank InfaCare and the committee members for the informative and robust discussion this morning.

We'll now proceed with the presentations from the FDA.

FDA Presentation – Shen Li

DR. LI: Good morning. My name is Steven Li. I'm the clinical pharmacology reviewer for this application. I will present the main clinical pharmacology findings of the proposed drug product, stannsoporfin.

Here is an outline of my presentation for today. First, I will provide pharmacokinetic information of stannsoporfin. Next, I will present the dose response and the exposure response relationship analysis for change from baseline in total serum bilirubin using data from supportive study 64185-202, in which a subset of neonates received phototherapy and from pivotal study 64185-204, in which all neonates received phototherapy.

For presentation purposes, these two studies will be simply referred to as study 202 and 204 hereinafter. Pharmacokinetics of stannsoporfin have been evaluated in healthy adults and also in

neonates with hyperbilirubinemia.

Following a single intramuscular injection in neonates, mean peak plasma concentrations of stannsoporfin were reached within 1.5 to 2.3 hours, and showing in the concentration time curve, Cmax and AUC increase with increasing dose from 1.5 to 4.5 milligrams per kilogram.

The apparent volume of distribution is estimated to be about 1 liter for a typical neonate weighing 3.5 kilograms.

Metabolism and the major elimination pathway have not been well characterized. However, in vitro data suggests cytochrome P450 enzymes are not involved in the metabolism of stannsoporfin.

In neonates, mean terminal half-life is 10 to 11 hours. Following a single intramuscular injection to healthy adults, urinary recovery of stannsoporfin varied from 0.2 percent to about 10 percent of the dose within the first 48 hours and was recovered in feces for up to 13 percent of the dose. After introducing the PK, I would like to focus on the dose response and the exposure

response analysis, starting from supportive study 202.

Study 202 evaluated 3 doses. Of note, not all neonates receive phototherapy in study 202. Patients were assessed for the need of phototherapy after receiving stannsoporfin.

As shown in the table, 8 of 15 neonates received phototherapy in the placebo arm. In 1.5, 3, and 4.5 milligrams per kilogram dose groups, 3, 6, and 2 neonates received phototherapy respectively.

The mean change from baseline in total serum bilirubin or TSB over time for all neonates are presented in a plot. As you can see in the plot, the orange line with diamonds represents placebo arm.

Stannsoporfin, 1.5, 3, and 4.5 milligrams per kilogram dose is represented with a purple line with squares, a blue line with triangles, and a green line with open circles respectively.

As shown in the plot, total serum bilirubin continues to increase in the placebo arm overall.

Treatment with stannsoporfin appeared to attenuate the increase in TSB over time as compared to placebo arm.

Dose response relationship was further evaluated using data stratified by phototherapy use. As shown in the left panel, the two lower doses of 1.5 and 3 milligrams per kilogram appear to attenuate a rise in TSB compared to placebo in neonate without phototherapy.

However, as presented in the right panel, this attenuation effect over placebo seems not evident in neonates who received phototherapy. The effect of 4.5 milligrams per kilogram dose on TSB change appears to be greater than the two lower doses regardless of phototherapy treatment, although it should be noted that, due to the small number of neonates in study 202, a definitive conclusion regarding dose response in neonates receiving phototherapy could not be drawn.

In addition, exposure response relationship or change from baseline in total serum bilirubin in study 202 was further explored using an inhibitor

emax model with individual stannsoporfin AUC values in neonatal patients and change from baseline TSB at 48 hours and 72 hours.

Of note, the exposure response analysis in the AC backgrounder were initially presented overlaying a linear regression line to display the apparent inverse relationship.

However, considering the mechanism of the proposed drug and the reasonable assumption that there is a maximal effect in terms of bilirubin production inhibition, an inhibitory emax model is considered to be more physiologically relevant and thus selected to better describe the data here.

As you will see in the next slide, overall graphical assessments of the exposure response relationship suggest there is an inverse relationship between increasing systemic exposure and change from baseline in total serum bilirubin.

This pattern appears to be in agreement with observed dose response relationship in study 202. That's showing the plot. Exposure response analyses were conducted using change from baseline

in total serum bilirubin at 48 hours, as shown in the left panel, and also change from baseline at 72 hours, plotted in the right panel.

In the plot, the red lines represent a predicted exposure response curve in TSB change versus stannsoporfin systemic exposure. Vertical black lines represented a predicted 90 percent inhibition for bilirubin production.

At 48 hours, 90 percent inhibition seemed to be associated with drug exposure of the 4.5 milligrams per kilogram dose. Shown in the right pane, there appear to be shifts toward lower drug exposure for the 90 percent inhibition at 72 hours.

It is important to point out that there are certain limitations of the kind of ER relationship analysis with regard to the patient population in study 202 since not all neonates receive phototherapy.

As such, the relationship between TSB change and the systemic exposure was further evaluated using data stratified by phototherapy use. Data in

neonates without phototherapy are plotted in the upper panels and data for neonates receiving phototherapy are plotted in the lower panels.

Because the sample size is small, subpopulation data cannot be reasonably characterized using the emax model. Nevertheless, phototherapy was not identified as a CV within the covariate in the ER analysis. As such, predicted inhibition curves showing the plot on the red lines and 90 percent inhibition, black lines here, based on pooled data are presented here in the plot when data are stratified by phototherapy use.

It should be noted that individual response was highly variable among patients without phototherapy treatment and it seems less variability in patients with phototherapy.

Again, the apparent ER relationships should be interpreted with caution due to the small sample size of the study. In pivotal study 204, 2 stannsoporfin doses at 3 and 4.5 milligrams per kilogram were evaluated in neonates with hyperbilirubinemia.

In the study, stannsoporfin was given within 30 minutes before or after initiation of the phototherapy treatment, as shown in the mean change from baseline in total serum bilirubin over time curve, compared to an apparent increase in TSB in the placebo arm. Both 3 and 4.5 milligrams per kilogram dose decrease TSB over time in neonatal patients. There was no apparent difference between 3 and 4.5 milligrams per kilogram, a change from baseline in TSB over time.

One thing I would like to mention here is that my presentation today is focusing on the absolute change from baseline in TSB.

The applicant also conducted analysis using percent change from baseline in TSB. Nevertheless, the dose response relationship of the percent change from baseline in TSB showed a similar trend to that for the absolute change from baseline TSB in both studies, 202 and 204.

To summarize, overall, there is an apparent dose-dependent attenuation of TSB as observed in study 202. Treatment of stannsoporfin appeared to

attenuate the increase in TSB over time as compared to placebo. ER analysis suggests there is apparently an inverse relationship between increasing systemic exposure and change from baseline in TSB regardless of phototherapy treatment.

However, the apparent relationship, particularly in neonates who receive phototherapy, should be interpreted with caution due to the small sample size of study 202.

In pivotal study 204, both 3 and 4.5 milligrams per kilogram dose decreased TSB over time as compared to placebo and no apparent difference in mean change from baseline TSB was observed between those two doses. So this concludes my presentation for today. Thank you. I will now turn the podium over to my colleague, Dr. Feiran Jiao.

FDA Presentation – Feiran Jiao

DR. JIAO: Good morning. My name is Feiran Jiao. I'm the FDA statistical reviewer for this NDA. In the presentation today, I will show you

the analysis of efficacy data for stannsoporfin.

Let us recap the study design for 204. The applicant submitted a single confirmatory study to establish the efficacy of stannsoporfin. Enrollment criteria are listed here. This study, 204, was designed originally as a phase 2b multi-center double-blind randomized placebo-controlled trial.

Ninety-one neonates were randomized in a 1:1:1 ratio to phototherapy in conjunction with stannsoporfin, 3 milligrams per kilogram, 4.5 milligrams per kilogram, or placebo and followed for 30 days after a single dose. The primary endpoint was the percent change from baseline in total serum bilirubin, TSB, at 48 hours post-treatment.

Based on the definitions from the 2004 AAP practice guidelines from the subcommittee of hyperbilirubinemia, you can see over 80 percent of the neonates enrolled in this study were in the medium risk group on the phototherapy nomogram.

We have examined individual neonates'

performance over time. In this figure, each line represented a neonate's TSB at various times of measurement.

The low black line represents the threshold for phototherapy for these neonates and the upper red line represents the threshold for exchange transfusion. Time along X axis has given us hours since birth. The starting point on each line is the TSB value at baseline and the black dot represents the first TSB measurement after the time of injection of stannsoporfin.

This figure described neonates in a high-risk group. From bottom to top are placebo, 4.5 milligrams per kilogram, and 3 milligrams per kilogram stannsoporfin. No doubt, at the upper left corner of the top graph, 1 neonate in the 3 milligrams per kilogram treatment arm had a TSB that exceeded the exchange transfusion's threshold at baseline.

We also note that the drug and placebo arms appear to be trending differently. The drug arms in the top two graphs appear to show a downward

trend. But the placebo arm had neonates' value closer to the lower bound of the PT's threshold.

A similar pattern was observed in the medium risk group. In particular, the TSB values for many neonates in the drug arms appear to decline faster than the placebo arm. The intention-to-treat population of study 204 included 91 neonates.

Multiple issues were identified regarding the study population. First, 11 neonates were found to have a TSB at enrollment that was 2 to 3 milligrams per deciliter below the age-specific threshold for initiation of PT. This violated one of the enrollment criteria.

For the first secondary endpoint, neonates time at which TSB crosses at or below the PT threshold, the applicant adopted a linear interpolation method. We note that the applicant's analysis had 15 neonates excluded automatically from the analysis through the software SAS implementation.

We then found that the 15 neonates' TSB fall below the PT's threshold at the first time visit

after they received the injection. And their time when crossing the age-specific PT threshold were estimated negative.

The negative time values were considered invalid and were removed from both the applicant's analysis and FDA's sensitivity analysis for the first secondary endpoint. Finally, 1 neonate in the 3 milligrams per kilogram arm had baseline TSB that exceeded the threshold for exchange transfusion and was transfused almost 11 hours after the injection of stannsoporfin.

These neonates were also excluded from FDA's sensitivity analysis. In order to have a consistent analysis population, FDA sensitivity analyses were conducted on these 64 neonates for all hypotheses.

The result of the primary endpoint, the percent change from baseline for TSB after 48 hours post-dose for two different analyses populations are shown here. The first row is the applicant's ITT analysis in 91 neonates. The second row is FDA's sensitivity analysis in 64 neonates.

Although the 15 neonates who had negative interpolated time were excluded based mainly on the analysis for the first secondary endpoint for consistency, FDA sensitivity analysis also removed these 15 neonates in the primary endpoint as well as the 11 who didn't meet the inclusion criteria and the 1 neonate who received exchange transfusion.

FDA's sensitivity analysis results shown in the second row are consistent with the applicant's. Compared to placebo, both 4.5 and 3 milligrams per kilogram dose arms are statistically significant with p value less than .0001.

It is unclear whether this observed difference in percent reduction from baseline for TSB at 48 hours post-dose are clinically meaningful.

Based on a sequential testing procedure since the results for the primary endpoint were statistically significant for both doses, the secondary endpoint will be sequentially tested following any hierarchical order, which is first

time in which TSB crossed at or below the age-specific PT threshold; second, PT failure, which includes restart of phototherapy, hospital readmission if IVIG was used, or requirement for exchange transfusion; and third, incident of rebound hyperbilirubinemia, which was defined as an increase in TSB above the age-specific PT threshold following discontinuation of the initial PT.

For the primary endpoint and each of the three secondary endpoints, testing started from the higher dose, 4.5 milligrams per kilogram. And if the higher dose is significant at alpha .05, then testing of the lower dose, 3 milligrams per kilogram, is performed.

There were discrepancies between the documents submitted by the applicant on how to proceed through the testing. To control the overall type 1 error rate, FDA adopted a procedure which stops testing if at any point the hypothesis testing yields a non-significant result.

The first secondary endpoint is the time-to-event analysis of the time in hours from injection

to the interpolated time when the neonates' TSB crossed at or below the age-specific PT threshold.

The applicant's results are shown in the first row. FDA observed 15 of 91 neonates in the ITT population had negative time values. In addition, the applicants imputed the time in hours from injection to discharge for the 11 neonates who were below the PT threshold at randomization and did not exclude it from the analysis.

FDA sensitivity analysis results are shown in the second row. We noted that the observed difference of median time for crossing the PT threshold between 4.5 and placebo is about 5.7 hours.

Although the 4.5 milligrams per kilogram arm appeared to be statistically different than the placebo arm in both FDA's and the applicant's analysis populations, this is not true for the 3 milligrams per kilogram dose, where the p values were greater than 0.1.

The second secondary endpoint, PT failure, was defined as a binary variable where neonates had

experienced at least one of the listed events. As you can see from the result, PT failure occurred more frequently in the placebo arm compared to the stannsoporfin arms.

For the third secondary endpoint, rebound of TSB to above the PT threshold, more neonates in the placebo arm experienced rebound hyperbilirubinemia compared to the stannsoporfin arms. However, these numbers are small.

FDA performed an exploratory analysis on the duration of hospitalization given its potential clinical significance. Duration of hospitalization was defined as the interval between injection and first hospital discharge.

However, while important, this endpoint is driven by many other factors unrelated to hyperbilirubinemia that can result in delayed discharge. When data for the duration of hospitalization were analyzed based on 91 and 64 neonates, all three treatment arms had a similar result.

Now I will summarize our findings. For the

primary endpoint, both the 3 and 4.5 milligrams per kilogram stannsoporfin dose experienced a greater reduction compared to placebo based on both the applicant's and FDA's sensitivity analysis. For the first secondary endpoint, the applicant's and FDA's sensitivity analyses indicated that neonates on 4.5 milligrams per kilogram dose crossed at or below the age-specific threshold for discontinuing PT sooner than the neonates on placebo.

FDA's sensitivity analysis for stannsoporfin, 4.5 milligrams per kilogram compared with placebo shows a key value, 0.014. There was only 1 completed study for this NDA, study 204. Whether the efficacy results are statistically persuasive will need to be considered and discussed in the meeting today. This concludes my presentation. Thank you for your attention.

FDA Presentation – David Joseph

DR. JOSEPH: Good morning. My name is David Joseph. I am the non-clinical team leader for this application and today I will provide a summary of

the major findings in the non-clinical safety studies.

When I advance the slide, I will. Okay? Sorry about that. So this is just a brief overview of my presentation and I'll begin with a description of a single dose phototoxicity study in neonatal guinea pigs in which animals were given a single injection of stannsoporfin and then exposed to operating room light.

Next, I'll present a summary, really a comparative summary, of the two pivotal toxicology studies in which neonatal animals, rats and dogs, were treated for 28 days with daily dosing.

Although a 28-day treatment duration would appear to be an excessive dosing regimen for a drug that's proposed for a single use in humans, I would just remind the committee that this design conforms with the standard regulatory recommendations for single-use drug products to support a marketing application.

Finally, I'll conclude with a review of some data from a tissue distribution study conducted in

neonatal rats using radio-labeled stannsoporfin and I'll focus on the data showing distribution in rat brain.

So stannsoporfin is expected to be photoreactive based on its porphyrin structure. So therefore, the applicant conducted several phototoxicity studies, but today, I'm only going to present the data from one of these studies in which neonatal guinea pigs were given a single intramuscular injection of 20 milligrams per kilogram stannsoporfin.

Now, this dose is 1.5 times the proposed dose in neonatal humans based on a milligrams per meter squared comparison. So based on this metric, this could be considered as a clinically relevant dose.

After injection of stannsoporfin, the guinea pigs were exposed for 6 hours to operating room light. Now, I would just remind the committee that operating room light is very different from blue light, so ORL is a broad-spectrum light, whereas phototherapy represents a narrow blue light

spectrum.

So the results were dramatic. 11 of 12 guinea pigs that received injection followed by ORL exposure had died by the end of the 6-hour light exposure. And this is compared to only 1 of 12 deaths in the control group.

The controls received a vehicle injection followed by exposure to operating room light. Now, this was clearly due to phototoxicity, so the effects could be mitigated by extending the interval between stannsoporfin injection and then initiation of ORL exposure.

So when the interval was extended to 5 days, that is, 5 days between stannsoporfin and then exposure to ORL, no deaths occurred. And also, filtration of the light also partially mitigated the toxicities seen in the animals.

So next, I will provide a comparative summary of the pivotal toxicity studies conducted in neonatal rats and neonatal dogs. So the same doses were tested in both studies, 0.1 4.5 and 20 milligrams per kilogram per day. However, the

plasma exposure or AUC differed substantially between the species.

In rats, the cumulative plasma AUC over the 28-day treatment period was 1.7, 11, and 53 times at the low, mid-, and high dose respectively, a multiple of the human AUC from single administration of the proposed dose of 4.5 milligrams per kilogram, whereas, if you look in dogs, the multiples are much lower, 0.3 at the low dose and 4.5 multiple of the human AUC at the highest dose tested.

So the message here is that the plasma exposure in dogs was about 10 percent observed in rats, although identical doses were used.

So just to summarize the key findings, there was growth impairment in both. Both rats and dogs did show signs of growth impairment. The effect was quite minimal in rats, so in the high-dose group, 20 milligrams per kilogram, the body weight at the termination of treatment was reduced by 5 to 6 percent.

In dogs, it was more prominent. At the end

of treatment, there was moderate growth impairment at the mid-dose and the high dose, where final body weight was reduced by 9 to 15 percent. So on this parameter, the dogs appear to be more sensitive than rats.

But a point of emphasis here is that these weight reductions occurred only after repeated administration in both species. So the first notable weight reduction in rats did not occur until after 18 days of treatment and, in dogs, not until 6 days of treatment. And therefore, we have to state that the growth impairment observed may not be relevant to the single use that is proposed in neonatal humans.

Neurobehavioral testing was also conducted in both studies. Effects were observed in both males and females, but they were observed in different tests. In male rats, on the day of the test, where effects were observed, the cumulative AUC was 6.7 times that of a human and, in female rats, where the effect occurred in the high-dose only, the AUC multiple was 34-fold. And again, for

both of these findings, this occurred in the context of repeated administration.

I would also note the results are deemed inconclusive for females. I'll be describing the outcome of these tests in some more details in just a couple of minutes, but again, we have to state that these results may not be relevant to single use in neonatal humans.

In dogs, there were no findings in neurobehavioral testing. It's difficult to know or interpret the finding in dogs because, as I said previously, the AUC was only about 10 percent of what was observed in rats.

Mortality; so there were deaths, but only in the dog study. 2 of 32 dogs in the high-dose group died and the deaths occurred at a cumulative AUC of 3.3 times the human AUC at the proposed dose. And again, this is in the context of repeated administration, so the deaths occurred on day 21 and day 23. No deaths occurred in rats, so again, on this parameter, too, dogs were clearly more sensitive than rats.

So both species did exhibit microscopic changes in liver, but the effects were quite different. So in rats, at the end of the treatment period, single-cell hepatocyte necrosis was seen with fairly high incidence in the majority of the high-dose group rats.

This effect was 100 percent reversible at the end of the 30-day recovery period. And in dogs -- and this data was discussed earlier today -- the only sign in liver was accumulation of pigment and this was very likely the drug since we know from the distribution data that the drug is highly concentrated in liver and its half-life is 34 days.

This was an irreversible effect out to the final sacrifice of the study, which involved a 6-month recovery period. Every dog injected with stannsoporfin exhibited the pigment accumulation in liver. The only other microscopic change of note was thyroid atrophy. It occurred at the high dose in dogs and, again, this was completely reversed after a 1-month recovery period.

So this slide goes into some more detail about the neurobehavioral effects in the 28-day neonatal rat tox study. The effects in males in rats were different. So males exhibited decreased motor activity in mid- and high dose. And this refers to time spent in motion.

So the reduction was 47 and 45 percent in the mid- and high dose respectively. This was statistically significant. I would also point out that the low-dose group also showed a reduction, about 27 percent. However, this did not reach statistical significance.

The test was conducted on study day 18. So on the day of the study, the approximate equivalent human age, what was about 2 years old, the effect was observed. In the mid-dose, the cumulative AUC was 6.7 times the human AUC of the proposed dose and in the high-dose group where the AUC multiple was 32 times.

The test was repeated on the 14th day of recovery. There was no statistically significant observation on this recovery day, but I would point

out that the motor activity did remain reduced in the high-dose group by 28 percent, but did not reach statistical significance.

Now, the female rats did not show any change in the motor activity evaluation. The high-dose females did exhibit a 31 percent reduction in response in the acoustic startle test. This was study day 19, so again, human age equivalence, about 2 years old on the day of the test.

However, the test appeared inadequate based on control values that deviated from the expected outcome, so we have to consider the results as inconclusive. But there did appear to be some drug-related effect at the high dose.

So this effect was observed at a cumulative AUC that was a 34-fold multiple of the human AUC at the proposed dose. Again, no effect in the mid-dose females where the cumulative AUC was 7. The test was repeated on the 15th day of recovery and the high-dose females did show, continued to show a reduced reduction on that day.

So to further evaluate the potential for

neurodevelopmental effects, which is one of the main issues in the overall safety assessment of stannsoporfin, it would be useful to review the tissue distribution data that included measurement of radio-labeled stannsoporfin in brain.

So the applicant conducted several distribution studies, as they stated before, using stannsoporfin containing a radioactive isotope of tin, shown here.

So this table shows the drug levels or radioactivity levels in brain following a single intramuscular injection in neonatal rats using a dose of 6 milligrams per kilogram, which is a clinically or should be considered as a clinically relevant dose based on the AUC.

So the AUC observed in this study was actually slightly lower than the AUC shown in human neonates at the proposed dose of 4.5 milligrams per kilogram. So the data shows that radioactivity for stannsoporfin was detected in 4 different brain regions at time points ranging from 1 hour to 72 hours.

Beyond 72 hours, radioactivity was below the limit of quantitation, so BLQ does not necessarily mean drug is completely absent. The levels just means low enough such that you can no longer reliably quantify amount of drug that's present in the brain.

I would note, in addition to the 4 brain regions, cerebrospinal fluid showed substantially higher levels of radioactivity. And this persisted all the way through the final time point, 1920 hours. That's 80 days after the injection of stannsoporfin. There's still relatively stable levels in cerebrospinal fluid.

Now, I just should explain this data a little more. The data are generated by measuring radiation release from tin in whole body autoradiography. And the numbers are calculated with the assumption that 100 percent of the radiation is related to unchanged drug. And I would say that, for these early time points, maybe 1 to 12, maybe even up to 24 hours, that's a reasonable assumption.

We know that radioactivity in plasma was about 95 percent unchanged drug. What's much less certain is the time points that go out further, particularly in a CSF up to 80 days after the injection. Whether that is still unchanged drug, I think we have absolutely no data or no basis to make any guess as to what the radioactivity is at that point.

So although we are uncertain about the clinical relevance of the behavioral effects in neonatal rats, the totality of the data suggests that there are potential mechanisms for the observed effects involving direct effects of stannsoporfin in the brain.

This is summarized in this next slide. So we know, as you just saw, that radiolabeled drug was detected in brain and CSF in neonatal rats after a single intramuscular injection of a clinically relevant dose, so again, the dose administered in rats was only 0.8 times the human AUC at the proposed dose of 4.5 milligrams per kilogram and 1.6 times the human AUC at

3 milligrams per kilogram, which was also tested clinically.

The brain distribution data suggests that the drug may accumulate with daily dosing, as in daily dosing that occurred in the 28-day rat study, and based on the observation that quantifiable levels remained in brain regions for at least 72 hours after a single dose.

I would also remind the committee that the drug target, heme-oxygenase, is expressed in brain and therefore, when stannsoporfin enters the brain, there is a potential for target-related effects or off-target effects.

Another issue is there is the potential for the release of tin as stannsoporfin is metabolized or degraded over time. And I think the last bullet is really meant as kind of a summary statement. And that's that the available animal data really provide minimal information about the potential for neurobehavioral effects from a single administration.

I think the most relevant data in the

overall dataset is really the distribution study that we just reviewed. And final thought; I'll just continue on the issue of the potential release of tin. So this is an additional safety concern, somewhat theoretical, but for safety assessment of metals in drug products, the FDA relies on ICH guideline Q3D, which provides a PDE value of 0.64 milligrams per day of inorganic tin via parenteral administration.

So when we calculate the dose of tin that could be delivered at the proposed dose, the value we derive ranges from 2.1 to 2.8 milligrams of inorganic tin at the proposed dose with the assumed birth weight of 3 to 4 kilograms.

Now, looking back over the data, it would be just interesting to see, were there any safety signals that would be even suggestive of tin toxicity. I would say one finding that was seen -- and then this is actually in both rats and dogs, but more prominently in rats -- there were slight but significant reductions in hemoglobin parameters, meaning mean cell hemoglobin and mean

cell hemoglobin concentration.

These are very small effects, 5 to 7 percent reduction, not a major concern. I would just note that such findings are consistent with the known toxicity of inorganic tin. Hemoglobin reduction is considered the most sensitive endpoint in animals, but I would emphasize this is certainly not conclusive of tin-related toxicity.

At this point, I'm going to turn the podium over to Dr. Veronica Pei.

FDA Presentation – Veronica Pei

DR. PEI: Good morning. My name is Veronica Pei and I'm a medical officer in the Division of Gastroenterology and Inborn Error Products. In the following presentation, I will be providing a focused summary of the FDA safety evaluation for stannsoporfin.

I will begin my presentation with an overview of the safety datasets. This will be followed by a brief summary of the safety evaluation based on short-term and long-term extension studies.

I will then end this presentation with a summary of the risk and benefit considerations for the committee.

Potential safety concerns upon review of the safety data from the short- and long-term studies include phototoxicity, as evident by dermatologic adverse events, thrombocytopenia, and potential for long-term neurodevelopmental effects.

Additionally, the liver was also identified as a target organ of toxicity based on non-clinical studies.

The applicant has presented data on liver safety which did not report any significant laboratory findings to suggest hepatotoxicity. Thus, my presentation today will focus on the other areas of safety concerns.

The applicant provided three separate integrated datasets under two different INDs, to support the short-term safety, long-term safety, and long-term neurodevelopmental safety for stannsoporfin.

The short-term dataset included two trials

that both enrolled neonates at risk for developing severe hyperbilirubinemia. The third study, 013W, enrolled a lower-risk population that did not have risk factors for severe hyperbilirubinemia.

The long-term safety database included pediatric patients that participated in the long-term extension of the three short-term studies. In addition, the applicant submitted supportive safety data from the six studies conducted under the initial IND 29462, which the applicant has been referring to as the Rockefeller IND.

It is worthwhile noting that the six studies conducted under the Rockefeller IND were not in compliance with current good clinical practice standards, which ensures protection of the rights of human subjects, data quality, reliability, and integrity.

Additionally, these studies were of various designs and enrolled a heterogeneous population that differed from the pivotal study population and therefore will not be the focus of our discussion today.

A total of 1,430 neonates participated in the stannsoporfin development program. Of those, 380 neonates participated under GCP compliance studies, including 152 controls and 228 neonates that received stannsoporfin at doses ranging from 0.75 to 4.5 milligrams per kilogram.

The control population included neonates that received placebo with or without phototherapy or phototherapy alone.

Next, I will summarize safety evaluation based on the pooled short-term studies. Across the three short-term studies, approximately 80 percent of neonates enrolled were within the AAP medium-risk category for initiation of phototherapy.

For the two studies that enrolled subjects with additional risk factors for severe hyperbilirubinemia, namely studies 202 and 204, the majority of the neonates were Coombs-test positive.

There were a total of 12 deaths that occurred in the stannsoporfin development program. Of the 12 deaths, 9 received stannsoporfin, 2 received placebo, and 1 occurred in a neonate

that was screened but not enrolled into a study.

In the GCP compliance studies, no deaths occurred in the short-term studies. 1 neonate in the 4.5 milligrams per kilogram arm died from SIDS during long-term follow-up.

In the non-GCP studies, all 8 deaths occurred in a single study which enrolled a population of pre-term infants. 6 of the 8 neonates received stannsoporfin and 2 received placebo. These deaths were thought to result from complications related to prematurity.

An additional 2 deaths occurred in patients under compassionate and emergency INDs. Both occurred in pre-term infants of 30 and 25 gestational age that receive stannsoporfin. 1 neonate died of SIDS at 5 months and the other decompensated during surgery for perforated necrotic bowel.

A serious adverse event refers to medical occurrences that result in death, a life-threatening event, or requires hospitalization or prolongation of hospitalization. SAEs were

reported for 27 neonates from the pooled short-term studies and most occurred in single occurrences.

One neonate in the 3 milligrams per kilogram arm reported an SAE of exchange transfusion. However, this neonate had a baseline TSB above the AAP threshold for initiation of exchange transfusion prior to receiving stannsoporfin.

This table shows selected SAEs that occurred in greater than or equal to 2 neonates in any treatment arm which included hyperbilirubinemia, anemia, medical observation for possible neonatal sepsis but were subsequently ruled out by culture, meningitis, and sepsis.

Numerically, more subjects reported SAEs in the 3 and 4.5 milligrams per kilogram stannsoporfin arm compared to placebo.

A treatment-emergent adverse event refers to any adverse event that started or worsened in intensity during or after exposure to the investigational product. As shown in this table, some of the most commonly reported TEAEs in the short-term studies included neonatal rash,

erythema, and thrombocytopenia.

Note that all 3 occurred more frequently in neonates that received 3 milligrams per kilogram or 4.5 milligrams per kilogram of stannsoporfin compared to the placebo arm. While the term "erythema" was pre-specified in the protocol to indicate a potential phototoxicity reaction, it is also possible that the drug exposure could have exacerbated a neonatal rash. Both dermatologic adverse events and thrombocytopenia will be explored in greater detail as adverse events of special interest in the following slides.

Given the potential for phototoxicity associated with stannsoporfin, dermatologic-related AEs were evaluated as an adverse event of special interest. While no skin-related SAEs were reported, it was the organ system with the most commonly reported TEAE. Specifically, skin AEs were more commonly reported in neonates treated with stannsoporfin compared to controls.

We also attempted to evaluate the risk of photosensitivity reaction due to exposure to

operating room lights. 16 patients required a surgical procedure during long-term follow-up, but all occurred greater than 140 days after receiving stannsoporfin. There were no reported photosensitivity-related AEs. Therefore, the risk of phototoxicity due to operating room light exposure immediately after drug exposure is unknown.

As discussed previously, thrombocytopenia was reported more frequently in neonates that received 3 or 4.5 milligrams per kilogram of stannsoporfin. Note that platelet counts were only evaluated in 2 of the 3 short-term studies submitted by the applicant, studies 202 and 204.

This figure shows the platelet count pattern in the pooled data from these two short-term studies. To orient you, each column represents times when the platelet counts were measured. Each row represents different study arms. A box indicates the platelet measurements during a specific time period for a specific arm. Blank blocks indicate that no measurements were obtained

during that time period. The height of the column reflects the number of neonates and the red color indicates those neonates that had a platelet count below the lower limit of normal, which is typically around 150.

As you can see, a greater number of neonates in the 3 and 4.5 milligrams per kilogram stannsoporfin arms have platelet values below the lower limit of normal at 48 hours compared to placebo, but this effect appears to resolve by day 14. This table summarizes the platelet levels collected for up to 30 days after drug or placebo exposure. Neonates with baseline thrombocytopenia were excluded from this table.

The lower limit of normal platelet count, as I mentioned, is approximately 150. As shown in this table, numerically more subjects experienced a fall in their platelet level to below 150 in the stannsoporfin arms compared to placebo, with an apparent dose-dependent relationship.

Increased risk of spontaneous bleeding is seen when the platelet levels fall below 50. And

we see that this occurred in 1 neonate in the 4.5 milligrams per kilogram arm. While no spontaneous bleeding events were reported in association with the thrombocytopenia effect, I want to mention that 2 neonates both with baseline low platelets required a platelet transfusion due to a further decrease in their platelet after receiving stannsoporfin. Both neonates were in the 3 milligrams per kilogram arm. These neonates were not included in these table because of their abnormal baseline. However, their baseline platelets were close to normal. One was close to 150 and the other one was approximately 100.

In summary, while the numbers are small, there appears to be a dose-dependent increased risk of thrombocytopenia associated with stannsoporfin. The underlying mechanism of this decreased platelet is unclear.

Next, I will briefly discuss the evaluation of potential long-term neurodevelopment outcomes. As we have already heard from Dr. Joseph, stannsoporfin was detected in the brain in CSF with

possible accumulation in non-clinical studies. However, the exact impact of tin exposure and heme-oxygenase inhibition on the brain is unknown. Based on known adverse neurological effects of other heavy metal exposure such as lead and the potential impact on neuroprotective function of heme-oxygenase on the developing brain, the Agency is concerned with potential long-term neurodevelopmental effects associated with stannsoporfin.

During the 2012 advisory committee meeting, the committee members expressed similar concerns and recommended the long-term neurodevelopmental outcome be evaluated in children at preschool age and during primary school age.

This table summarizes the available data from long-term extension trials. Note that study 205, the long-term extension trial to the pivotal trial, 204, is incomplete and still ongoing. At the time of the NDA submission, 35 pediatric patients completed year 1 assessment and 9 patients have completed year 2 follow-up assessments.

However, year 2 neurodevelopment assessment data was only available for 7 subjects. Only 23 patients from the long-term extension trial of the supportive study 202 completed the 3-year follow-up. Note that the majority of the long-term safety data is from study 01C3W, which enrolled a lower-risk population that is different from the pivotal study population.

Review of the integrated long-term safety data showed that pediatric patients treated with stannsoporfin reported numerically more speech and hearing disorders compared to placebo. It is interesting to note that 9 of the 10 patients who reported a speech disorder and 4 of the 5 patients who reported deafness in the 4.5 milligrams per kilogram arm were from study 01C3W, which enrolled a lower-risk population without risk factors for severe hyperbilirubinemia. As such, these patients would not be expected to be at risk for speech and hearing deficits associated with bilirubin neurotoxicity. This finding is concerning, but limited by the small sample size.

This figure shows the multiple instruments the applicant used to assess long-term neurodevelopmental effects in study participants for up to 6 years. Data from study 205, which is the long-term extension trial to the pivotal study, is shown in bold and italics.

At the time of application submission, year 2 data was only available for 7 patients in study 205. Note the lack of standardization and the type of instruments used across studies in the small number of assessment results currently available. Once again, majority of the long-term neurodevelopmental assessment data are from study 01C3W, which enrolled a lower-risk population than the population studied in the pivotal trial.

The applicant has discussed results from the long-term neurodevelopmental assessments in detail in their presentation earlier today. In general, similar results were observed across treatment arms within individual assessments.

However, we did note some differences between treatment arms that cannot be explained.

For example, in the Mullen scale, the drug groups scored lower at month 3 across all areas measured and also in visual reception at year 2. Again, this finding is limited by the small sample size and it is also unclear if the studies are adequately designed and powered to detect a long-term safety signal.

There are a number of limitations in the available long-term neurodevelopmental assessment data. First, study 205, the long-term extension study to pivotal trial 204, is ongoing with limited available data. For the completed studies, a high number of pediatric patients were lost to follow-up, discontinued, or did not enroll in the long-term extension trials. Majority of the neurodevelopmental data came from study 01C3W, which enrolled a lower-risk population than the pivotal trial. There is also a lack of standardization across studies in the enrolled population and in administration of the neurodevelopmental assessments. As shown previously, there was also variability in the

instruments used at different age ranges across studies. As a result, the data are not poolable across studies and limits the ability to detect a long-term safety signal.

So in summary, there is a need for additional therapies in neonates at risk for bilirubin-induced neurological dysfunction. There is a potential additive effect from stannsoporfin as an adjunct to phototherapy, including the potential to reduce the need for exchange transfusion. However, there are also a number of risks and uncertainties. There is an increased risk of photosensitivity-related adverse events and thrombocytopenia. Pediatric patients treated with stannsoporfin also appeared to have a higher rate of abnormal speech and hearing. The sparse long-term neurodevelopment data has not adequately assessed the potential neurodevelopmental adverse events for the duration recommended previously at the 2012 advisory committee meeting. Remaining uncertainties include the strength of the evidence demonstrated by a single pivotal trial as well as

the clinical meaningfulness of the percent change in total serum bilirubin alone. While the applicant proposed a dose of 4.5 milligrams per kilogram, the 3 milligrams per kilogram dose also achieved a statistically significant reduction in TSB in the pivotal trial, although this trend was not statistically significant in the secondary endpoints and in the supportive study 202. Finally, it is unclear if the limited long-term clinical outcome data is adequate to detect a long-term safety signal.

Given the risks and uncertainties that I have outlined in the previous slide, the agency is proposing implementation of additional safety post-marketing requirements if stannsoporfin is approved. Post-marketing requirements could include completion of the ongoing long-term extension study of the pivotal trial, study 205, and additional clinical studies to obtain adequate long-term neurodevelopmental data.

I will now turn the podium to my colleague, Dr. Charlotte Jones, from CDER's Division of Risk

Management. Thank you.

FDA Presentation – Charlotte Jones

DR. JONES: My name is Dr. Charlotte Jones. And I am a medical officer in the Division of Risk Management. During this presentation, I will review the regulatory authority and factors to be considered when the agency determines a risk evaluation and mitigation strategy, referred to as a REMS, is required.

I will briefly review the safety issues of stannsoporfin, which you have heard about in detail earlier. Finally, I will discuss the applicant's submitted proposal with the NDA for risk management and the FDA's REMS proposal.

A REMS is a risk mitigation plan that involves strategies to mitigate the risk beyond FDA-approved professional labeling. The FDA has the authority based on the Food and Drug Administration Amendments Act to require a REMS to achieve specific goals to mitigate risks associated with the drug when the agency determines that a REMS is necessary to ensure the benefits outweigh

the risk.

REMS allow patients to have access to medication with known or potential side effects that would preclude approval or lead to the drug being removed from the market.

The FDA has the authority to enforce REMS. When determining the need for a REMS, the agency must consider the estimated size of the population of patients likely to use the drug, how serious is the disease or condition that the drug treats, the benefit of the drug relative to the disease or condition, the length of time that patients will receive the drug, the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Lastly, is the drug a new molecular entity? The components that comprise a REMS include a medication guide or patient package insert which provides patient-friendly information, a communication plan to aid the sponsor's implementation of the REMS or inform providers

about serious risks, elements to assure safe use, which I will describe more fully with the next slide, an implementation system to ensure the REMS is implemented by the applicant in line with the FDA requirements.

Finally, a REMS must include a time table for submission of assessments. Assessments are done regularly to determine if the REMS is meeting its goals and if changes need to be made to improve its function.

Elements to assure safe use are requirements of the REMS that are put in place to, as the name implies, assure safe use. The regulations identify the following elements, but all may not be required.

Requiring healthcare providers to be certified or have received specialized training in order to prescribe the drug, requiring pharmacies or other dispensers of the drug to be certified, limiting the setting from which the drug can be dispensed or administered, for example hospitals, requiring specific safe-use conditions such as

counseling of patients or parents prior to treatment, requiring patients to undergo specific monitoring, and enrolling patients in a registry.

When determining the need for a REMS, the agency must consider, is an ETASU necessary? The ETASU must be commensurate with the risks in the label. ETASUs cannot be unduly burdensome to patient access, particularly those with serious or life-threatening disease, or patients who have difficulty accessing healthcare.

To minimize burdens, ETASUs must as is practical be designed to work with established distribution, procurement, and dispensing systems. The agency has identified the following factors contributing to safety concerns regarding the long-term neurodevelopmental risks in the developing brain; the presence of tin, a heavy, non-essential metal in the drug.

Stannsoporfin is an inhibitor of heme-oxygenase, which is reported in some studies to play a neuroprotective role in the brain. Additionally, there were preliminary safety

concerns for speech and hearing in the available data. Lastly, the long-term follow-up study is still underway at this time.

Based on these safety concerns, the agency considered how best to mitigate the risk and achieve the aims listed above, thus creating the proposed REMS that I will describe next.

How to restrict to the hospital setting, how to support use in the indicated population, how to support parents' desire for information and recognize their individualized risk-benefit assessment with counseling and the agency believes an enforceable risk management plan is appropriate.

The applicant submitted with the NDA application the above risk management plan, which included voluntary restriction to hospital pharmacies, which we note does not meet the aims we have just identified, including the lack of required counseling of parents to maintain risk transparency and a lack of enforceability.

The agency is proposing a REMS with the following ETASU with the letters from the

regulations identified. Drug is only dispensed in certified hospitals, safe-use conditions are present, parents are counseled, and patients are enrolled, and there is a registry of enrolled patients.

The agency is proposing a REMS with a goal of mitigating the potential risks of neurodevelopmental toxicity in neonates following the use of stannsoporfin by ensuring that stannsoporfin is dispensed and administered in healthcare facilities that are certified and, as a condition of certification, have expertise in the treatment of hyperbilirubinemia in neonates who may require an exchange transfusion, ensuring that healthcare providers are educated about the approved indications and limitations for use of stannsoporfin and the potential risk of long-term neurodevelopmental toxicity associated with its use.

Additional REMS goals include ensuring that parents are informed about the potential long-term neurodevelopmental risk of stannsoporfin and are

counseled on the need for obtaining neurodevelopmental screening. Lastly, all patients will be enrolled in a registry.

To achieve the goals just described, the agency is proposing the following REMS requirement. The restriction to healthcare settings requires that stannsoporfin is restricted to certified hospitals that attest they provide care for neonates with expertise in the treatment of hyperbilirubinemia in infants who may require an exchange transfusion.

The restriction to hospitals with expertise in caring for neonates who may require an exchange transfusion is a method of operationalizing that a hospital has staff with expertise in treating hyperbilirubinemia in order to become a certified healthcare setting in the REMS.

It also reinforces that the drug is not indicated to replace exchange transfusion, for example in infants with symptomatic acute bilirubin encephalopathy who, according to the 2004 AAP guideline, need treatment even if the bilirubin

level is falling.

Certified hospitals must implement within their own system policies and procedures to ensure that prescribers are trained, parents are counseled, and patients are enrolled.

The literature supports that parents have a desire to be aware of the risks of medical interventions, including drugs, their child receives.

In recognition of the value of patient voice and transparency as well as each parent's personal risk-benefit assessment, the REMS will have the proposed safe-use condition that the patient's parent is counseled regarding the potential long-term neurodevelopmental risk and the occurrence of counseling is documented on a patient enrollment form.

Lastly, the REMS proposal includes a registry. The registry will have two objectives. It will be used as a source of information to aid in the assessment of whether the REMS is meeting its objective related to whether the indicated

population is receiving the drug and are parents being counseled.

Independently, the registry will serve as a source for patient demographic information that will allow the applicant to approach parents who may elect to participate in potential post-marketing research.

The agency recognizes there are burdens associated with the REMS. These include hospitals using stannsoporfin which we will be required to put processes in place within their own medication use system so that patient selection, counseling, and enrollment take place as required by the REMS.

For parents, the burdens include they must receive counseling during what we acknowledge is a stressful time and they must enroll their child in a registry by providing demographic information which will support the REMS program functioning and provide a list of children who have received stannsoporfin whose parents may subsequently elect to participate in potential post-marketing research. Thank you.

Clarifying Questions

DR. COLE: We will now take some clarifying questions for the presenters. Please state your name for the record. And if you can, please direct questions to a specific presenter. Also, for those who wish to ask questions, please stand up your nametag, name badge. Yes?

DR. DRACKER: Bob Dracker, Syracuse. Not to belabor a point, but I just want to mention phototherapy alone is known to induce transient thrombocytopenia in newborns. It's thought to be possibly related to the phototherapy itself or perhaps the fall in bilirubin.

Second of all, I would have liked to have seen, again, a comparison of oxidative stress in the trial 64 looking at phototherapy versus stannsoporfin, especially if there's combined modalities.

Finally, I feel the oxidative stress issue may be related to both the decrease in the platelet count, although transient, and possible neurodevelopmental effects.

DR. COLE: Thank you. Any response from the FDA to any of those comments? Hearing none, Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I have a question for Dr. Jones about the REMS. I did not know if the REMS could be written such that it could be restricted to only be given to babies who fail phototherapy, so essentially, could the REMS be written in such a way that it's only allowed to be given in babies who fail phototherapy, who people are then preparing for an exchange transfusion, therefore not giving it to every baby who is at risk, but giving it to babies as people are preparing for the exchange. And I'm not a neonatologist.

DR. WILKINS-PARKER: Hi, I'm Jamie Wilkins. I'll be answering the REMS questions. To address your question, anything that's required in the REMS will follow the labeling. So the product labeling would need to restrict the product to only use in babies that fail phototherapy. And therefore, that requirement could be written into any REMS program.

DR. COLE: Very good. Dr. Rosen?

DR. ROSEN: So I have two questions. One is to Dr. Joseph and then the second is to Dr. Jones. So what you heard Dr. Havens and I still concerned about is the accumulation of this in the liver. Right? And what is this doing to the shift? And I didn't really get an answer about, like, is this going to shift the bilirubin curve so we're getting late peaks because this drug is hanging around in the liver?

Do you have any sense from animal data about if there's models of hyperbilirubinemia where this drug was used to see what this does to shift the curve? And is there any evidence besides the ones that you presented in animal models to show kind of what the sustained liver exposure does to the bilirubin curve.

Then I guess for the risk evaluation, I'm trying to envision what an informed consent for a family would mean. So we're basically asking a family to take a drug that may have neurotoxicity to prevent something that might cause

neurotoxicity, with no numbers to give the family on risk on either side. And I think this is what I think a lot of us are uncomfortable with, because I don't know how to give an informed consent to this family or to explain this to a family. What's the risk of neurotoxicity related to the fact that you have hyperbili.

Well, it's not just the hyperbili. It's the other risk factors, too. What's the risk factor of neurotoxicity of this drug? Well, I don't know that, either, so I think it's very hard for a family to make an informed decision when we don't really have numbers on either side, so I guess I would ask how does that factor in?

Kind of giving the family information is an important part of this risk evaluation, but I as a physician don't think I can do that based on any of the data that I have. So how do you envision that when we don't have the perfect data?

DR. JOSEPH: Again, my name is David Joseph from DGIEP. First thing I should do is apologize, because I don't think I can answer your question

regarding the testing of stannsoporfin in models of hyperbilirubinemia.

The sponsor did cite an old publication in neonatal rats, which spontaneously develop hyperbilirubinemia. They just showed that the drug is effective. Or the applicant may actually be able to better respond to your question or not.

I do want to add a couple of comments. The liver accumulation was seen in dogs. It was not seen in rats. And sometimes, two species will give you two different findings. We don't know which one is really relevant or predictive to what happens in humans unless the applicant has some information that they want to share.

Another point -- and I should have made it in my presentation -- yes, we did see marked drug accumulation in dog liver, but there was no pathology, no sign of hepatocellular injury.

DR. ROSEN: To begin to address that, did you want to start?

DR. KORVICK: Dr. Korvick, deputy director for safety, DGIEP. And I wanted to address your

question a little bit. I'm not going to give you the answer, but I think regarding how you would get informed consent is a question that you may need to approach after the committee decides what they think about the efficacy and safety of the drug, because it would seem that you would have to make the decision as a clinician as to whether or not this patient would qualify for this drug.

I think that's an important part of the consideration and then, maybe in our discussion later, we can talk about how the consent might work or at least the documentation that they received the materials. Whether or not you had a REMS or a risk management program, you're going to have to present some information to the parents of the patient.

DR. COLE: Thank you. Dr. Adams?

DR. ADAMS: I have a couple of REMS questions. So the first question is regarding the recommendation to ensure that hospitals really are certified to use this treatment and deliver it appropriately. And I wonder also about whether the

FDA has considered further certification regarding the back end long-term neurodevelopmental follow-up to ensure that there was an infrastructure and qualified persons in place to conduct the neurodevelopmental assessments in the out months and years for these children, since this seems to be a key question in the safety data.

Related to that, I would also ask -- and this might be a question both for FDA and for the sponsor, how then, even if folks are identified who can conduct that assessment, how that actually takes place.

In my experience as a clinician, a clinical researcher, often being asked to do these long-term assessments, what happens is that a provider comes to me and says this child is due for their 4-year follow-up and you're the neuropsychologist here at this hospital. Can you do the assessment? I say, "Great. How are we funding that? How are we covering that?"

So insurance isn't going to cover it and the sponsor doesn't cover it in their budget because

the kids are now 4 years out from participating and receiving the drug and there's no research budget, either. So we have to think about the practicalities of that and not leave it in the lap of the families to figure out how they go about getting these assessments that were recommended to them and that should be informative, not just for the safety monitoring long term, but also potentially the services that their child requires.

DR. COLE: Thank you. Dr. Newman?

DR. NEWMAN: Thank you. So just in answer to Dr. Rosen, actually, the risk of bilirubin neurotoxicity at bilirubin levels in this range is unmeasurably low. It's just they're far, far away from the range where we would worry about that.

So really, what we're talking about is shortening the duration of phototherapy, possibly reducing the risk of exchange transfusion, but if that's the indication for which the company wants to sell the drug, then they should do a study that shows that it does that, which they haven't.

I want to sort of echo what Dr. Adams said

about my concern about the plan to do a long-term follow-up cohort study of 800 to 1,000 kids. It looks like I'm looking at slide 16 here of the evaluation of potential long-term neurodevelopmental outcomes that, in the studies that were done by InfaCare, I guess to help with approval, the loss to follow-up rate was about 60 percent or, I mean, it looks like you end up with a small subset of those that you actually can -- and that's only for, like, two or three years.

Getting into school age is -- I think Dr. White should be able to tell whether they're actually having problems with school -- even harder. And then the problem you have is it's not blinded and you have no control group, so the people who continued to participate may be the ones who are worried about their child not doing well and wanting to get all that testing, so then the results become very hard to interpret.

DR. COLE: Dr. Adams?

DR. ADAMS: If I could just jump in, I want to piggyback on what Dr. Newman is saying. Yes,

folks who follow up may be more motivated to do so because they have some concern about signal of neurodevelopmental issues, but also families who follow up may have more resources to do so.

So that may also bias and skew your findings. I forgot to also ask about, on that slide, which is I believe slide -- goodness, whatever it is; it's the slide that lists the assessments that would be considered for the REMS, a global measure of development and intellect, slide 22.

There's been so much discussion from both sides about potential speech and language disorders as where the greatest signal is. So I would wonder about requiring assessment of speech and language, not just global evaluations in cognition or development.

Then I think the rest can wait.

DR. WILKINS-PARKER: Can I make a clarification about the REMS? The REMS and the long-term follow-up studies are different entities. The REMS registry would provide access to the

demographic information of all the patients who received the drug in order for parents to elect to participate in those long-term follow-up studies.

DR. ADAMS: Thank you. Thank you very much.

DR. COLE: Dr. Havens?

DR. HAVENS: I had a couple of questions. One, since the REMS suggests a registry, would that be anticipated that, that would require IRB approval at each site since we can't put any of our patients in any registry without IRB approval? I assume that would be similar at other sites.

Has that been the FDA's experience with these registries?

DR. WILKINS-PARKER: So again to clarify, there is a statute in the FDA Amendments Act about REMS registries, that a REMS registry functions as a repository of demographic information for access to post-marketing studies.

That post-marketing study would be what would be conducted by the sponsor to get those further safety data that they were describing earlier. So the REMS registry itself isn't an IRB

function. It's simply a way to give us the regulatory authority for the sponsor to have access to the information for their post-marketing studies.

DR. HAVENS: Then as a part of that, you require that they do the studies and pay for them in follow-up?

DR. WILKINS-PARKER: The parents?

DR. HAVENS: That you require that the sponsor perform the study and do the follow-up on patients whose names they have?

DR. WILKINS-PARKER: That would depend on the structure of their post-marketing study. I'm not sure if our clinical reviewers have any other comments on that, but the post-marketing requirement studies would be a part of their approval and whatever they would need to be required to do to execute those studies would be part of their approval package.

DR. HAVENS: Thank you. Then I had a separate question on the low platelet counts. And who did the thrombocytopenia, the awesome

thrombocytopenia slide? Thank you very much. So whoever did that gets extra credit. Okay?

So was there a relationship with infection and thrombocytopenia? I ask that because heme-oxygenase is an antioxidant. And if you block heme-oxygenase, then you may increase the oxidative damage caused by any infection. We saw in the sponsor's presentation that hearing loss was associated with infection. Presumably, the kids in the other group had as many otitis media episodes as the kids in the treated group.

So you would have to argue potentially that the effects of the infection, because of the loss of an antioxidant effect from heme-oxygenase blockage might make the effects of the infection worse. So I was interested to know, in this context of thrombocytopenia, were they associated with infection?

Then do you know how many infections happened in the groups without thrombocytopenia again and untreated, arguing for the potential for increased oxidative damage related to blocking

heme-oxygenase activity?

DR. PEI: So I think your point is well taken and an important one. We have not conducted the specific analysis to look at the relationship between infection and thrombocytopenia, but I do note that the applicant has done a lot of research as far as looking into the possibility to explain the mechanism of thrombocytopenia.

Also, in the 2 patients that required platelet transfusions where their platelets fell significantly below to less than 50, both of them; they were not associated with sepsis, or one was being worked up, but ended up that the culture was negative, so did not require, and the other was in conjunction with a post-exchange transfusion thrombocytopenia, which the applicant attributed to exchange transfusion.

But perhaps the applicant would like to comment on the thrombocytopenia in association with infection.

DR. OMOKARO: I would just add, prior to that, that while we will perform those subgroup

analyses as you have suggested, the information from the database is very small to be able to make conclusions.

DR. HAVENS: Thank you.

DR. COLE: Dr. Assis?

DR. PEI: Yes, David Assis, hepatology. I have a question, one about efficacy and one just a follow-up question about safety. To follow up on Dr. Newman's comments, at least in adult hepatology and part of GIDAC meetings, I think we've spent traditionally a tremendous amount of time trying to understand what is a surrogate marker for the outcome of interest and what is the true outcome of interest.

I have to confess I'm a bit confused in this situation. I think the opening statements here led me to believe that the prevention of neurotoxicity from hyperbilirubinemia or ultimately kernicterus was the overall goal.

I realize that a study that would account for those very rare events would not be feasible and so I'm assuming, perhaps incorrectly, that a

surrogate for that would be perhaps exchange transfusion or some combination of events.

So what my question I guess to FDA is, when looking at reduction in total bilirubin at 48 hours, is that sufficient surrogate of a surrogate? And specifically because the populations had a preponderance, from what I understand, of patients at moderate risk and there were no exchange events.

So was this an adequate study to answer the ultimate question? And if not, what are we looking at with the primary endpoint. Was that truly a surrogate and has that been developed as far as FDA is concerned?

Then a brief comment as far as safety; I realize that different models, I should say, that you could have a different response in terms of liver staining and so forth. But since induction of heme-oxygenase can be quite helpful in preventing significant inflammatory injury to the liver, it would be helpful if there had been studies performed in both models to see if, long term, there was any prevention of inducible injury

to the liver because I think that long-term liver response such as by macrophages would be quite relevant to study.

DR. OMOKARO: Thank you for your questions and comments. Regarding your first question regarding efficacy; I think really, that's what the FDA is grappling here with the data and looking towards the committee, the expertise in the committee to be able to help us really delve into and consider, you know, whether bilirubin is a biomarker, is a surrogate marker, reasonably likely to predict benefit or, you know, what other possible sort of outcome measures that we could look at here within the study to be able to answer these questions.

So I think it's really important to discuss today what you've mentioned. And in terms of your second comment, Dr. Joseph, do you have any further -- okay. So just continue discussion within the committee today.

DR. COLE: Thank you. Dr. Khurana?

DR. KHURANA: Sandeep Khurana, hepatology.

I just want to echo Dr. Assis's comments, but in a much more 40,000 view. Based on the toxicity profile for this new drug, you almost think if phototherapy alone or placebo is an appropriate comparator to the study.

That's something to keep in mind because I would assume that exchange transfusion is probably the other form of therapy. So is it an appropriate comparator when it comes to looking at the impact of the drug, something that we can discuss further, but that's exactly, I think, what Dr. Assis was getting to.

DR. COLE: Dr. White?

DR. WHITE: Michael White, New Orleans. I've got several things I'm confused about. One, in the dogs that you were giving pretty hefty doses that didn't grow -- and I think that was Dr. Joseph maybe. Did you see catch-up growth when you stopped giving it?

You didn't sacrifice the animals for 6 months, it sounds like, from what you were describing. Did those dogs show catch-up growth

afterwards?

DR. JOSEPH: David Joseph from FDA. So just to clarify on the study design, there was actually 4 sacrifice time points. So you had a group sacrificed at the end of 28-day treatment, 30 days, a 30-day recovery, 3-month recovery, and finally 6-month recovery.

I'm trying to recall. So there was growth after discontinuation of treatment and, as I recall and the applicant can correct me, in the high-dose dogs, the growth never did recover completely equal to the control animals. I believe, at least in the high-dose dogs, even up to 6 months after termination of treatment, final body weight was still lower than the control group. And I believe that was only in the high-dose group.

DR. WHITE: Then the other question I had was -- and I think you spoke to this as well -- the radioactive tin labeling of the brain; we still don't understand the metabolism of the drug that we're dealing with. How do we know that radioactivity in the brain that stays there is the

drug, or not a metabolite, or not just hanging around in some phagocytic cell inside the Golgi apparatus, or just kind of hanging out?

DR. JOSEPH: That's an excellent question.

DR. WHITE: I mean, it strikes me that, if we really wanted to know the answer to that, we could grind up some rat brains and run them off on a gel and find out if it's the right molecular weight or not to even know that it's the same compound that we're concerned about.

I mean, if it's just radioactive tin and this drug is not associated with it, that's a totally different endpoint that might not distress me so much because we're not going to be giving radioactive tin when we give this to the kids.

DR. JOSEPH: I mean, we have no data. I mean, the assumption would be of course stannsoporfin used clinically contains tin, not radioactive tin, but if radioactive tin persists into the brain and more so in the CSF, it would be a reasonable assumption that non-radioactive tin would persist in the same way.

DR. WHITE: But you would think that -- I mean, I cook with some things that have tin in them and I'm sure I get tin in my water. So I'm not sure that this means anything if it's just the radioactive tin that we're picking up.

DR. JOSEPH: Yes. It's difficult. It's really difficult to assess.

DR. WHITE: I'm sorry. I'm persisting because I'm confused again. You were speaking to the heme. As the heme levels go up, it induces the heme-oxygenenase. So the questions about what's happening with this question of radicals; I'm sorry.

Dr. Dracker, you were worried about the oxidative stress because this is being inhibited by the drug, but the inhibition by the drug is going to be very slow or very short lived because it's only a half-life of 10 hours.

During that period of time, the heme is going up and inducing the oxygenase. I'm very confused by what the sum total of this might even be.

DR. DRACKER: Michael, what I was suggesting is that it was an indirect effect on increasing oxidative stress by decreasing unconjugated bilirubin, which is a major antioxidant for newborns.

DR. WHITE: I still can't put that together quite in my head.

DR. HAVENS: But there would be a direct effect on increasing oxidative stress as we've heard over here because heme-oxygenase is an important antioxidant.

DR. WHITE: I know, but it's being induced by the increased heme.

DR. HAVENS: But it's being blocked by the drug itself.

DR. WHITE: Only for maybe 3 days.

DR. HAVENS: Well, no. That's only if you assume that it's the plasma concentration that is the most important part of it and there's tissue deposition and the drug lasts longer than that, especially at the higher dose, because it keeps the bilirubin down. So I think that, I mean --

DR. WHITE: The metabolism and how it functions in a half-life of 10 hours don't all fit together in my head at all. It raises questions and goes back to what's in the head with the tin as well. And then finally, in the information you guys gave us, the third endpoint that you were going to look at was rebound hyperbilirubinemia as defined in the protocol was not met with statistical significance between the groups.

So it doesn't look like we can really comment about whether there's a significant degree of rebound hyperbilirubinemia in the face of the 3 milligrams per kilogram or the 4.5 milligrams per kilogram dose. Is that fair; we just don't know or we didn't look at it because the secondary endpoint wasn't met, so we didn't look at the third one?

DR. OMOKARO: Yes. We looked at it in terms of clinical interest, but in terms of the statistical procedure that was pre-specified, if there was any non-significant result.

DR. WHITE: You didn't go to the next one.

DR. OMOKARO: Exactly, but just looking at the data, we did present the data on rebound hyperbilirubinemia in slide 14 of our efficacy slides and you can see that the 4.5 milligrams per kilogram for both populations that were described had 1 patient that experienced it in the 4.5 and no patients in the 3 milligrams per kilogram compared to 3 in placebo.

DR. WHITE: So I'm sorry. Was that statistically significant because of the numbers? That's very small numbers.

DR. OMOKARO: I think I'll have our stats colleagues comment on this. Because of the testing procedure, I'll just have them speak to that point.

DR. FONG CHEN: This is Yeh Fong Chen. I'm a statistical team leader. Because of the procedure we adopted, they failed on the 3 milligrams for the first key, so technically, they shouldn't continue to test for the other keys.

DR. COLE: We have time for two more clarifying questions before we break for lunch. We have the open public hearings coming up where we

have invited guests. We want to try to stay on schedules here.

DR. WHITE: Thank you for your indulgence.

DR. COLE: Dr. Aly?

DR. ALY: Yes. I just want to stratify two different conditions here. There's one condition, a baby who has a very high bilirubin level that's close, what Dr. Newman has brought in the first stage that is very close to exchange transfusion or even without exchange transfusion. Studies showed that babies with high bilirubin neurodevelopmentally are not the same as babies with lower bilirubin levels and we have seen a drug here that is efficacious in bringing that bilirubin down.

Then there is another condition that a baby who just has hemolysis with reticulocyte count of 6 percent or higher, but not necessarily very high bilirubin level that is close to exchange transfusion.

So now, we have the dilemma in this other population. So we have a drug that potentially can

add to the oxidative stress in a baby who basically the bilirubin could have been fixed by the phototherapy alone, but will take an extra 10 hours.

But the first population I'm coming back to, which is a baby with a very high bilirubin, could potentially need exchange transfusion. We don't currently treat these babies with phototherapy alone. We start to use off-label IVIG that is not studied and though here at least we have data on some safety compared to IVIG that we don't have that data, so it's important to look to these two different stages.

DR. COLE: Thank you. Ms. Boyce?

MS. BOYCE: Hi. So Danielle Boyce, and I'm a patient rep. So I understand that we're trying to prevent kernicterus, which has horrible neurodevelopmental effects. And I understand what that's like because I have a child who had infantile spasms. And he has an intellectual disability.

But at the same time, what I'm struggling

with is this long-term data on neurodevelopmental effects and it's unclear to me what to make of this and the safety data.

The applicant mentioned mother's age as a potential explanatory factor for the speech and language problems. And I'm wondering if the FDA can speak to that or do we not feel we can stratify by that because the N is so small?

DR. OMOKARO: I think both those answers; we have not looked at that yet, but the numbers are too small to make conclusions, is what we're saying.

Just in terms of how that would actually impact on neurodevelopment, I think maybe the neurodevelopmental experts in this room may be able to comment on that.

DR. COLE: Dr. Adams?

DR. ADAMS: I think, like the early discussions about how hyperbilirubinemia and risk for it is defined not just by TSB level, but by multiple risk factors, the same is also true for risk for language and speech delay or other

neurodevelopmental delays. And so I wouldn't hang it on maternal age without understanding the totality of what the story is.

But age alone of the mother shouldn't predict a child's neurodevelopmental outcome, assuming the mother is a healthy child-bearing adult, so just to answer that question specifically.

DR. COLE: So we'll take three more clarifying questions after lunch, so we'll adjourn for lunch now. Please be in your seats with your white traveling jerseys with the blue numerals on them by five minutes of 1:00. Thank you.

(Whereupon, at 12:19 p.m., a lunch recess was taken.)

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

(12:58 p.m.)

Open Public Hearing

DR. COLE: Good afternoon. Please take your seats. We're now about to begin the open public hearing. We'll take three additional clarifying questions from the committee members for the FDA at the end of the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may

include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ROSENFELD: Good afternoon. I'm Dr. Warren Rosenfeld. I am chairman of pediatrics at South Nassau Communities Hospital. I'm also a professor at the State University of New York in Stony Brook. I'm a neonatologist and pediatrician.

I was an investigator on the 204 and 205 study and had been on the scientific advisory board of InfaCare.

I am pleased to have the opportunity today to talk to you about what I think is an important step forward in the treatment of neonatal jaundice. Jaundice remains a clinical issue in 80 percent of the 4 million babies born in the United States each year and, every day, any clinicians seeing babies in the nursery must make a decision about bilirubin.

Fourteen years ago, the American Academy of Pediatrics created a subcommittee to develop

guidelines for the management of hyperbilirubinemia. And I along with several other people that are here in the room have the privilege of sitting on that committee.

The guidelines were successful in creating a rational and organized approach to the management of neonatal jaundice. It provided a guideline on how to monitor patients for hyperbilirubinemia and, once it did occur, on how to treat it, usually with phototherapy.

At that time, there were no options available to prevent bilirubin production.

Today, there are several additional factors that come into play about how we handle hyperbilirubinemia in the nursery. One, it is difficult to define when a baby's bilirubin level will peak and, in most babies, that occurs at 72 to 96 hours, except in those 83 percent of breastfed babies in the United States now whose bilirubins usually peak about a day after.

This creates a dilemma for us as clinicians to try to predict what the bilirubin level is going

to be after the baby is discharged and Dr. Bhutani helped us out by trying to find a way to predict this risk.

As a result, many newborns not only are checked for bilirubin in the nursery, but also require coming back to the hospital to be checked in subsequent days. I also, like most providers, believe that we had an effective means of treating babies with jaundice and that was phototherapy.

I was one of those complacent clinicians who marveled how quickly we could reduce bilirubin levels, especially as we increased the intensity of our light sources. When phototherapy was first introduced, we were happy to generate 5 to 10 microwatts per centimeter squared per nanometer of irradiance.

We exposed only 40 percent of the baby's body to phototherapy. Today, we're generating 30 to 40 microwatts of irradiance and we're covering 80 percent of the baby's skin.

Does this new intensity come at some cost? Some studies have looked at the potential side

effects of phototherapy and, while not definitive, they certainly raise questions that need to be pursued. I'd also like to talk about oxidative stress. One of the ways phototherapy could potentially cause harm is that it is a very photooxidative-generating treatment.

Other side effects of phototherapy, while not as dramatic, have significant importance to new mothers and their babies. Mothers are separated from their babies and breastfeeding is often stopped.

All of these issues add to the difficulty of treating babies with hemolysis and this is where I believe stannsoporfin can be useful and effective. It can best be illustrated by telling you about a baby I had in the nursery just last week. A 36-week infant, diabetic, breastfed baby with ABO incompatibility was placed under phototherapy at 10 hours of life.

The lights were stopped at 23 hours of age when bilirubin levels fell far below treatment threshold. Rebound bilirubins were measured over

the next 24 hours and remained stable.

The baby was discharged with an outpatient follow-up in 24 hours. And lo and behold, at 4 days of life, the bilirubin had again risen to levels that were far above the treatment level requiring the baby to be readmitted to the hospital and continue to be followed after that second course of phototherapy.

This is not an unusual occurrence, as demonstrated by the data presented this morning, where one quarter of the babies in the placebo group required a second course of phototherapy.

This brings us to consideration of stannsoporfin as addition to the strategies to treat hyperbilirubinemia. If we can prevent bilirubin production, phototherapy may be shortened and numerous blood tests eliminated and readmission prevented.

As an investigator, it was gratifying that no serious effects were found to see how effective stannsoporfin was. In this high-risk group for hyperbilirubinemia, the duration of phototherapy

was decreased, hospital stays were shortened, and readmission greatly reduced.

Neonatal jaundice is an old problem and we still have old and only partially effective treatments. It is my hope we may still have a new treatment and another treatment option available to treat this condition. Thank you.

DR. COLE: Thank you, Dr. Rosenfeld. Will speaker number 2 step up to the podium and introduce yourself? State your name and any organization you are representing for the record.

MS. BUCK: Good afternoon. My name is Lauren Buck.

DR. COLE: Could you try to get that microphone right down close to your face there? Thank you.

MS. BUCK: Can you hear me again? Okay. My name is Lauren Buck and I'm here all the way from Las Vegas, Nevada. I'm 21 now, but when I was pregnant at 18, I knew my whole life was about to change. I was carrying a little life inside me that me and my fiance (phonetic) at the time were

so excited to meet.

We were ready to be parents, but as any other young parents, also a little scared. I went to all my check-ups and monitored how I felt through my pregnancy like normal and my baby boy was always right where he should be developmentally based on what the nurses and doctors would say. It never crossed my mind that, as soon as he came out into this world, he would have any sort of health issues since nobody ever told me that it was possible.

I thought the baby in my belly would be the strongest and healthiest baby that was ever born. Who knew I wouldn't have control over what happens to him so soon after meeting him? It was my job to protect him.

I'm here to talk about my son, Jace, and I's experience after giving birth to him and having been told he was diagnosed with jaundice. I didn't know what that was and, when they said he only had a mild case, they wanted to monitor him very closely so it didn't get worse.

Unfortunately, it did and he was admitted into the NICU. I myself was recovering from the birth, so it was an emotional rollercoaster finding out that I didn't get to go home with my new baby boy. I couldn't imagine how scared he felt laying on that table with the lights being blasted on his body and having to wear glasses to cover his eyes that he barely knew how to use.

My biggest goal and what I couldn't stress enough to all the nurses I met was that I wanted to breastfeed and only breastfeed for at least the first year. That was my goal. One thing I was told that made a lot of sense to me was that I knew as soon as he drank formula that, that experience was ruined.

It's more filling. It's less intimate and pretty much would ruin my bond with my baby if I didn't breastfeed. Up until the day I had to leave the hospital without my baby, I thought it was going great. I'm going to really try hard to do this and it's what I'm meant to do. Breast is best, is what I was always told.

But him being in the NICU away from me stopped that experience in its tracks. They gave him formula in there. They said he needs it since I wasn't there, but that's not fair. I wanted to be there, but I needed rest myself and the hospital already checked me out.

I had to go home and leave my baby alone with people he didn't know and was not his family. Not too soon before I got checked out of the hospital, I remembered a guy coming in my room to say that there was something we could do to make this process speed up and get my baby back into my arms.

He said we can administer this shot. It's not quite yet approved from the Food and Drug Administration, but it has been proven over years and years of different cases, that this shot is our best option for a quicker recovery.

He explained the study and what the drug is supposed to do. I believed in it and let them put my baby into the system as a child case. I was told we don't actually know whether or not he got

the drug or a placebo shot, but I don't think it did any harm.

Obviously, I've never been a mom or had a baby with jaundice, so I wouldn't know the normal duration of the sickness, but I do believe the nurses did everything they can to get him out of there in a timely fashion.

I finally got home with my baby and that's when the real bonding began, but, like, going back and forth through the hospital was the hardest part. It was really tough on me and my family. I was recovering from the birth, so the only one who was able to help me get back and forth to the hospital was my grandma, who came into town from Oregon.

Everybody else had to work. Nobody could put their life on hold just to help me and my son. She would run out over to the front of the hospital, grab a wheelchair, and push me all the way up to the NICU, where my baby was.

I never imagined having my grandma push me in a wheelchair. I always thought it'd be the

other way around one day. Jace's the strongest man and I'll never stop loving him. That is my son.

I took him to all his check-ups and eagerly waited for the pediatrician to give us the okay and tell him that everything was fine. And he always was. I wanted to share my story with you today to help you understand why a treatment like this is needed.

Like I said, I don't know if he got the shot or not, but I don't think it did any harm and he's amazing. He's huge. He's very on track with developmental, so that's all I have to say. Thank you.

DR. COLE: Thank you very much. Will speaker number 3 step up to the podium and introduce yourself? And please state your name and any organization you represent.

MS. CONWAY-ORGEL: A little step up. Good afternoon. My name is Margaret Conway-Orgel and I'm a neonatal nurse practitioner at the Medical University of South Carolina. My travel has been supported by Mallinckrodt Pharmaceuticals.

However, I have come here on my own time to speak to you about how stannsoporfin can possibly provide advancement in treatment of hyperbilirubinemia in the neonatal population.

I've been a neonatal nurse practitioner for over 35 years, so I am here to share my clinical experiences over the years. In addition to my clinical expertise, I am a mother of premature twins and have had the experience of being unable to provide comfort or nutrition to my children due to phototherapy to treat hyperbilirubinemia.

Hyperbilirubinemia has a major impact on long-term developmental outcomes and that we know in the neonatal population. And phototherapy, while beneficial, is a physical barrier to the critical interface that takes place at the same time between a mother and her children.

While reducing serum bilirubin to decrease the risk of kernicterus is a priority, establishing and sustaining breastfeeding during this time is also a priority as a concomitant therapy and reduction in bilirubin and as a crucial component

in optimizing nutrition and conveying immunity to the vulnerable child.

Phototherapy to a parent is scary. It is also a physical barrier and can send a message that the baby is not well despite assurances that the baby is okay. In many situations, parents are discouraged from holding their infant while under phototherapy with additional limitations of time that the baby can be held, only to be breastfed or bottle fed.

This in turn reduces the time at breast, delaying lactogenesis and possibly extending the time that phototherapy is needed. Babies are generally uncomfortable while receiving phototherapy and, to a mom who is unable to hold her baby to offer comfort because the baby is under lights, this will increase her stress, anxiety, feelings of guilt or inadequacy to provide comfort or care for her child.

The emotional stress can also reduce breast milk production, thus continuing the cycle of decreased lactogenesis and, in some cases, the

choice will be made to give her baby formula to provide a measurable volume of feeding.

Additionally, if phototherapy alone does not reduce very high bilirubin levels, as a part of my treatment, I may need to give this infant IVIG, which is intravenous immunoglobulin, or perform a double-volume exchange transfusion, possibly exposing a baby to antibodies for multiple blood donors and, in the case of an exchange transfusion, putting an otherwise healthy child at risk for such things as clotting disorders, electrolyte imbalances, infection, or necrosis to the bowel.

Babies who require this degree of invasive intervention are hospitalized in neonatal ICUs for an extended period away from their families and at risk for complications associated with hospital stays.

With the introduction of stannsoporfin into the toolbox of neonatal clinicians, I may now be able to reduce the amount of time that a select group of term and late pre-term infants and their moms are kept apart due to the confines of

phototherapy.

I could also reduce the chance that this at-risk population would require things such as double-volume exchange transfusions or administration of IVIG. Stannsoporfin can also help reduce the degree that bilirubin rebounds after phototherapy is discontinued, reducing the chances that a baby may require phototherapy for a second time.

This is also important, as I may be able to discharge a baby sooner to his family with less concern for either frequent bilirubin checks in the pediatrician office that need to start home phototherapy or even readmission to the hospital due to a return to a high level of bilirubin that would necessitate, excuse me, close monitoring.

Having the knowledge that stannsoporfin will be available to a pediatrician in their office will also provide me reassurance that there is an additional layer of safety for those at-risk infants who are discharged home at 48 hours with their moms.

When infants follow up the day after discharge, I know that there is a rapid rate of rise at this time and that the pediatrician, if needed, could administer the medication, which would help reduce the bilirubin levels in subsequent days and keep babies home with their moms.

As much as we would like to believe that, in 2018, infants don't develop kernicterus, it is still occurring and, even with close monitoring, there will be at-risk babies who will quickly reach dangerous levels of bilirubin and half-life long disabilities.

I am confident that, after reviewing the data presented today, this panel will approve the use of stannsoporfin in treating hyperbilirubinemia. And thank you for allowing me to present my opinion.

DR. COLE: Thank you very much. Will speaker number 4 step up to the podium and introduce yourself? State your name and any organization you represent.

MR. CLINGHAM: Good afternoon. Thank you for allowing me time to address today's advisory board. My name is Gavin Clingham and I am here representing the National Coalition for Infant Health.

The National Coalition for Infant Health is a collaborative of over 150 professional clinical community health and family support organizations focused on improving the lives of premature infants and their families.

The coalition's mission is to provide lifelong clinical, health, education, and supportive services needed by premature infants and their families. The coalition prioritized the safety and development of this vulnerable population and their access to approved therapies.

Extremely premature infants are incredibly vulnerable and an often voiceless population that faces very serious medical complications due to their early birth. These complications could have lifelong impact not only on the baby, but also on the family.

In spite of the many complications in these patients' vulnerability, innovations related to therapies specifically for neonates are lagging.

Due to the difficulty of developing these new therapies, lack of incentives for investment, and challenges with testing these therapies, a new drug has not been approved to improve survival and outcomes in the premature infant population in more than 20 years. That's about the time of the original Blackberry, Napster music downloads, and AOL instant messaging, all ancient technology by today's standards.

Almost two decades represents an eternity in the field of science, medicine, and technology. The coalition is pleased to see a new therapy before the committee today because it means that there are companies out there working to innovate and provide new treatment therapies that are specifically designed and approved for the neonatal population.

Premature infants are not tiny adults. We need innovation tailored to these tiniest babies.

The therapy being considered here today and others in the pipeline will begin to fill the innovation gap that currently exists and will give clinicians, parents, and caregivers more treatment options for their babies.

New approaches and new options for treating conditions like jaundice could mean improved experiences for the baby and the mother. Physicians and nurses need to have access to a wide range of safe, approved therapies so they along with parents can determine what is the best course of care for these babies.

Thank you for considering this application today and thank you for the opportunity to speak.

DR. COLE: Thank you very much. Will speaker number 5 step up to the podium and introduce yourself? State your name and any organization you represent.

MS. FERGUSON: Good afternoon again. I am here to represent Sonya Ferguson, who is unfortunately unable to be here due to illness. I'm just going to read to you what her statement

was, so please bear with me.

So it says, "My name is Sonya Ferguson and I am here representing Hand to Hold, a nonprofit organization that supports parents of premature and medically fragile children in the NICU. I am also the parent of a premature child who spent 75 days in the NICU.

"I am here representing the tens of thousands of family like mine that Hand to Hold supports each year. Of the 500,000 premature babies born each year, 75 percent of them are born between 34 and 36 and 6/7 weeks' gestation.

"Late premature infants account for about 20 percent of admissions to the NICU and are more likely to be re-hospitalized within the first two weeks of discharge. The morbidity rate approximately doubles for every week below 38 weeks' gestational age that a baby is born.

"Research indicates that even if a full-term baby of 38 weeks gestation has double the mortality of a 40-week infant. Over the past decade, medical professionals have had an increased awareness of

the special problems that the late pre-term and near-term populations often face, including higher risk for jaundice, breathing problems, increased blood sugar, and feeding issues, which would be related to the inability to regulate suck, swallow, and breathing, which is required to nurse or bottle feed.

"They are more likely to require admission to the NICU and, sadly, their challenges do not end at hospital discharge. This medically fragile population is more likely to be readmitted to the hospital because of their underdeveloped immune system.

"Research indicates that the risk for developmental delay or disability is 36 percent higher than full-term infants. While doctors are more acutely aware of these challenges, few advancements in the treatment of the late pre-term and near-term populations have been made.

"Along with the difficulties that premature infants face in battling for their lives comes the added negative impact of parental bonding

difficulties. From firsthand experience, I can tell you that trying to make a connection with your child from the outside of a glass box is heart-breaking.

"Not knowing if your child knows who you are, can sense your presence, or will ever properly connect with you is debilitating. Will my child know my touch, my smell? Will he know how to breastfeed when he's ready? And all the while, blaming yourself for making this happen.

"The Huffington Post recently released an article on the prevalence of post-partum depression in the NICU mothers, stating, 'Based on the most conservative of estimates, 11 percent of moms in the United States suffer from symptoms of post-partum depression and post-partum anxiety may be even more common.'

"But NICU mothers suffer from post-partum mood issues at much higher rates. There are no hard and fast numbers, but studies have suggested that up to 70 percent of women whose babies spend time in the NICU experience some degree of post-

partum depression, while up to one quarter may experience symptoms of post-traumatic stress syndrome.

"Knowing what we know about how critical bonding is for both the health of the child and parents in the NICU, it is imperative that we seek ways to decrease the amount of time that both parties are kept separated.

"In the case of the treatment of jaundice, many NICU babies will spend days, sometimes weeks quarantined in their isolettes under bright blue lights in order to combat this illness, all the while having precious moments to bond with their parents through skin-to-skin contact slip away.

"But what if we could change this? What if we could regain this time by treating jaundice in a way that doesn't keep babies isolated from their parents? From a personal standpoint, I can tell you that there is nothing as precious as time spent with your baby in the NICU.

"The time allotted to you to hold your baby in the midst of battling for its life is the most

precious gift of all. I speak for the millions of NICU parents in the world who only want for one thing, for their child to live and to hold them as they battle their way to health.

"Hand to Hold is here today in support of NDA 209904 by InfaCare Pharmaceutical Corporation. We feel that this injection of intramuscular use would greatly benefit our children and families by allowing for uninterrupted skin-to-skin bonding time during the treatment of jaundice and ask that you consider our plight in your decision." Thank you.

DR. COLE: Thank you very much. Will speaker number 6 step up to the podium and introduce yourself? State your name and any organization you represent. Is Mr. Nealon here? How about Dr. Wagner? Please.

DR. WAGNER: I also have slides. Great. I'm a neonatologist with the Medical University of South Carolina.

DR. COLE: Can you get that microphone right up close to your mouth?

DR. WAGNER: Hi, I'm a professor of pediatrics at the Medical University of South Carolina and I've been a neonatologist for the last 25 years. I was a site PI at MUSE for stannsoporfin, a multi-site trial. My travel for this meeting is being reimbursed by the sponsoring company, but I am not being compensated for my time and I have no other financial disclosures.

So really, why am I here today? I'm here today as a practicing neonatologist, really out of my frustration with the treatment of babies with hyperbilirubinemia, secondary in this case with blood incompatibilities, Rh and ABO incompatibilities, as Margaret detailed.

Really, the only treatments that we have and have had for the last few decades are phototherapy, intravenous, immunoglobulin, and double volume exchange transfusions, the latter of the two involving blood product exposure and of course double volume exchange transfusion really carrying significant morbidity and potential mortality.

It is really such a struggle as a

neonatologist where we have to wait for the blood to come up from blood bank and, as those hours are ticking, you know that the bilirubin, despite triple phototherapy and IVIG, is being elevated.

There's also the cost of hospitalization that certainly is lengthened by days of phototherapy and the cost to the family where mother and baby are separated, really preventing bonding and breastfeeding and certainly with the extended family.

What I see in daily practice really has been reiterated and, for the sake of time, I would just say that we have babies who require IVs and IV fluid, IVIG, the double volume exchange transfusions. They require central lines. And it's really a struggle.

Parents ask why and they say, "Isn't there something else that you can do?" And you talk about the toxicity of tin and the toxicity of heavy metals, but I can tell you the toxicity at 2:00 in the morning of a double volume exchange transfusion.

It's really not a pleasant task and really you don't know the long-term outcomes of high bilirubin in that baby. You hope that what you're doing will make a difference.

So the use of stannsoporfin is really something that I feel offers an opportunity of treatment for these babies. And it is really my medical opinion based on years of clinical practice that this drug would decrease the need for the burden to the patient, the healthcare burden to the patient, the family, and society of hemolytic disease of the newborn. And it would offer an alternative treatment for those babies.

I would like to show you this is a mom who participated in the trial at MUSC. She was not compensated for this and this video is what she said in the interview.

(Video played.)

DR. WAGNER: Thank you.

Clarifying Questions (continued)

DR. COLE: Thank you very much. Is Mr. Nealon here? No. Okay. The open public

hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The committee will turn its attention to address the task at hand, which is the careful consideration of the data before the committee as well as the public comments. We'll now proceed with the questions to the committee and panel discussions.

However, I think we have three questions left over, clarifying questions left over from before lunch. Dr. Havens, did you have a clarifying question for the FDA from the discussion before lunch?

DR. HAVENS: Yes, I did. Thank you very much. Peter Havens. There was no notice of thyroid toxicity in dogs and I wondered if there were data on thyroid toxicity in humans.

DR. PEI: Veronica Pei, FDA. I don't think TSH was measured as part of the laboratory data submitted, but I'll turn it over to the applicant to verify that.

DR. RUIZ: Thyroid function tests were not measured in the acute studies.

DR. COLE: Thank you. Dr. Guillory, clarifying question for the FDA?

DR. GUILLORY: The first question I had is, in terms of what was said previously, bilirubin toxicity then should occur in 2 per 200,000 live births. That means we would expect about 20 babies in the U.S. And if that is true, what I did not understand and what we always do is, do the benefits versus risk -- and in this case, are we doing, like, a cost analysis, how many babies you have to treat with this drug to get a decrease in either bilirubin toxicity or do we have a decrease in the time the babies are on phototherapy? I really have to have an understanding of the measurements.

The second question I had is when we look at late pre-term babies, which was mentioned previously, is there an increased risk, it appears, in that subset versus the term babies? And the third thing is what was mentioned previously.

Liver function studies, thyroid function studies, and I'm not even sure, for the pharmacist, can you really measure tin levels in babies?

Then number 5 is, when we talk about the registry, I'm not sure I understand who's going to man that registry, who's going to pay for it at the hospital level so that we can actually collect this data. Are we putting a burden on the many hospitals to really get the data that we may need to have beforehand?

DR. COLE: So a series of clarifying questions, I think the number needed to treat and the economic question first.

DR. OMOKARO: So in terms of the number needed and the cost analysis, well, I'll start with the number needed to treat. It's previously mentioned by the applicant the study wasn't designed or powered to be able to get that information.

So we do not know that information and, if the outcome being prevented is kernicterus, that would be a very large study, as has been mentioned

today. And in terms of a cost analysis, that was not performed by the FDA because that is not under our purview.

Then your next question had to do with late pre-term babies. Now, we have only one subject who was 35 weeks of age within the study, so those are very small numbers to be able to identify any impact within that population.

So your comments are well taken. And in terms of liver function, thyroid function, and tin levels in babies, I will look to my colleague, neonatologist, Dr. Gerri Baer to see if she has any comments on that.

DR. BAER: Could you restate the question about liver functions? I did understand your question about tin levels, which are not routinely measured.

DR. GUILLORY: Absolutely. I was just following up on one of the previous questions. We have said that the drug affects liver, so we were questioning about, in the studies or any of the studies, are we looking at liver function studies

in the babies that were treated?

In this case, we talked about tin being a toxin and I just simply question; we know the dosage that is expected, but can we even measure that in babies?

DR. BAER: The tin level?

DR. GUILLORY: Yes, tin levels.

DR. BAER: I'm sure it could be measured, but as you probably know, it's not a routinely done test and I'm not certain whether it was done in the trials. I don't believe tin levels were checked in the trials.

I do know that, as a standard part of adverse event evaluation and recording, liver functions were followed and I don't recall there being any concerns with liver function tests in the short-term.

DR. GUILLORY: Thank you.

DR. COLE: Thank you. And I believe Dr. Smith?

DR. WILKINS-PARKER: I'm sorry, I wanted to address her question about the registry.

DR. COLE: Yes.

DR. WILKINS-PARKER: So the agency sets forth under a REMS a set of requirements for the applicant. And it would be the applicant's responsibility to actually operationalize their REMS before their drug can be introduced into interstate commerce.

With regard to the data for the registry, the applicant would be the repository of that data and they'd be responsible for collecting it.

DR. GUILLORY: Thank you.

DR. COLE: Dr. Smith?

DR. SMITH: Brian Smith, Duke University. The question is how to interpret the efficacy outcome from the 204 study given that all three groups were limited to single phototherapy, including the placebo group when the standard of care for an infant with hemolysis and a rising bilirubin would be addition of a second light.

DR. OMOKARO: So let me just clarify your question. So you're indicating that intensifying phototherapy would be the next level of treatment?

DR. SMITH: Yes. I would think most babies in the placebo group, that their bilirubins were rising over time, the next step would be to add a second light. And so the comparison group in the 204 study has a group, a placebo group, that's sort of artificially letting the bilirubins rise more than they would in a clinical setting.

DR. OMOKARO: I'll have the applicant speak to that question.

DR. HILL: The question is how many microwatts? Dr. Maisels?

DR. SMITH: How many lights or how many microwatts?

DR. MAISELS: Yes. The protocol called for 30 microwatts per nanometers squared per centimeter and they were universally given a single light. The protocol called for a single overhead phototherapy light delivering 30 microwatts.

DR. NEWMAN: It was measured periodically?

DR. MAISELS: It was measured regularly, yes, and confirmed.

DR. OMOKARO: Does that answer your

question, Dr. Smith?

DR. SMITH: Not entirely. I mean, I get it. Clinically, we use a single light and the bilirubin goes up and, if we want it to go down further, we add a second light.

DR. OMOKARO: So you're making the point that a second light wasn't added onto the placebo group?

DR. SMITH: Correct.

DR. OMOKARO: Thank you.

DR. NEWMAN: If the bilirubin is going up, there was no option to add a second light.

DR. MAISELS: No. There was an option to increase the irradiance and to add a second light.

DR. NEWMAN: There was an option?

DR. MAISELS: Yes, if it continued to go up.

DR. NEWMAN: But that didn't happen, but --

DR. MAISELS: But no, it didn't go up in any of the cases of the drug.

DR. COLE: So speaker number 6 is now here from the open public hearing and I'd like to ask speaker number 6 to come forward and address the

committee, please.

Open Public Hearing (continued)

MR. NEALON: Good afternoon and, first of all, I apologize very much. I was in Philadelphia for American Liver Foundation event last night and there was a derailment on the Amtrak between Philadelphia and Washington, D.C. that caused my train to be about two and a half hours late, so I am very sorry for the delay and I certainly appreciate you accommodating me and letting me speak now.

The American Liver Foundation is a 501(c)(3) organization. It's a patient support and a patient advocacy organization that does receive contributions from a number of pharmaceutical companies, including Mallinckrodt. But this in no way affects ALF's statements as an advocacy organization on behalf of patients.

My name is Tom Nealon and I am the president and chief executive officer of the American Liver Foundation. As you know, ALF was founded as a trusted voice and resource for patients living with

liver disease.

Our mission is to facilitate, advocate, and promote education, support, and research for the prevention, treatment, and cure of liver disease.

We have 16 divisions across the country that provide boots-on-the-ground support, deliver patients and their families, as well as the general public. In all of these divisions, we have medical advisory committees that are composed of distinguished, experienced, and dedicated members of the local medical community.

There are over 100 different liver diseases that affect millions of Americans. Given the frequent association with the liver, the American Liver Foundation is keenly interested in hyperbilirubinemia in newborn infants, often known as neonatal jaundice.

We are often the first lifeline for parents reaching out for support and information. Our website gets over 2 million visits a year and our help line gets more than 1,000 a month, not on this issue alone, but certainly people reach out the

moment they hear jaundice and associate that with the liver.

We understand the burden on the newborn and the parents when the joyous occasion of a new family member becomes a matter of terrifying, confusing, and potentially worrisome journey. Instead of their newborn entering the world as a healthy baby, parents are faced with multiple treatments that may or may not work, insecurity about long-term effects of this condition, and perhaps advanced or invasive treatments that raise levels of concern for both the family, the mother, and certainly for the infant.

We recognize that this is an area that has lacked treatment advances for nearly 50 years. At ALF, we encourage innovation in all areas associated with the liver. It is our belief that supporting innovation for this neonatal population now can help expand options for patients down the road.

I want to stress that, of course, any new therapy that safely and effectively treats children

should receive serious consideration from the panel so that medical professionals have another option for treating these precious patients.

It is therefore imperative that physicians have these multiple options, including those that treat jaundice. We welcome your review and respectfully ask the advisory committee to recognize the needs of newborn infants with hyperbilirubinemia and help bring new treatment options to the patients who need them most.

Thank you very much for the opportunity for me to address you and I certainly appreciate the accommodation for my late arrival. Thank you.

Questions to the Committee and Discussion

DR. COLE: Thank you. Now, the open public hearing of this meeting has concluded and we will no longer take comments from the audience. The committee will turn its attention to address the task at hand, which is the careful consideration of the data before the committee as well as the public comments.

We will now proceed with the questions to

the committee and with the panel discussions. I would like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I'd also ask the panel to be sure to speak directly into your microphones so everybody can hear each other. And so if we could start with question 1, the applicant has submitted a single, adequate, and well-controlled study as evidence to support the approval of stannsoporfin.

Discuss the clinical meaningfulness of the primary endpoint of "percent change from baseline in total serum bilirubin at 48 hours post-treatment with stannsoporfin." So this discussion question 1 is now open for panel comment, question, and discussion. Dr. Newman and then Dr. Havens?

DR. NEWMAN: I think, as I said before, there's not any question in my mind that the drug works. It will keep bilirubin levels from rising compared to no treatment or with phototherapy compared to phototherapy alone.

So the question is how to compare that benefit to the unknown, but possible risks that have not at all been ruled out. And I think what we heard, I think partly from a lot of the public speaking and also, as I said from Jeffrey, one of the benefits that is best quantified by this pivotal study was shortening the duration of phototherapy.

Some of the other outcomes in this study were things like decreased rebound and decreased readmissions. This study had an artificially high rate of rebound because they stopped phototherapy sooner than most people would.

So on the one hand, that gives them more rebound in the phototherapy-alone group, the placebo group. On the other hand, that diminished the apparent benefit in terms of the number of hours of fewer hours of phototherapy that they got.

So if they had used a more realistic, if you just keep the lights on longer, the risk of rebound goes down. Okay? So they could have prevented readmissions, could have prevented what they called

failures of phototherapy by just treating the bilirubin and having it go down lower.

But then they also would have had a longer potential benefit. So the real question I guess we'll get to later is the safety. It works. If they want to market it --

DR. COLE: The question we have now before us is what is the clinical meaningfulness of this primary endpoint?

DR. NEWMAN: The primary outcome of percent change in bilirubin, I don't think, is very meaningful. I think I couldn't use that to explain to a parent, if we give your child this drug, the mean squared change in bilirubin will be 20 percent more than if we didn't. That doesn't help at all.

DR. COLE: Other members? Dr. Havens?

DR. HAVENS: Specifically speaking to the question at hand about the endpoint of percent change, it of course depends on where you start. So you can modify the percent change depending on where your starting point is. We see that in the comparison between the 3 and 4.5 milligrams.

When you look at total milligram change, as the FDA did, they find a different answer for the difference in the doses. So this is not just a clinically meaningless endpoint. It's potentially misleading as you try to understand the potency of the drug in bringing down bilirubin.

DR. COLE: Dr. Aly?

DR. ALY: I may disagree. It is very meaningful for the baby who has a critical value of bilirubin. So if the baby has a very high level, I'd be very desperate in bringing it down as soon as I can with any percentage possible.

DR. COLE: Dr. Assis?

DR. ASSIS: My concern about clinical meaningfulness is whether the populations studied in the pivotal trial was at high enough risk of severe effects because, while I certainly understand and appreciate the comments about time in the hospital and it's very meaningful and bonding, I think that, given long-term safety events, which we'll get to, I think that clinical meaningfulness needs to be taken into consideration

with the degree of risk and severity at the outset and that I think is left to be desired in my opinion.

DR. COLE: Dr. Smith?

DR. SMITH: The point about which babies this would be most critical in, which would be the baby sort of on the cusp of meeting IVIG or an exchange transfusion. It brings me back to sort of the primary outcomes measured at 48 hours. And so the change in bilirubin over a 48-hour period would not be of interest in that baby, where you're needing to bring the bilirubin down in 4 or 6 hours.

DR. COLE: Dr. Levine?

DR. LEVINE: Thank you. Just from an industry perspective, I would ask the committee to consider sort of the art of drug development, where you have to choose a specific endpoint and taking into consideration what some of the challenges are with regard to other clinical outcomes and the difficulty in designing and executing trials when those outcomes are rare.

DR. COLE: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I just wanted to say that I think it's probably a reasonable thing to measure because it is true that, if you're going to say that you're going to measure exchange transfusions that did not happen, it's hard to measure things that did not happen.

So I think, in lieu of that, measuring bilirubin is certainly a reasonable marker for it. So that's all.

DR. COLE: Yes?

DR. HUNSBERGER: Sally Hunsberger, statistician at NCI. So I understand the drug development issue, but this was set up as a phase 2 study, which you usually look at activity of a surrogate endpoint, which is what this study did. They could have -- if you were going to move into a phase 3 study, there are other endpoints you can look at, that get closer to clinical relevance, like how many people did you prevent from having to get the blood exchange, without having to go into huge numbers?

So there is another step that they could do that would get us closer to the more informative endpoint.

DR. HAVENS: Can I ask the statistician to comment on the specific choice of surrogate endpoint here, which was percent change from baseline, as opposed to looking at the milligram decrement?

I applaud the concept that you'd want to use a hard sort of categorical endpoint but did it make a clinical difference or not, but just in terms of this percent change versus milligram change, which the FDA had made a point of showing the milligram change data.

DR. COLE: Dr. Hunsberger?

DR. HUNSBERGER: So the question was, was this change that they looked at relevant?

DR. HAVENS: Well, trying to understand why they chose percent change versus milligram change and how that might affect the answer that they found, because if the choice is between a 3- and 4.5-milligram dose, which was not shown to be

different when you looked at milligram change as I understand the FDA data, then the choice of the percent change variable seemed to make a difference in the analysis.

DR. HUNSBERGER: Right. I think, since I'm not a clinician, I don't really know which endpoint is the most relevant. To me, it almost seems like the more clinically relevant would be, did we lower the bilirubin enough so that we don't have to give anymore therapy.

That would be a percent of patients, which is going to increase the sample size. So I assume that's why they didn't use that endpoint.

DR. COLE: Dr. Hill, would you like to comment on this?

DR. HILL: Yes, I think there's a very good answer for that. In the AAP guidelines, there are two figures, the figure two for the initiation of phototherapy and then figure 3, which was the initiation of exchange transfusion. Pardon me?

So the difference between those, the initiation points, depends on the baby and some of

the places, but it's about 6 milligrams per deciliter. The absolute change on TSB in study 204 was almost 3.

So you can put that in context of the therapeutic setting, where you begin phototherapy and then you're starting to worry and you want to, you need to initiate exchange transfusion. The magnitude of the treatment effect by adding stannsoporfin is half that distance. So we do believe this is very clinically meaningful.

DR. COLE: Other questions, Dr. White? Sorry.

MS. ELLIS: Thank you. Annie Ellis, patient representative. I was 20 years old when my newborn daughter went under the lights. And I can tell you that, as a new parent trying to make these decisions, having the best information is really important. And all I understand at the time was possible brain damage, here's my baby.

So this was very confusing to me, all the different studies and all the different study groups, and endpoints, and everything. Now, my

understanding is, study 204 was 91 babies. Is that correct?

DR. COLE: That's correct.

MS. ELLIS: I understand the numbers did go down and there were other studies. But if this question is based on 204, is that really enough information that gives us confidence for this to go forward?

DR. COLE: Yes. I think we'll have a chance to talk about the safety issue in one of the other questions. I think, right now, we're specifically addressing whether or not the percent change from baseline in total bilirubin at 48 hours is a clinically meaningful primary endpoint.

Any other questions? Yes, Dr. White?

DR. WHITE: I'm sorry, I'm probably going to confuse things. We're obligated to discuss that specifically as the endpoint as opposed to comparing the curves of rise toward exchange transfusion through the rate of rise and change at 6 hours, 12 hours.

I mean, the curves are what would provide

the information that would convince me that it might be very useful, not the percent change. Is that a fair discussion to open?

DR. COLE: It's certainly fair. I would say that I think that the percent change at 48 hours was 1 surrogate for trying to describe the curve as a quantitative sort of strategy for addressing drug efficacy.

DR. WHITE: But it's really the comparison of the curve to the curve for starting phototherapy or exchange that makes in my mind the argument that it is successful.

DR. COLE: I think that, while we may have other ideas about how this might have been different in terms of another specific parameter or metric for clinical meaningfulness, I think what the FDA is asking the committee is, do we feel that the primary endpoint of percent change from baseline in total serum bilirubin is a clinically meaningful endpoint? That's what they're asking. Dr. Smith? No, you're not in. Dr. Assis?

DR. ASSIS: Just a very brief comment. From

my perspective, at least what seems to be missing here is the background work potentially of taking a cohort of patients retrospectively even, and constructing a database, and seeing how often changes at this level go on to correspond to clinically meaningful endpoints that would establish the presence of this as a surrogate and I don't see that work having been done unless I missed it.

DR. COLE: Dr. Newman?

DR. NEWMAN: Yes. I just want to say one of the troubles with this percent change, besides that you can't get a number needed to treat from it, so in response to you, where, yes, if it's getting up close to the exchange, then by all means it's good to lower the bilirubin, but the question is how many babies do you need to treat to prevent one from exceeding the exchange level? And this outcome, if they had studied a group of babies at much lower risk, say 5 below the level at which we recommend phototherapy, they would have gotten substantially the same result probably.

They would have been able to show, yes, the percent change in bilirubin is lower in babies, even those who don't need phototherapy. The point is, we're so far from a level of toxicity that just changing the bilirubin alone doesn't really justify giving a drug that you don't know the long-term effects of.

DR. COLE: Yes, one more.

DR. BEITZ: I just wanted to clarify perhaps the difference between the question we're addressing now and the third question. So the question we're addressing now has to do with the pre-specified primary endpoint for study 204 and what your thoughts about that are.

But when we get to question 3, we like to hear about other data that you see in this application that provides support for efficacy. So we can talk about other kinds of data you are looking at that are helpful to you, but for this question, it's just the primary endpoint.

DR. COLE: Yes, Dr. White?

DR. WHITE: One last question; was there not

a pre-specified clinically significant number that they were aiming for? Was that not pre-defined when you designed the experiment?

DR. OMOKARO: There was not a specific change or absolute or percent that was pre-specified. It was really just looking at what the change was, not that they selected it ahead of time. Is that your question?

DR. WHITE: It sort of is. If you don't know exactly what you're looking for, it's hard to know how to design the experiment. And this looks to me like we're going to do the experiment to see what we come up with and then decide if it's significant or not.

DR. COLE: So if I can summarize the discussion here, I think, in response to this specific question, certainly the drug design, the study design, and the statistical understanding of trying to quantify a specific situation that's going to be different from baby to baby is a nontrivial undertaking.

Trying to design an approach that's

quantifiable, that can identify clinically meaningful charges in bilirubin rise or fall, I think, is also sort of a nontrivial issue.

So I think the study design was developed in an attempt to do the best that it could to try to demonstrate efficacy. There are, I think, concerns from the panel about whether this particular measure, which is percent change from baseline in total serum bilirubin at 48 hours post-treatment is the best or most meaningful one measure to use today.

I think it's safe to say that there is diversity of opinion about that among the panel and certainly no consensus about the clinical meaningfulness of that particular metric.

Let's move on to question 2. Question 2 is, discuss your recommendations for dosing, 3 milligrams per kilogram versus 4.5 milligrams per kilogram, single dose based on the available information. So what do we think about dosing?

DR. WADE: Kelly Wade. I'm concerned about discussing two different doses in a comparison

group that's as small as what was presented to us. And I'm concerned that among our higher risk babies are the 35- and 36-week-late per-term infants. And in the 204 pivotal trial, there was only 1 baby that was 35 or 36 weeks to the best that I can determine from the data.

So given the inconsistencies in the performance of how the 3 milligrams per kilogram dosing fared in 202 and 204, and the absence of 35- and 36-week babies in 204; I think it's really hard for us to have enough data to compare the 3 versus the 4.5.

DR. COLE: Other committee comments about trying to make a recommendation, Dr. Callahan?

DR. CALLAHAN: If we determine that this is safe and effective from a risk-benefit profile, I'm in favor of the 4.5-milligram dose because there are many instances that I can think of in our field of neurology where various doses were studied and shown to be effective.

Often, the lower dose is the only one that ever got approved. And we have data on higher

doses that we end up using, but then the patients are always concerned that we're using higher doses than are FDA approved.

So I think, if the 4.5-milligram dose is just as safe as the 3-milligram dose, then I'm in favor of the higher dosing.

DR. COLE: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I would actually argue that, if there's a discussion about it, that it should be the lower dose. And that's mainly based on the concerns from tin. So they said that 0.64 milligrams per day is the dose of IV tin you would want to give someone if you wanted to give it to them.

Based on my math, if you do the 4.5 per kilo, a 3 kilo baby, it's .7 milligrams per kilo, which is above the dose that's recommended for parenteral tin. So I think that the biggest one of our concerns is neurotoxicity and what are the long-term outcomes of this. And it's uncertain what the life history of tin would be.

We should certainly not start out

recommending something that has higher than the recommended dose of parenteral tin per day for a newborn.

DR. COLE: Dr. Aly?

DR. ALY: There's one of the statistical analyses done by the FDA for the interpolated total serum bilirubin. It's showing only the 4.5 as the one that has statistical significance and the 3 did not have statistical significance.

DR. COLE: You mean in terms of lowering bilirubin?

DR. ALY: Yes, slide number 12 in the presentation by Dr. Feiran Jiao.

DR. COLE: So could the FDA comment on the 4.5 versus 3 efficacy issue?

DR. OMOKARO: So slide 12 is actually the first secondary endpoint, time in hours from injection to TSB crossing at or below the age-specific PT thresholds. And yes, you are correct, it was only the 4.5 for that secondary endpoint. But the primary -- exactly.

DR. COLE: But primary endpoint in the FDA's

analysis was significant in both 3 and 4.5?

DR. OMOKARO: Yes, and again in terms of bilirubin crossing a threshold in hours, what does that mean? I think probably goes back to a lot of the discussion you had about the primary endpoint.

DR. COLE: Other questions or discussion from the committee about 3 versus 4.5 as a dose recommendation?

So if I can briefly summarize, I think again, there was diversity of opinion about this among the committee. Certainly, there is only a small N in each of the comparison groups, 3 versus 4.5, and in fact only 1 or 2 babies in the 35- to 37-week gestational age range were included in either 3 or the 4.5 milligrams per kilogram dose group.

So certainly one opinion is that it's hard to make a recommendation given the paucity of data. Certainly, the experience suggests that another opinion is that, since 4.5 milligrams per kilogram dose did have a favorable impact statistically on the primary endpoint.

That higher dose should be considered as the committee's recommendation. On the other hand, given the fact that 3 milligrams per kilogram also achieves statistical significance in the primary endpoint, the 3 milligrams per kilogram dose would provide each treated baby with a lower amount of tin. And since the tin amount administered was certainly eye catching and relative to the recommended daily dose, that might be an advantage for the 3 milligrams per kilogram dose.

Finally, it was pointed out that the 4.5 milligrams per kilogram dose did achieve significance with the first secondary endpoint, but 3 and 4.5 both achieved significance at the primary endpoint.

So I think the tin consideration, the smallness of the comparison groups makes it difficult to have a recommendation specifically about this. I would say that the committee basically did not achieve consensus about this particular recommendation. Anybody object to that? I'm happy to reopen, reconsider.

(No response.)

DR. COLE: Question 3 is a voting question, so that means that, at the end of our discussion, we're going to enter our votes on the pad in front of you and Jay will tell us how to do that in just a second. And then we'll each be asked to say what we voted and why in brief. Okay? Is that right?

Sorry. So here's question 3. Has the applicant provided substantial and persuasive evidence of effectiveness for stannsoporfin as an adjunct to phototherapy in neonates greater than or equal to 35 weeks gestational age with laboratory evidence of hemolysis and hyperbilirubinemia, meeting the American Academy of Pediatrics criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia, so substantial and persuasive evidence of effectiveness of the drug.

Comments from the committee? Dr. Havens?

DR. HAVENS: Thank you. One way to --

DR. OMOKARO: Excuse me. I'm sorry to interrupt. I think it's voting first followed by

the discussion.

DR. FAJICULAY: Hi, this is Jay, designated federal officer for the Gastrointestinal Drugs Advisory Committee. So the chairperson will be reading the question followed by any clarifying questions and discussion prior to that.

DR. COLE: So it's okay if we go ahead and talk about this?

DR. FAJICULAY: Any clarifying questions.

DR. COLE: So now I guess we're talking about clarifying questions before we vote about question 3.

DR. HAVENS: Thank you very much. So the clarifying question is, substantial and persuasive, okay, those are people's opinions. But effectiveness, we haven't seemed to be able to come to a consensus about.

So is there a specific definition of effectiveness that this question is asking me to vote on? Is the question, did the sponsor show that it decreases the percent change from baseline in total serum bilirubin or is the question do I

think that is evidence of effectiveness? Do you understand my question?

DR. OMOKARO: Yes, I think I see your point. It's not necessarily focused on just the primary endpoint, but based on the available information that you've seen today on efficacy and effectiveness, has the applicant provided substantial and persuasive evidence to support stannsoporfin as an adjunct to phototherapy. Does that help or are you still --

DR. COLE: I think that the question also will reflect some diversity of opinion about each committee members view of what the clinical meaningfulness is of the primary endpoint.

Dr. Newman?

DR. NEWMAN: Yes. I'm sort of having trouble with the last phrase, where it says, "Who are at risk of developing complications associated with severe hyperbilirubinemia." Normally, I would think that, if the people are at risk, then you have some events in the placebo group or in the control group, so that then you can see that you

reduced them with the drug.

This drug was studied in a group whose risk of developing complications associated with severe hyperbilirubinemia was so low that there were none. I guess there was 1 exchange transfusion in 1 baby who got drug, but the risk was so low that there was no way to quantify it going down.

So even if we believe it lowers bilirubin, it's going to be hard to say the group studied was at risk of developing complications associated with severe hyperbilirubinemia unless you say everybody is.

DR. COLE: Right. I think another part of this question in terms of substantial and persuasive evidence is basically focused on the pivotal study and how each committee member feels about the pivotal study in terms of its design and results and then how each committee member weighs the other studies that were included back through the 1970s.

One can focus on the pivotal study and say, I'm just going to focus on that and that's going to

be my opinion maker, the individual committee member might say, I'm going to focus on the pivotal study plus whatever, those two other studies which were included, or you can use all the non-GPC studies.

I think all those data were presented, but it's each committee member's responsibility to try to figure out how each of you feels in terms of that global amount of data being substantial and persuasive with respect to effectiveness.

Dr. Rosen?

DR. ROSEN: So I guess, along the same lines, it's the same issue as the timeline. Right? Are we looking at effectiveness in reducing it at 48 hours or effective in reducing any serious sequalae over 5 years? I mean, the timeline, I also take issue with this question because I'm not really sure if we're talking at 48 hours versus longer.

But to your point, you can use whatever studies you want to make that decision, so okay.

DR. COLE: Dr. Strate?

DR. STRATE: I just wanted to clarify that we're answering this question separate from any safety or risk data.

DR. COLE: I would seek some advice from the FDA.

DR. BEITZ: Yes, yes. We have safety questions following this.

DR. COLE: So this is a clinical efficacy question. Dr. Newman or Dr. Havens, either one? Dr. Havens first?

DR. HAVENS: So a lot of my interpretation of the effectiveness comes from FDA slides by Dr. Jiao, slides number 4 and 5. And I don't remember seeing slides that were comparable to that in the sponsor presentation. And I wonder, is it okay for me to ask if the sponsor has slides that would be comparable to that, that they think would refute the FDA presentation of the data in those two slides.

DR. COLE: I think if Dr. Hill or his designee could speak to that?

DR. HILL: Which slide?

DR. HAVENS: It's in the analysis of efficacy data presented by Dr. Jiao, Dr. Jiao's slides 4 and 5, which show the individual trajectories of bilirubin on the Bhutani nomograms for both high-risk and medium-risk neonates.

DR. HILL: I don't believe we have that slide, but let me see what we do have that we can show. These were subgroups. Right? They had selected out subgroups that started at different risks in different risk categories and then the spaghetti plot time over time.

DR. HAVENS: Yes, sir. And to me, it gets to this issue of clinical effectiveness showing that the placebo guys go over towards the black line, no matter what happens to them and you can't say that the treated guys go down faster, except in the 3 per-kilo group, but that helps you understand why the percent change is a difficult endpoint, because they started it at a higher level.

So if you're looking at percent of a higher number, it's going to be a smaller number, so it's not going to make it look as good. And so this

series of 6 graphs helped me best understand how to respond to this question. And I wondered if you had data that you wanted to show that were similar or different?

DR. HILL: Yes. I have three slides, spaghetti plots where the three treatment groups from study 204 are plotted. They're separate. So here is the placebo. And then for comparison, I'll show you the 4.5-milligram.

I mean, I think when you're looking at this, you're looking for a difference in the slopes on the individual cases and how far they're shifting. Dr. Ruiz presented data showing that 87 percent of the patients for whom stannsoporfin was added to their phototherapy shifted 1 to 2 categories versus those who did not receive stannsoporfin. Only 40 percent of them had that effect.

This does, I think, address some of the conversations about clinical meaningfulness. I understand, as Dr. Newman has pointed out, the difficulties in assessing the meaning of changes in this space in TSB, but all I think we can go back

to is the Bhutani nomogram that characterizes the risk for these patients for severe hyperbilirubinemia.

So if we are changing their risk category and if the Bhutani nomogram represents clinically meaningful risk categories, then this is a clinically meaningful effect.

DR. HAVENS: Right. Could you show me then the 3 milligrams per kilogram slide?

DR. HILL: Yes. Do we have the 3 milligram? This is the 3.

DR. HAVENS: Thank you. That's helpful. It's interesting to note that, in the data presented by the FDA, the change in that hospitalization time was only 1 hour. So that moving across 1 line or a second line may be different, have a different impact on issues of hospital discharge or actually getting out of the light, as we've heard from Dr. Newman. Thank you. Thank you for showing those data. I appreciate it.

DR. COLE: Yes, Dr. Adams?

DR. OMOKARO: Just one comment from the FDA;

did you want to speak? We wanted to just indicate that the nomograms that are being displayed are two different nomograms, just so you're clear on that. The nomogram that FDA presented was from the AAP guidelines while the nomogram presented was the Bhutani nomogram.

So any slight differences are probably related to the nomogram. And I would just add one point to Dr. Smith's question before about, in placebo patients, whether additional light was possible to be added. We did check the protocol and there was no pre-specification to add additional lights. It was the 30 microwatts that was mentioned earlier, a single blue light.

DR. BAER: I'm sorry. One further clarification from Stephanie; the nomograms are two different nomograms. They're all in the AAP guideline, but the applicant's nomogram was the risk for developing severe hyperbilirubinemia.

The nomograms that Dr. Xiao presented basically incorporated the treatment, whether it be phototherapy, the bottom line, or exchange

transfusion. So the treatment nomograms are different from the risk nomogram.

DR. COLE: Yes, Dr. Adams?

DR. ADAMS: So because I'm not a neonatologist, these questions may be really simple, but it'll help me to understand this question. So I have two questions. My first clarifying question is to ask about this decision to not use this, what I understand now to be the standard of care, which is if the bilirubin continues to rise and a baby is getting phototherapy, that you add a second light, you increase the dose.

My understanding is that, in the pivotal study, that was not done. And so a question I have to help me clarify my understanding here is whether that could potentially amplify differences between the treated and the untreated groups.

The second question I have, again, is to ask for some further clarification on what is meant in our voting question about effectiveness. Are we looking at whether the applicant's drug,

stannsoporfin, is effective at reducing total serum bilirubin, percent change from baseline by a certain amount, or are we looking at whether it's effective in reducing TSB at 48 hours to a degree that's clinically meaningful?

I'm really trying to struggle with which of these I would be voting on.

DR. COLE: Dr. White?

DR. WHITE: Michael White, New Orleans. This is based on the pivotal study 4, but this is to address your concerns about exchange transfusion. There's a study 6 that had 41 subjects. 18 received placebo, 19.75 milligrams per kilogram and 1.5 milligrams per kilogram for 18.

So under the placebo, 9 of the 18 had exchange transfusion. 1 of the 0.75 had exchange transfusion and 2 out of 18 of the 1.5 milligram. So there is some data regarding exchange transfusion and whether this seems effective or not, I just don't know why this wasn't really brought up, other than that we're focused on the

study 4, but there is some data about it and I was shocked at the rate of exchange transfusion because 9 out of 9, I haven't seen that since I was a resident.

DR. COLE: Yes, FDA?

DR. PEI: Veronica Pei, FDA. So the reason that we have not focused analysis on 06 is because it was an open-label trial that did not start with a control group. The control group was added mid-trial, so overall, we felt that the study design could not give us, provide evidence really to support efficacy, because it was not a well-designed trial.

DR. COLE: Dr. Adams, do you have one more question?

DR. ADAMS: I don't have another question. I just was hoping for answers to my two questions.

DR. COLE: So from the neonatologist, do you want to just restate quickly your questions here?

DR. ADAMS: The first question was whether the decision to not use the standard of care of increasing the dose of phototherapy potentially

amplify differences between the groups, treated and untreated.

The second question is understanding whether the vote is a decision on the effectiveness of the drug to reduce total serum bilirubin, present change from baseline to 48, or if it's a decision about the effectiveness to reduce TSB to some clinically meaningful degree or in some clinically meaningful way.

DR. COLE: Comments from anyone on the panel? Dr. Newman?

DR. NEWMAN: Yes. So in answer to your first question, yes, theoretically, if they gave less phototherapy, that might amplify the difference between the groups, but when I look at this figure here at the placebo group, there really looks like there was only one baby who was, like, going up and approaching the exchange line, where the clinicians taking care would say we need to do something more.

Most of these babies never got anywhere close, so I don't think that's a big limitation. I

just wanted to correct one thing. The Bhutani nomogram and the labeling of it is a source of confusion to a lot of people because it says, like, high risk and many people have interpreted that as high risk of severe hyperbilirubinemia, or some sort of brain damage, or some sort of bad thing.

So severe hyperbilirubinemia has various definitions but none of them is as low as the endpoint for that nomogram, which was the 95th percentile. So it was about the risk of exceeding the 95th percentile in this study.

Most of those babies are babies like in the study. They get some phototherapy. They do fine. So severe hyperbilirubinemia, a level at which you might consider exchange or worry about brain damage is not what the Bhutani nomogram is about.

DR. COLE: I think we're going to proceed to vote and here's how we're going to do it. So the question we're voting on, has the applicant provided substantial and persuasive evidence of effectiveness for stannsoporfin as an adjunct to phototherapy in neonates greater than or equal to

35 weeks' gestational age with laboratory evidence of hemolysis and hyperbilirubinemia meeting the American Academy of Pediatrics criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia.

So we will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash, even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed his or her vote, the vote will be locked in. The vote will then be displayed on the screen. Jay will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state her or his name and vote into the record. You can also state the

reason why you voted as you did if you want to.

So please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash.

If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed. So are we ready to vote here?

So switch number two; there are four -- am I one of those people? Okay. Here I go. Please repress your vote.

(Voting.)

DR. COLE: The answer is?

DR. FAJICULAY: For the record, the results are 6 yes, 17 no, and 1 abstain.

DR. COLE: Now that the vote is complete, we'll go around the table and have everyone who voted state her or his name, vote, and if you want to, you can state the reason why you voted as you did into the record.

We will start, I guess, with Dr. Hunsberger.

DR. HUNSBERGER: I voted no. I think this is not a clinically relevant endpoint to show effectiveness. I think we need to do another study to get closer to the clinical effectiveness. This is an activity endpoint.

DR. COLE: Dr. Smith?

DR. SMITH: I voted no also and I would just add that it was not substantial. The sample size was way too small.

DR. NEWMAN: Tom Newman. I voted no as well for reasons just stated and other things I've said already.

DR. ADAMS: Heather Adams. I was the abstain, as you can see, and I voted that way because I still was uncertain whether I was determining whether this drug was effective at reducing TSB or whether it was effective at reducing it in some clinically efficacious meaningful way.

DR. GUILLORY: Charleta Guillory, and I voted no, especially because of the late pre-term

babies which are going to be affected by this. And I did not have enough data in that group.

DR. CATALETTO: Mary Cataletto. I voted yes primarily on the basis of the FDA's slide and this slide that Dr. Havens had referenced, the graphs, based on the definition that they gave, and the change in the primary endpoints, and the secondary endpoint where the TSB crossed below the phototherapy threshold.

DR. HOEHN: Sarah Hoehn. I also voted yes based on the strict definition of the language of the question, which is that I do think the data shown today shows that the drug lowers the bilirubin level in a way that is potentially meaningful, partly based on the differences in exchange in the study we didn't talk about.

DR. HAVENS: Peter Havens. I voted no for reasons that have already been stated, including the very small sample size.

DR. FEAGINS: Linda Feagins. I voted yes. And I have to admit I struggled some with my answer to this question, but I ended up voting yes just

based on the ability that they showed that the drug could actually lower the bilirubin.

DR. DRACKER: Bob Dracker. I voted yes primarily because I thought the data demonstrated efficacy as defined by the FDA. However, I personally wanted to see additional toxicity data that I hope will be pursued in the future.

MS. ELLIS: I'm Annie Ellis. I voted no. I wanted to vote yes because I do think it's shown that it is effective at lowering the TSB. However, the greater than or equal to 35 weeks' gestational age, 35 to 36, 37 weeks is kind of missing and that made it a no for me.

MS. BOYCE: Danielle Boyce. I voted no for exactly the same reasons that Annie voted no.

DR. MCVEY HUGICK: Joy McVey Hugick. I voted no for reasons already stated.

DR. RAUFMAN: Jean-Pierre Raufman, I voted no.

DR. COLE: This is Sessions Cole. I voted no.

DR. ASSIS: David Assis. I voted no. I

feel that the link between reduction in TSB and effectiveness needs to be demonstrated first.

DR. ROSEN: Rachel Rosen. I voted no for the same reason, that the sample size didn't really reflect who's going to ultimately get this drug.

DR. CALLAHAN: David Callahan. I voted yes because I believe that it is effective in lowering TSB. That's it.

DR. KHURANA: Sandeep Khurana. I voted no for the reasons we already discussed.

DR. WADE: Kelly Wade. I voted no. The numbers are too small and I would really think it's important to have 35- and 36-week babies in the cohort.

DR. STRATE: I'm Lisa Strate and I voted no.

DR. SAYEJ: Wael Sayej. I voted no for several reasons. There are many unanswered questions. The sample size is too small. I think to calculate the number to treat is not going to be an easy task. In addition to that, to calculate the number to harm is also even more difficult because the number of cases that progressed to

kernicterus is so small, I think focusing on the clinical outcomes, which is the development of kernicterus, is probably more fruitful than just focusing on decreasing the total bilirubin level.

DR. WHITE: Michael White. I voted no for several reasons, some of them that are probably in my head. One is the age 35, 36 weeks. We don't have a whole lot of data and we're including them in this vote for yes.

I think that there's clearly a trend toward decreasing the levels of total serum bilirubin, but I think we failed to demonstrate what clinical significance that really has, particularly if we exclude that study number 6, which seems to suggest it might be very helpful in borderline cases.

I just think there needs to be some clarification in what is a clinically significant endpoint in considering this drug, although in my head I think it's probably a pretty good one.

DR. ALY: Hany Aly. I voted yes. I think the drug is promising. My understanding is that this is not at phase 3, so we still have lots of

babies to be enrolled in the subsequent phases. And then we can give the drug the opportunity to work.

DR. COLE: Thank you very much. We'll now move on to question 4, which is also a voting question. Are the submitted data on long-term safety assessments adequate to characterize the potential risk of stannsoporfin -- yes?

DR. BEITZ: Yes, FDA has a clarifying point to make before you start to vote. Dr. Joseph?

DR. JOSEPH: David Joseph from DGIEP. Could we bring up slide number 10 from my presentation? So there's been some expression of concern regarding the dose of inorganic tin that will be delivered at the proposed dose of stannsoporfin.

So I just wanted to revisit this slide briefly just to be sure that we're seeing this information in the best context. So in the first bullet, where I cite the ICH Q3D guideline, where it states a permitted daily exposure of 0.64 milligrams per day of inorganic tin, the key word in that first bullet is in parenthesis.

It says "lifetime." What that means is a lifetime daily administration of 0.64 milligrams of inorganic tin per day. The second bullet where we're discussing stannsoporfin, we can calculate a range of 2.1 to 2.8 milligrams tin. It's a single-use product.

So that's a once-in-a-lifetime dose of tin in the context of the proposed drug use. And I hope that's helpful.

DR. COLE: Thank you very much. We'll now go on to question 4. This is also a voting question. Are the submitted data on long-term safety assessments adequate to characterize the potential risks of stannsoporfin-related adverse neurodevelopmental outcomes.

So this is now open for discussion. Let's see. Dr. Newman first?

DR. NEWMAN: Yes. I just want to sort of point to basic epidemiology. When you're looking for adverse effects, the most relevant thing you're looking for is the upper limit of the 95 percent confidence interval of the absolute increase in

risk, meaning just the fact that they look for stuff and didn't find things that were bad that were statistically significant, that could be partly due to small sample size, and short follow-up, and a lot of loss to follow-up.

So what you want to do for these things -- and there were worrisome trends like for speech and platelets. And so some way would be to calculate the point estimate of the risk difference, look at the 95 percent confidence interval, and then basically how bad could it be.

When you do this, this drug could be pretty bad. Even the point estimates in some cases, even if that were the true result, would be kind of scary. So don't be fooled by just the fact that some of these things are not statistically significant.

DR. COLE: Dr. Baer?

DR. BAER: Thank you. I wanted to just go back quickly to what may or may not be a small point. Dr. Smith brought up the question of phototherapy and standard of care. And though we

often do add extra lights, I believe the protocol specified 30 microwatts.

That is the standard for intensive phototherapy in the AAP guideline and exposing as much skin as possible. So I'm not certain that we could say that, that placebo group did not get the standard of care.

DR. COLE: Thank you. Dr. Adams?

DR. ADAMS: So my questions about the neurodevelopmental outcomes fall into three categories generally. I have questions about the analytic approach that the applicant took. I have questions about the interpretation of those data once analyzed and I also have questions about the front-end design and some of the decision making.

So at the beginning of the day, I had a couple of very granular questions about the analytic approach. I'm not sure if the applicant can address those here, if they have someone who can speak to this.

One of them had to do with how they handled the Child Behavior Checklist data, which are

behavioral outcomes for these children. Another had to do with the presentation of age-equivalent data, analyzed as though it were interval data.

The next question generally is a broader question about the appropriateness of pooling data from different studies where the baseline characteristics of the neonates were different and the designs of the studies were a bit different and whether it's appropriate to then take the neurodevelopmental data from those disparate studies and pool them.

I'll stop there and let you address those first.

DR. COLE: I think the committee would certainly be interested in your opinion about whether or not pooling data is or isn't a good idea.

DR. ADAMS: Fair enough.

DR. COLE: If we wish to ask the applicant, we can do that as well.

DR. ADAMS: I don't consider it appropriate, but the applicant would certainly be welcome to

counter that in with their response. But my concern is that it's not appropriate for the reasons stated. Actually, that's sufficient for my questions related to the analytic approach. Do we want to take those first?

DR. COLE: Dr. Hill, do you want to take a crack at that?

DR. HILL: Well, no, Dr. Cole. I won't interrupt every time I object. That's not my point of standing up. I just wanted to add a comment that I thought there was interest in and that was regarding the use of phototherapy in the increasing phototherapy irradiance or additional lights, as allowed by the protocol.

It was allowed by the protocol, so the placebo group was not handicapped in some way by that restriction. I just wanted to clarify that because I think there was perhaps some misinformation.

DR. ADAMS: Thank you. I did misunderstand, so thank you.

DR. COLE: Dr. Rosen? Dr. Aly?

DR. ALY: I just need a clarification from FDA. The studies that are shown or presented today; my assumption that these are phase 2 studies, so it's not really when we are voting on this that's going to be in the market tomorrow.

If we have compelling and persuasive data based on phase 2, then what is the purpose of phase 3? So if that is fair to say, if I see a drug that is promising and seemingly safe, then that would be okay to proceed to phase 3. That is very different than we are in phase 3 already and the drug will be finally authorized. I just need clarification on this.

DR. COLE: So FDA, phase 2 versus phase 3?

DR. OMOKARO: Yes, you're correct. This is a phase 2 study, though, that was submitted as a new drug application, so essentially bypassing the phase 3, suggesting that there was enough evidence in terms of efficacy and safety to support a marketing application.

Then to us, that becomes a review issue. We have to look at the information to be able to make

the determination because, sometimes the sample size, the measures, the outcomes, all the things that you have been discussing may have been addressed within a phase 2, but currently, this is a study that's submitted for a marketing application.

DR. COLE: Dr. Sayej?

DR. SAYEJ: I just would like to point out one thing. Looking at the debriefing from the FDA that we received, the phototherapy treatment itself, there was a systematic review in the literature about the long-term safety measures, including the neurodevelopmental complications.

Based on the FDA's summary, there was not enough data out there to make that connection. And therefore, phototherapy is obviously used a lot more frequently than what this drug will be if it does get approved and therefore I think is going to be almost impossible to figure out what the long-term effects are from a neurodevelopmental perspective and to show cause-effect.

DR. COLE: Dr. Adams?

DR. ADAMS: Here are some of my other observations regarding the neurodevelopmental outcomes and how we interpret them. If we look at the slide from the applicant, their slide CO-95, they have a very nice table outlining children who had speech and language disorder outcomes and in the 4.5 milligrams per kilogram dose in the placebo group.

One of my observations is that there are some confounding factors listed for actually all of these babies that potentially could explain the findings. I guess I would argue that perhaps another way to answer this question about confounding factors is to look at the base rate of these particular confounding factors across all neonates in both of these groups and determine, of those two groups, in those two groups, what proportion of children with those confounding factors then went on to have these outcomes?

That may not be possible to address because of the small numbers, but I think I don't know that you can do this post hoc and then just kind of fit

in and say, well, they had this factor and that factor.

Let's take a look at how many kids in each group actually had these confounds before we then try to make some attributions about it.

Another comment I have is, in the briefing materials that we received on page 119, there were some comments about a couple of children not being testable or not having valid IQs because of behavioral problems. And obviously, I don't know much about these babies at all, and what sort of behavioral problems they had, and why they were difficult to test.

But in my experience, both clinically and in research settings, when children's IQ is low because of behavioral problems, it's not that the behavior caused the low IQ. It's that the low IQ is one expression of the challenging behaviors that you see in the testing setting.

So I don't think we can dismiss the findings from those kids out of hand and say that the differences observed were as a consequence of

children being uncooperative with testing. We have to take a look at what their limitations were that drove that uncooperativeness.

Likewise, on that same page, there's a comment that there was higher function in the placebo group and differences that were observed and neurodevelopmental outcomes were purely attributed to a higher function than expected in the placebo group.

So I think we have to take a look at the fact that these groups were well balanced demographically. The kids in this study, whether they are in the placebo group or in the treated groups, they had the same background characteristics.

So if we see a higher than expected IQ score in the placebo group, we would expect if the treatment does not have any effect on IQ, that similarly, you're going to have that higher than expected IQ in the treatment group. So that was another comment I had.

Finally, going back to CO-95, again from

their presentation, I was struck by the number of males who were impacted or who were described as having these speech and language disorders.

I think 8 or 10 of the 12 children, compared to the females, only 2 in both groups. And I just was curious about that and if we are concerned about any sex differences here in the neurodevelopmental outcomes.

DR. COLE: Thank you. Dr. Havens, then Dr. Callahan, then we'll vote, I hope?

DR. HAVENS: Thank you very much. Still on this slide, the issue about males and females, I think, mirrors what was found in some of the animal studies.

DR. ADAMS: That's right, yes.

DR. HAVENS: So I think that's a very important issue. I applaud your findings or your focus on those two untestable children. Our experience is the same in that regard. Those children should be counted in the bad group. And here, this gets to my point as of potentially taking away an important antioxidant.

So first of all, this inhibits heme-oxygenase. Heme-oxygenase does interact with toll-like receptors. Toll-like receptors are your interface with a variety of different infections. So even though these are potentially viruses and bacteria, there's a plausible reason why this could increase the risk of infection, number one.

I share your concern that there was the same number of infections in the non-treated group, but these people had perhaps a different impact from the infection. Again, oxidation is an important factor in tissue damage after infection and, if you take away the antioxidant capacity, then you would get increased physical findings after normal infections.

So I think this is an important slide and has biological plausibility for why the drug might be impacting these outcomes even though it's not either tin or porphyrin doing the damage, but rather that those are in a plausible pathway towards damage.

DR. COLE: Dr. Hill, do you want to make a

few comments?

DR. HILL: I just wanted to remind the committee that the point at which those observations are made are years after exposure. So the inhibition of heme-oxygenase 2 or 3 or 4 years previous; it would be difficult to expect that there would be some kind of effect at this time that could have resulted in infections that then were secondarily causing other observations.

DR. COLE: Thank you. Dr. Callahan?

DR. CALLAHAN: Yes. As far as neurodevelopmental testing for speech and language delay, speech and language disorders and autism are much more common in males than females. So if you look at toddlers and preschoolers who are receiving early intervention, it's predominantly males.

But we often refer to many of them as developmental delays. And so you really need to wait until they're 7 or 8 years old because, by then many of these speech and language problems resolve themselves.

So from the point of view of the company,

it's to their benefit to do this testing out to age 7 or 8 years so we don't identify kids with speech and language disorders from a drug that resolved. And on the other side of the coin, you can correct me if I'm wrong, but IQ testing in 5-year-olds is not very reliable.

That's the other reason you want to wait until they're about 7 or 8 years old, to get more reliable IQ testing to identify cognitive deficits. And learning disabilities and attention disorders often won't show up until first and second grade. So if you really want to know the neurodevelopmental effect of this drug, we need to have studies that can follow a group of these kids until they're 8 years old to get answers to these questions.

DR. COLE: Thank you. Dr. Assis?

DR. ADAMS: If I can just respond, I wanted to confirm that, that is correct, that we don't really consider an IQ measurement at age 4 or 5 to be predictive. It's descriptive of the child at that point in time, but we really want to see IQ at

age 6, 7, 8 to really see a stabilization of those measurements.

DR. COLE: Yes, Dr. Assis?

DR. ASSIS: Yes, just briefly. I would second the concerns by Dr. Havens. I was also struck by the increased incidence of complications and I think nothing prevents a theoretical second-hit phenomenon between modulation of heme-oxygenase and subsequent risk of infections.

I think that, even if it were years afterward, I think the burden would be on the drug development aspect, perhaps even pre-clinically to study better the residual effect of that, for example in the liver or elsewhere with secondary hits and pre-clinical models, and I think for an IND that's been around for about 20 years or so, that type of data would have been very helpful.

DR. COLE: Thank you. I think we'll go ahead and vote. I think the discussion has been quite robust. I would say that, as pointed out in the application, there have been more than 1,000 babies who have been exposed to this drug and over

a couple of decades.

But certainly, the committee has had some important questions about the specifics of the neurodevelopmental follow-up. So please press the button on your microphone that corresponds to your vote. And the question is, are the submitted data on long-term safety assessments adequate to characterize the potential risk of stannsoporfin-related adverse neurodevelopmental outcomes.

So please press the button firmly.

(Voting.)

DR. COLE: Then we'll go around the room as we did before so that people can provide their vote and their name.

DR. FAJICULAY: For the record, the results are 3 yes, 21 no, and 0 abstain.

DR. COLE: Dr. Hunsberger, let's start again with you.

DR. HUNSBERGER: Sally Hunsberger. I voted no. I think the sample size was to small to really know. We do have a lot of historical data, but it's not in a randomized setting, so we can't

really compare. It's not exactly in the population that this drug will probably used in and I think there is a hint of some safety signals.

DR. COLE: Dr. Smith?

DR. SMITH: Sorry, Brian Smith. So I voted no, same reason and also the other signal that's there in the pre-clinical and clinical model would make me concerned about the study drug.

DR. NEWMAN: Tom Newman. I voted no for the same reason.

DR. ADAMS: Heather Adams. I voted no for the reasons that have been discussed by myself and others. I also think that, while the choice of gold standard measures was commendable, the decisions to switch back and forth between some of these measures within and across studies is a concern.

I also am very concerned about the very low numbers of kids we have at the long-term follow-up, where we can really truly tell if there's a signal for safety or not.

DR. GUILLORY: Charleta Guillory. And I

voted no. One reason is that I'd like to see the follow-up in study 5 to find out what happens in a longer-term basis. I'm still very concerned about that.

I am concerned about the different tests that we're using and how are you going to standardize that for follow-up of all of the babies?

DR. CATALETTO: Mary Cataletto. I voted no because of the potential safety signals and the overall number of children.

DR. HOEHN: Sarah Hoehn. I voted no for the reasons people have already stated.

DR. HAVENS: Peter Havens. I voted yes because I think the submitted data are adequate to characterize the potential risk related to -- I show up as a no?

DR. HOEHN: You show up as a no.

DR. HAVENS: I show up as a no? Well, I think the data are adequate to identify the adverse neurodevelopmental outcomes in terms of hearing, language, seizures, death in prematures,

phototoxicity, thrombocytopenia, increased infection. So can I change my vote or not?

(Fajiculay indicates no.)

DR. HAVENS: So the data are sufficient. The answer to the next question may focus on a different answer.

DR. FEAGINS: Linda Feagins. I voted no because I feel like the sample size is too small and we don't have enough follow-up.

DR. DRACKER: Bob Dracker. I voted no, but Dr. Havens has me completely confused at this point.

DR. HAVENS: Did you actually vote yes?

DR. DRACKER: No. I'm voting no. But the reason I feel I'm voting no is because I think the oxidative stress data is critically important to explain possibly the thrombocytopenia and the potential for long-term outcome.

MS. ELLIS: Annie Ellis. I voted no. I just wish there was a study 5, the long term, more long-term safety data.

MS. BOYCE: Danielle Boyce. I voted no for

reasons previously stated, mostly due to the sample size. And if Dr. Dracker is confused, imagine how I feel.

DR. MCVEY HUGICK: Joy McVey Hugick. I voted no for the reasons already stated and mostly because of the small sample size, but also the loss to follow-up.

DR. RAUFMAN: Jean-Pierre Raufman, I voted no.

DR. COLE: Sessions Cole, I voted no.

DR. ASSIS: David Assis. I voted no for reasons already stated.

DR. ROSEN: Rachel Rosen. I voted no and I just want to stress that I think getting this right really is important because, when the outcome is neurotoxicity from hyperbilirubinemia, you have to make sure that what you're saying is an outcome of a drug, it is not the hyperbilirubinemia, and vice versa, so this is a must-do.

DR. CALLAHAN: David Callahan. I voted no.

DR. KHURANA: Sandeep Khurana. I voted yes for the reasons that Dr. Haven actually

characterized extremely well. Thanks for reading my mind.

DR. WADE: Kelly Wade. I voted no for both the small number and loss to follow-up, but also, I think, in envisioning counseling parents, it's going to be important to characterize this number needed to potentially harm and to really get the safety signal around neurodevelopmental outcomes and speech and hearing and the thrombocytopenia so that we can say maybe we can shorten hours of phototherapy, but this is the added risk. I think it's really important that we get that information.

DR. STRATE: I'm Lisa Strate and I voted no.

DR. SAYEJ: Wael Sayej. I voted no for the reasons stated.

DR. WHITE: Michael White. I voted yes for Dr. Havens's arguments and focused on that assessments adequate to characterize the potential risk. And I don't think we'll ever be able to get beyond adequate to characterize the potential risk because of all the confounding factors, and statistical analysis, and numbers it would take to

differentiate between the effects of having an elevated bilirubin and then taking the drug.

DR. ALY: Hany Aly, I voted yes. Kernicterus is a disaster for the brain and if a drug can effectively decrease that without causing comparable to kernicterus, then that is good and for the current phase of the studies, so that would be adequate.

DR. COLE: Thank you very much. I think we'll take a 12-minute break. We'll reconvene at 3:15 for the last three questions.

(Whereupon, at 3:02 p.m., a recess was taken.)

DR. COLE: Welcome back after the break. Question 5 is a voting question. Does the long-term and short-term safety profile of stannsoporfin in the proposed indicated population support approval?

So this question is now open for clarifying questions and then we will vote. Question 5, who has questions about question 5, long-term and short-term safety profile? If you're all convinced

you know the answer, we can vote. Wait. Sorry. We're missing one person now. Be thinking now.

So question 5 is, does the long-term and short-term safety profile of stannsoporfin in the proposed indicated population support approval? Are there clarifying questions from committee members about this question 5?

Sorry, yes, Dr. Hunsberger?

DR. HUNSBERGER: It's not clear to me how to vote if I voted no on both the previous two. This is kind of assuming I voted approval on the previous two.

DR. COLE: I think this is a specific question that's aimed at each committee person's evaluation of the long-term and short-term safety profile of the drug. And I agree that there is some intertwining of the last couple of questions and this one. But the specific question here is, do you think that the long-term and short-term safety profile support approval of the drug by the FDA? Any other clarifying questions?

(No response.)

DR. COLE: Hearing none, please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly.

(Voting.)

DR. COLE: Mine worked.

DR. FAJICULAY: For the record, the results are 2 yes, 21 no, and 1 abstain.

DR. COLE: Dr. Aly, we're going to start with you this time rather than Dr. Hunsberger; your name, your vote, and if you choose, why you voted that way.

DR. ALY: Hany Aly. I voted yes. They are building on the previous questions, which is for me satisfied.

DR. WHITE: Michael White. I abstain. I just couldn't decide.

DR. SAYEJ: Wael Sayej. I actually voted no, not yes, mostly for the previous reasons I discussed with the long-term results.

DR. STRATE: I'm Lisa Strate. I voted no based on our discussion on the previous two

questions.

DR. WADE: Kelly Wade. I voted no.

DR. KHURANA: Sandeep Khurana. I voted no.

DR. CALLAHAN: David Callahan. I voted no.

DR. ROSEN: Rachel Rosen, I voted no.

DR. ASSIS: David Assis, I voted no.

DR. COLE: Sessions Cole, I voted no.

DR. RAUFMAN: Jean-Pierre Raufman, I voted no.

DR. MCVEY HUGICK: Joy McVey Hugick. I voted no. I wish I could vote yes, but I just don't think we're there yet with the information.

MS. BOYCE: Danielle Boyce. I voted no.

MS. ELLIS: Annie Ellis. I voted no.

DR. DRACKER: Bob Dracker. I voted no. I don't think the long-term data is truly long term.

DR. FEAGINS: Linda Feagins. I voted no.

DR. HAVENS: Peter Havens. I voted no. I think there's too much toxicity data already available. It should not be approved.

DR. HOEHN: Sarah Hoehn. I voted no for reasons people have already stated.

DR. CATALETTO: Mary Catalano. I voted no.

DR. GUILLORY: Charleta Guillory. I voted no.

DR. ADAMS: Heather Adams. I voted no.

DR. NEWMAN: Tom Newman. I voted no.

DR. SMITH: Brian Smith. I voted no.

DR. HUNSBERGER: Sally Hunsberger, no.

DR. COLE: Thank you very much. We'll now move on to question 6. Is that what it is we're up to? Question 6 is a discussion question. Discuss whether additional interventions beyond FDA-approved labeling such as a risk evaluation and mitigation strategy are necessary to ensure that the drug's benefits outweigh its risks.

Discuss the risk evaluation and mitigation strategy proposed by the FDA, which consists of healthcare setting certification for dispensing and administration, safe use conditions, and a registry.

So we're now discussing for the FDA this issue about the REMS as proposed by the FDA. Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. My thoughts about the REMS were that there's probably a very narrow population who could benefit from this drug. And my thought is, if there was some way to phrase the risk mitigation to babies that are only 38 weeks, given the paucity of 35- and 36-weekers included, and if there was any way to restricting it to babies who either had a contraindication to phototherapy if there is such a thing or if they had failed phototherapy.

Some people have talked a lot about how, after the first 4 to 6 hours, you know if you're going to have to be prepping for an exchange transfusion. Is there any way to narrow the indication more to focus it on those babies who are the ones who are going to progress to exchange transfusion?

DR. COLE: Thank you. Dr. Havens?

DR. HAVENS: As Dr. Aly had pointed out, this seems like a phase 2 study. The standard approach after a phase 2 study is a phase 3 study. And then you go for FDA approval. The REMS

approach seems like an end run around a phase 3 study which is doomed to failure and will not give the data that you need to convince anybody that the drug is safe and clinically effective.

So if the sponsor wants to continue with drug development, they should do it in a standard way which is a phase 3 study that follows the current phase 2 data that we have, and do it the right way, and spend the money instead of hoping that the healthcare system and parents will undertake the burden.

DR. COLE: Ms. Boyce?

MS. BOYCE: Yes. Danielle Boyce. So my son was on a REMS drug, a different REMS drug for six years and, because it was ongoing, he was taking the drug every day, we had, every three months, a specific medical follow-up that needed to be reported as a condition of the REMS.

What concerns me about this is it's sort of like they're registered, and then it just goes to the sponsor, and it doesn't sound like there's any follow-up from the FDA in keeping track of what's

happening or the parents aren't reporting as a condition of this, because it's a one-time drug.

So that is what concerns me about this REMS, that yes, it educates, yes, there's almost like a consent form. That's what we had and we go over the risks with the physician. And then you hope that there's long term. They're recruited for a study by the sponsor, is what I'm hearing. So it doesn't help me to address that safety piece in that sense, if that makes sense.

DR. WILKINS-PARKER: This is Jamie. Can I clarify one thing?

DR. COLE: Dr. Wilkins-Parker, yes.

DR. WILKINS-PARKER: This Jamie Wilkins from FDA. I wanted to clarify again that all REMS are actually operationalized and executed by the applicants of the drug. The agency sets forth the requirements and so the program for your son's drug was actually executed by that sponsor or the applicant with the requirements set forth by the agency.

For this particular product, because it is a

one-time administration, practically from the agency's perspective, the follow-up would need to happen in that post-marketing requirement study and not through ongoing requirements in a REMS.

MS. BOYCE: Can I just clarify, though, there isn't a requirement as of now for that post-marketing study, is there?

DR. WILKINS-PARKER: That's something that we can discuss, but there would be something as part of the approval of the drug if it were to be approved as a requirement to have that study.

MS. BOYCE: But we're not voting on that today as to, yes, if you do the study. It's just yes and then it's discussed later if the study is done, yes or no, and then we discuss later. That's my concern.

DR. COLE: I'll take a little chair's prerogative here and I would say, having been involved in a substantial number of follow-up studies, the infrastructure required for follow-up studies is not trivial.

If one were to get to this point, hopefully

there would be a partnership developed between the applicant and individual organizations with relevant infrastructure and a demonstrated track record of greater than 90 percent follow-up, because, I mean, 90 percent is sort of follow-up for babies. That's generally sort of the NICHD network sort of gold standard.

So Dr. Assis?

DR. ASSIS: I think, from my perspective, in the context of the uncertainty regarding safety data, particularly for this drug, I think the downside of a REMS, given the phase of this drug's development, is potentially just transferring that uncertainty and anxiety, I would say, to patients, families, and even to the providers.

So I think, if we are very uncertain, I don't know how there could be an informed way of dealing with that out there in the community. And I think that even the risk-benefit ratio, which is an upcoming vote would depend on the population that's targeted. And I think that's very much not clear. That's very unclear based on those

presented, so I think REMS in this case is not helpful.

DR. COLE: Yes. And I would say we need to focus on the question, the discussion, which is the FDA's proposal for the REMS. And it sounds like what you're saying is that their proposal for a REMS, given our uncertainty about the outcomes, would effectively transfer that uncertainty to families and to providers.

DR. ASSIS: That's my concern in this instance.

DR. COLE: Dr. Khurana?

DR. KHURANA: I just want one clarification from the FDA on this. Would a phase 3 study qualify as an additional intervention here?

DR. OMOKARO: Do you mean an additional study prior to approval? Is that what you're asking?

DR. KHURANA: Yes, yes.

DR. OMOKARO: Yes, that is definitely a possibility.

DR. COLE: Dr. White?

DR. WHITE: Michael.

DR. COLE: Dr. Pei?

DR. PEI: I was going to clarify about the post-marketing requirements and the difference of that versus the REMS. Is that those are two separate considerations and I know there was concern about the consent and there was no requirement for the sponsor to ensure that the patients are enrolled into a post-marketing study, but I think that's the same when you have to consent any patient into a study.

The patients have to be willing. The agency can make certain requirements and, in my last slide, I did point out that we are considering potential safety post-marketing requirements. And if the drug is approved and the marketing requirements are required, is determined to be required, then it is the sponsor's ability to provide the opportunity for these patients to enroll. And then really whether they enroll or not is really the patient's parents -- they have to consent to enroll in the study.

DR. COLE: Dr. White?

DR. WHITE: Michael White. Thank you for clarifying because the REMS study is one thing and the registry is another, which it seems to me that the need for long-term follow-up in order to figure out any signal that might be attributable to this drug as a child, an infant later in life, needs, like, 10, 15 years of development to figure it out.

It needs to be tied to the electronic medical record and this is a good opportunity to try to learn how to set up a registry if indeed you choose or are chosen to do that, this is a good opportunity to set up a registry involving electronic medical records and a way of tracking people that are involved in studies.

So we can find out what happens to these kids when they're 8, 9, and 10 years old.

DR. COLE: Dr. Adams?

DR. ADAMS: This is a clarifying question to the FDA. If it is determined that a REMS would be implemented and the particular topics would be covered under the REMS, how prescriptive is the FDA

able to be in terms of the particular information that's disseminated to families, disseminated to providers.

So it's one thing to say the REMS is going to inform parents about the risk of neurodevelopmental outcomes and that your child needs to be followed. It's another thing to say, these are the time points at which we think your child should be followed. These are the assessments that should be done. This is how and by whom they should be done, and the types of domains that need to be followed and what have you.

So how prescriptive should the FDA be about that?

I understand that may shift into the post-marketing approval research or surveillance, but nonetheless, I think that starts at the REMS.

DR. WILKINS-PARKER: That's actually a really good question. One thing that is a benefit of having a REMS is, it's an agency-approved set of documents, so the agency would be able to review and approve the information, and all of the

documents, and all of the educational materials versus a voluntary risk management plan from the sponsor or something that they control the information inside.

So with a REMS, the agency actually reviews the information to ensure that it aligns with any of the prescribing information, with the indication, and whatever the restrictions are included with the program.

DR. ADAMS: Thank you.

DR. COLE: Dr. Hunsberger?

DR. HUNSBERGER: In order to understand the cognitive impairment that could occur, you really need to have a control group and so I'm worried, with this, there's no real way to have a control group.

DR. COLE: Yes, Dr. Adams?

DR. HAVENS: Is that true, can we confirm that the REMS doesn't have a control group?

DR. WILKINS-PARKER: To repeat, the REMS is not a study. The PMR is the study, so I would have to defer about the PMR.

DR. OMOKARO: Yes, that's correct. The REMS does not have a control group. For a post-marketing requirement study to have interpretable information, would be best to have a control group within that study.

DR. COLE: Yes. Ms. Hugick?

DR. MCVEY HUGICK: A couple things, and actually, Dr. Parker, you just brought this up. So this applicant submitted a REMS proposal, which is voluntary. And this slide from the applicant, CO-100, if anything, by preparing that, it made me want a REMS more than I already did.

So I would just say a couple of things that jumped out at me for that, that were really important, the certification of the facilities, so it's not just a NICU; it's a NICU that actually has experience treating these at-risk neonates. And really, I could go through each of these points and say that, for the reasons underlined or the reasons that I actually think a REMS is important in this case.

I do want to acknowledge, though, the points

and the comments made by the public today were very compelling and moving. And I just want to put that on the record, that I very much appreciate and value the fact that the mother and child interaction is so important.

But safety is also important and so, for all the reasons that have already been stated, I think a REMS would be crucial here and that's where I'm at.

DR. COLE: Thank you. Dr. Havens?

DR. HAVENS: Thank you. I'm still trying to get it straight. If we think about levels of evidence and what level of evidence we want to be able to put in place to be able to make a rational decision about approval of this drug, a phase 3 trial would have specific requirements, would be randomized and controlled, and with follow-up that would be agreed upon by the sponsor and the FDA.

A post-marketing requirement is one level lower than that. Can a post-marketing requirement also include a control group as a part of that?

DR. OMOKARO: So let me just clarify. A

post-marketing requirement only happens after a drug is approved.

DR. HAVENS: No, I understand that. But could it have the same level of --

DR. OMOKARO: Yes, yes. It's an adequate, well-controlled study where the design elements are designed and agreed upon between the applicant and the FDA.

DR. HAVENS: The REMS is one level below that because it has no control group, although there might be a little more power for you to get stuff you want.

DR. WILKINS-PARKER: Again, the REMS is actually a risk mitigation program that's going to restrict, if approved, this product to certain hospitals that have certain expertise, where those are the only places that will have access to the drug to administer it.

The registry portion of the remainder of that restrictive distribution program would be access to the information for all patients who have received the drug in order to then facilitate that

post-marketing study.

DR. HAVENS: But the only one of these activities that would enforce somebody to support -- as Dr. Cole points out, all of this stuff that we're asking for is expensive. And families of course have to decide if they're going to enter or not. But there has to be a structure in place to make it happen.

The only one of these mechanisms that actually has money associated with the structure needed to get the data that we want to make a rational decision as a phase 3 trial. Is that accurate?

DR. KORVICK: Can I answer?

DR. OMOKARO: No, the phase 3 trial as well as the post-marketing requirements, the PMR.

DR. KORVICK: So basically you can think of it like this. And I would ask you what your answer would be as far as what information that you would like to have. Dr. Korvick, deputy director of safety, DGIEP.

DR. COLE: Can you state your name?

DR. KORVICK: Dr. Korvick. So I think you know, if you guys think that you would like a controlled trial to study long-term safety, you have to think, tell us that that's what you'd like to do. And we will take that.

You can ask for that kind of study before approval. If it's done after approval because it's related to serious safety risk, we call it a PMR, which is a required post-marketing study.

Will every patient that got stannsoporfin get into a post-marketing study? Not necessarily because you know you have to want to enroll in the study, and then go for the visits, and do all that.

The registry that we're talking about in the REMS is a word. It's a mechanism to get somebody's name and telephone number so that the investigators and the sponsor could offer those people this trial and follow up or those people who -- the patients who got it could call the sponsor and say I know you have a study. I'd like to enroll.

So however you view this, pre- or post-approval, the design that you would want to have in

this randomized controlled study for safety could be the same. Otherwise, you could have in post-marketing an open-label study if you're not recommending a controlled study.

So it goes back to what kind of study would you like to see and would you like it done before or after approval. I hope I'm clear.

DR. COLE: Dr. Aly?

DR. ALY: Yes. I'm just interested in the very, very small population who are just at the age of getting exchange transfusion. So these babies we know already have problems and this drug can be available then, so if we do a REMS for this group of babies, that would save us lots of time and would be helpful.

DR. COLE: Dr. Guillory?

DR. GUILLORY: I think my question was answered, but again, as a neonatologist, every day, you're having to make decisions about risks and benefits as to which drug we use, what's the risk and benefits. And here, I have to understand, am I trading one thing for something else and trading

one illness for another illness. And that's what I wanted to clarify.

Again, the healthcare setting certification is still very confusing to me. How are you going to get certification for NICUs? And we don't have definitions of NICUs yet.

DR. COLE: Dr. Newman?

DR. NEWMAN: Similar to Dr. Guillory, a big part of this proposal is education and making sure that the people who are making the decision have enough information to make the decision and the doctors are trained.

I think it would be really hard to prepare those materials, given what we know now, that would allow people to make an informed decision. And the registry alone; registries work great if you have some very rare adverse effect that basically never happens in people who don't get the drug.

Then you can say they have the event. It must be from the drug. But when you're talking about speech delay or behavior problems, or any of these things that we worry about for

neurodevelopmental toxicity, they occur a lot in people who aren't exposed. And then it just becomes impossible to tell whether you have an excess in an observational study. That's why you need a randomized trial.

DR. COLE: Dr. Adams?

DR. ADAMS: So there was a question earlier in this discussion about, post-approval, how would you have a control group. I think there are two ways to compare or two general approaches that I would think about to compare neurodevelopmental outcomes in treated children to some other group.

One option is to take a look at the performance on standardized tests of children in a treated group compared to the test normative data. The disadvantage of that is that we don't know whether the characteristics of those two groups are similar. And so that may not be a fair comparison.

I think the other option is post-approval to have follow-up not just of children who received the drug, but follow-up of the babies whose parents elect not to receive it. And those kids go into

the registry, too, and you compare them. The challenge of that is that, if it's done post-approval, I wonder if there's going to be clinical equipoise on the part of the providers who are offering the treatment on the part of the parents who are electing or not electing to receive the treatment for their child.

DR. COLE: Dr. Khurana, last point.

DR. KHURANA: Just a clarification for the FDA, is REMS tied to phase 2 studies only or can it also be tied to phase 3?

DR. WILKINS-PARKER: REMS themselves aren't necessarily associated with studies. They're associated with the risk-benefit profile of any product.

DR. KHURANA: I just wanted to clarify whether there's an obligatory rule with phase 2 only or --

DR. WILKINS-PARKER: A REMS is independent of study phase.

DR. KORVICK: A REMS can be looked on as an intermediate between full approval and IND access

to a drug. So it puts in these elements to assure safe use to make sure that whatever uncertainties and so forth or even what certainties you know can let you write that prescription rather than having an IND.

It's sort of to cover how you would use the drug safely, more than just what's written in the label if you approve the drug.

DR. WILKINS-PARKER: Again, it's used to mitigate a risk, so we have a toolbox that we can use for many things, not just what you saw proposed here, to mitigate a specific risk for a specific drug. The approval decision is something that takes a REMS into consideration and the totality of the risk-benefit balance.

DR. COLE: So if I could try to summarize this robust and informative discussion, I think the consensus of the panel members is that the drug needs more study. Is there anybody going to object to that?

(No response.)

DR. COLE: No. So then I think the next

sort of step in that is, what is the best mechanism to assure to the panel's degree of certainty or comfort that, that study information is going to be obtained? And certainly one strategy is REMS. Approve the drug and then institute REMS.

I think that there was certainly some discussion about the pluses and minuses of that. One possibility that was suggested was to restrict the study population or the population for which the drug is approved to a very narrow population of babies and then try to figure out whether you can get enough information via the registry and other things that are being suggested in the REMS to be able to evaluate the drug after approval.

A second possibility that was discussed is the idea that some of the panel members felt that we may not know enough today to approve the drug and so therefore further study before approval is a better strategy than REMS, than approval and REMS. And I'm not sure there's consensus about that one way or the other.

I think, in terms of the specific elements

of the REMS, I think that the people who spoke to those elements seem to favor the REMS proposed by the FDA in terms of certification of NICUs despite the fact that there's heterogeneity of how NICUs are certified, et cetera.

But I think there's certainly experience out there that would provide some road map to making sure that the REMS proposed by the -- if the drug were approved, the REMS proposed by the FDA would be the preferable one over the REMS proposed by the applicant.

So I've tried to summarize the discussion. I know it's a little bit of Brownian motion here, but are there members of the panel who want to add, revise, delete any of that somewhat sprawling summary here?

(No response.)

DR. COLE: Hearing none, we'll go on to question 7, which is a voting question. Does the risk-benefit profile of stannsoporfin support approval; A, yes without a REMS; B, yes with a REMS; and C, no? So are there clarifying questions

about this particular question 7, the risk-benefit profile supporting approval? I'm not feeling the love here. Yes, sorry. Ms. Ellis?

MS. ELLIS: A lot has been covered here. You know I'm slow, but it's approval as indicated in the application as of right now with none of those other considerations added.

DR. COLE: So I think the approval means, does the risk-benefit profile support the idea that the FDA would approve the drug as we currently understand the risks and benefits of the drug?

DR. OMOKARO: I would just add, because I think your question is getting at, what population has been discussed, but it should be the population that has been studied, because that's what we know about.

DR. COLE: So are there other questions, comments about the risk-benefit profile supporting approval?

DR. WHITE: Michael White. That is with the specific circumstances defined by the FDA in which the drug is used appropriately. We can't use it

off label if it has a REMS. Correct?

DR. OMOKARO: Correct.

DR. WHITE: Thank you.

DR. COLE: I would just temper that question by, the neonatal intensive care unit is not a place where off-label drug use is unknown. That's a double negative, which is to say we use off-label drugs all the time. Other questions or comments? Okay. So please press the button on your microphone that corresponds to your vote.

There are only two buttons -- or I'm sorry. There are three buttons to press, A, B, or C.

(Voting.)

DR. FAJICULAY: For the record, the results are 0 yes with a REMS, 3 yes -- excuse me. I redact that. The results are 0 yes without a REMS, 3 yes with a REMS, and 21 no.

DR. COLE: We'll start with Dr. Aly this time. Please state your name, and your vote, and if you wish, why you voted that way.

DR. ALY: Hany Aly. I voted yes with a REMS for consideration of babies with very high

bilirubin or can be at risk or who are already at risk for kernicterus. I would like to have this option available for them.

DR. WHITE: Michael White. I voted yes with a REMS, but it has to be clearly specified under what circumstances it can be used in. It has to be in circumstances where the REMS has a certified facility that will be using it appropriately.

DR. SAYEJ: Wael Sayej, I voted no. Again, I think there are a lot of unanswered questions and a lot of ifs with regards to the future before the medication should go in.

DR. STRATE: I'm Lisa Strate. I voted no.

DR. WADE: I'm Kelly Wade. I voted no. I'm also concerned that the last three exchange transfusions I did were in pre-term babies less than 35 weeks. And so those that I'm most concerned about would also not be covered by this data. And I think we're doing a lot of work in the NICU to help be more supportive of families whose children are undergoing these procedures.

DR. KHURANA: Sandeep Khurana. I voted no

for the discussion we have had over the last couple hours.

DR. CALLAHAN: David Callahan, I voted no.

DR. ROSEN: Rachel Rosen, I voted no.

DR. ASSIS: David Assis, I voted no. I would just say that there probably is a group of patients who will benefit from this therapy. It clearly does something and it would be helpful if that population were studied more properly in terms of preventing actual events of interest or surrogates thereof because the risk-benefit tolerance for risk, rather, would be very different if that were clearly specified.

DR. COLE: Sessions Cole. I voted no.

DR. RAUFMAN: Jean-Pierre Raufman, I voted no.

DR. MCVEY HUGICK: Joy McVey Hugick, I voted no.

MS. BOYCE: Danielle Boyce, I voted no.

MS. ELLIS: Annie Ellis, I voted no. I just wish there were a more narrow indication and get this drug that seems to do what it does to get to

patients who need it. I wish there was a stronger biomarker to identify risk earlier.

DR. DRACKER: Bob Dracker, I voted no. I agree with that comment because I think it's very valuable for a subgroup of patients, but we don't have adequate clinical data and a REMS should be conducted regardless.

DR. FEAGINS: Linda Feagins, I voted no.

DR. HAVENS: Peter Havens, I voted no.

DR. HOEHN: Sarah Hoehn. I voted yes with the REMS and I sort of outlined what the criteria I would recommend if it were up to me. And I said 38 weeks' gestation, level 3 NICU. The babies would have to fail phototherapy, which I defined as first 6 hours.

Then to me, the other thing we didn't discuss today, but one opportunity where I think this could be really helpful is families who refuse blood products. So I think it should exist somewhere so people have access to it for families who are refusing blood products or families who are refusing exchange transfusion.

It comes up frequently that people say can we do something in lieu of a blood transfusion? And if I were a family that was going to refuse blood, I would want to know about this opportunity.

DR. CATALETTO: Mary Catalano, I voted no.

DR. GUILLORY: Charleta Guillory, I voted no.

DR. ADAMS: Heather Adams, I voted no.

DR. NEWMAN: Tom Newman, I voted no. I think Dr. Hoehn has a good point, but my concerns are just still that the evidence of harm and risk and benefits, I don't think, are sufficiently mitigated by the REMS proposed.

DR. SMITH: I'm Brian Smith. I voted no.

DR. HUNSBERGER: Sally Hunsberger, I voted no.

DR. COLE: So now we're on to the final question, which is question 8. This is the final question. Right? You're not sneaking up another one on us here? Okay. All right. So this is a discussion question. Discuss the necessity of additional studies, clinical or non-clinical, with

stannsoporfin to assess the potential for adverse neurodevelopmental outcomes.

Comment on potential design elements. So this question is basically advising the applicant and the FDA about what we think would be the best ways to study neurodevelopmental outcomes in infants who have received the drug. Dr. Dracker?

DR. DRACKER: Bob Dracker. I think, again, the need to look at the oxidative stress characteristics of the use of this drug to lower bilirubin itself is very important.

I also think this should be a consideration that, if that is in fact the case, currently approved therapies, as I mentioned, as alpha tocopherol, as an adjunct for certain infants should be considered as well. I know it has nothing to do with this drug approval per se, but I think it's a clinical consideration.

DR. COLE: Other discussion about suggestions? Yes, Dr. Assis?

DR. ASSIS: I would just suggest development with whatever retrospective data is available of

some sort of surrogate outcomes of interest. It would certainly strengthen this field.

DR. COLE: Dr. Callahan?

DR. CALLAHAN: Yes. As we discussed before, I think any good testing, not necessarily so frequent, so some measure of cognition, a measure of language, and then screening for learning disabilities and behavior disorders.

I don't think it's necessary every year, like at age 2, 3, 4, 5, 6, but just age 2, age 5, and age 8 would probably be sufficient.

DR. COLE: Sorry. Dr. White?

DR. WHITE: My wish for you to be able to design the study that would be able to differentiate between the damage done by an elevated serum bilirubin at the same level that you might choose to use this drug is significant.

But my confidence that you can design that study over a period of 8 to 9 years of observation for these children is very, very pessimistic. I just don't see how you can design the study that we all want. I don't think it can physically or

logistically be done because we're looking at a very small group of subjects, we need control subjects, and we need long-term follow-up.

The loss to follow-up is going to be most of the subjects that get signed up by the time they're 5 years old. I don't know how we can design it, but I really would like to see it for many reasons.

DR. COLE: Dr. Adams?

DR. ADAMS: So I think that it would be very helpful to have an additional study of the potential for adverse neurodevelopmental outcomes. And I think that some of the choices that could be helpful would be to take a look, first of all, at the existing data.

There may be opportunities to examine those data in some other ways to better understand what the safety signal is from the available data. I also think that, for new studies going forward, it'd be very helpful to really sit down and prospectively think about the minimum number of assessments that could feasibly answer these questions, speaking to the issue of having families

come back and needing to have retention strategies to have families come back multiple times.

There are options to use perhaps shorter batteries, shorter assessments that don't require going to a developmental specialist or neuropsychologist for years, and years, and years, but potentially could be given in a standardized way, in a psychometrically sound way in the clinic setting where these children are already followed up.

I'm thinking of things like the NIH toolbox, which we know is available to be given by coordinators or clinical staff, so I think there are ways to specifically design a study that could better follow kids. And I do think it's going to be very important to take a look at where they're at, not just at age 5, but where they're at, at age 8 when they're in the classroom and they're having to use their brain to function in a learning setting.

DR. COLE: Dr. Newman?

DR. NEWMAN: Tom Newman. Just to address

Dr. White's question, I'm just trying to think what would make this practical? One possibility might be to see about studying it in another country. In some of the Scandinavian countries, where you get a number at birth and they use these studies where they link perinatal outcomes like how kids do in school and all the way out to their military exams, but something like that where the loss to follow-up wouldn't be nearly as big a problem and the expense could be less.

It would be a lot of years, but even just to get through school, so that would be one possibly feasible way to do it. An intermediate thing that would definitely be worth doing, a lot of the people who spoke in favor of it spoke about the possible beneficial effect on breastfeeding.

I don't know if you looked at that in the randomized trials you did, but that I mean, if you could show that in fact it does improve breastfeeding rates, that would at least be something because that is sort of how it's being promoted, so actually look at that and see how many

more women breastfeed if the baby gets this intervention.

DR. COLE: Dr. Aly?

DR. ALY: Yes. The drug is bringing a new strategy, so we'll always have bilirubins in babies, but there are a higher level that are dangerously high. But the option of having too low bilirubin was not existing before the drug. And if we are doing the drug for babies who are not very sick, so it is so important to monitor the lower bilirubin and then follow the neurodevelopmental for these babies.

DR. COLE: Dr. Smith?

DR. SMITH: So for the comments on the neurologic follow-up, it seems like 2-year follow-up has been the standard for neonatology for follow-up of drug trials. That would seem reasonable for pre-marketing requirements. If longer-term follow-up is wanted, that could be a post-marketing requirement. I feel like the population that we would likely use it in, in the U.S. is so sick and relatively rare that it would

make the study not feasible.

And then to give it to kids who are similar to the 204 study, where they're just on single phototherapy, given the known toxicity profile, which there's a little bit of a mortality signal. There's liver. There's brain. There's phototoxicity, thyroid, thrombocytopenia, hearing. Seems a bit much, given the fact that we have a known tetramer for kids who have hyperbilirubinemia.

DR. COLE: Dr. Havens?

DR. HAVENS: I think the last comment brings up an important issue, which is the relationship between the effectiveness of the drug and the toxicity. This conversation has mostly been about toxicity and we are all willing to accept more toxicity if a drug has proven benefit in a bad situation where there are no other potential interventions.

So I think one of the challenges with designing a study like this is to really think about, first and foremost, the primary efficacy

endpoint. The efficacy endpoint has to be more compelling than the percent change in total serum bilirubin, or there's no amount of toxicity that you can really say is acceptable.

So one approach to a study would be to get together a group of neonatologists to ask what would be the appropriate endpoint that would compel you to want to study this drug in the neonatal network or something like that.

DR. COLE: Dr. Wade?

DR. WADE: Two different comments; one, we've talked a lot about our concerns about neurodevelopmental outcomes and part of the concern, I think, grew when we were looking at radioactive tin labeled stannsoporfin data.

We talked about the difficulties of extrapolation or interpretation of rats and dogs. And I just wonder if there is a role for a primary model to actually see the penetration of the drug into the brain or the effects of heme-oxygenase in the brain in a primate model?

I just wonder if that would be helpful. And

then separately, we all heard very passionate stories from parents today and we do experience, we do see what they were experiencing in the newborn ICU. And we're wrestling with how parents would mitigate this risk-balance between how much risk of hearing loss, speech, neurodevelopment are you willing to take for a shortened hospitalization and improved time for bonding.

I think that would be an interesting question for a parent group to give us information about how they would try to balance those risks. And I think there are parent groups working in this field right now who are anxious to be involved in parent input as we try to design these very difficult neonatal trials.

DR. COLE: Dr. Smith? Dr. Adams?

DR. ADAMS: Just one final comment; I think that, when we think about what additional studies might look like, my own experience today has been that I'm the only neuropsychologist in the room where a lot of the discussion has been about neuropsychology. And that's been very lonely.

It's unfortunate that there wasn't the folks from the applicant side to have that dialogue and I would really welcome the opportunity to have that engagement and try to understand from their perspective what their decisions were around their approach to following kids to look at these outcomes.

DR. COLE: I'd like to take the chair's prerogative to ask Dr. Maisels to say a word here for us, help inform our final discussion here.

DR. MAISELS: Thank you, Dr. Cole. First, I'd like to thank the advisory committee and everybody who's worked on this project for quite a long time, for the time and the effort that has gone into this.

I admit to having been stung by your initial vote as to whether or not this drug works. The evidence that this drug works is overwhelming. It's not just one study that has been done, 204, 202. There are 9 Rockefeller studies, every one of which is 100 percent agreeable with the findings that this drug is highly effective, highly

effective in lowering the bilirubin level, in reducing the risk of needing phototherapy, in reducing rebound. And there is no question about its efficacy, no question about its efficacy.

So I have to tell you I just do not understand. I did my first study on jaundiced babies in 1967. I published a paper in 1971. I submitted a paper just two weeks ago again. So I've been involved in taking care of jaundiced babies all my life and I take care of well babies in the nursery even though I'm a neonatologist.

So I just wanted to say that not only does the drug work, there are other issues which you raise which are perfectly legitimate, but is there a benefit? Is it a benefit? And there is a definite benefit. The benefit of families is enormous with this one.

DR. COLE: I got it. I think we have the point. Thank you. Thank you, Jeff. So any other comments about question 8 in terms of the decision? So I think, in terms of answering the question about the necessity of additional studies, I think

the consensus on the panel is yes. The answer to that question is yes. Anyone object to that consensus?

In terms of non-clinical studies, I think the suggestion of a primate model is an interesting one. That certainly would be a consideration in terms of clinical studies. There was a variety of different suggestions in terms of characteristics that ought to be included in the clinical studies.

I think oxidative stress has been a theme that we have seen, we've discussed. I think that the idea of making sure that cognition is measured at several time points in childhood, not only at 2 years of age, but likely at later time points, 5 and 8 years of age.

I think that the possibility of using a variety of different testing strategies for children that may or may not require subspecialty visits is an interesting suggestion. There was a suggestion possibly of studying the drug in another country, where there is a more robust electronic infrastructure, to be able to follow children

longitudinally.

There has also, I think, been a consistent theme that including neuropsychology and neuropsychological assessments in the planning of future studies would be a good idea. One strategy that we have not discussed is the use of twins. Monozygous twins are terrific experiments of nature. I don't know how many monozygous twins who are isoimmunized pop out in the United States every year, but the advantage of twins is generally that they are, you know, consistent with respect to genetic background.

They all experience the same environment growing up and you have a lot of confounding variables included in that study design. However, I'm just not sure how many isoimmunized twins there are born in the United States on an annualized basis. But the study number would be much smaller than some of the study numbers that we've discussed so far.

So I think we've tried to comment for the FDA. The necessity of additional studies, I think,

is yes. We've given them a few suggestions and a few study design elements. Are there any other suggestions from the panel members for the FDA about studying adverse neurodevelopmental outcomes for this drug?

Hearing none, let me see what my next script here says. So now we are about to adjourn. Panel members, please leave your name badge here on the table so that they may be recycled.

Pardon me? FDA wants to make some more comments. FDA, any more comments from the FDA, questions?

DR. OMOKARO: We would just like to thank the committee and Dr. Cole for all your discussion today and your expert input. It has been very informative in helping us to continue our review of the application. So thank you for that.

Adjournment

DR. COLE: Great. Please take all your personal belongings, as the room is going to be cleaned at the end of the meeting day and meeting materials may be left on the table. And they will

be disposed of. Thank you very much.

(Whereupon, at 4:08 p.m., the meeting was adjourned.)