Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Gastrointestinal Drugs Advisory Committee and Pediatric Advisory Committee Meeting May 3, 2018

Location: DoubleTree by Hilton Hotel Bethesda – Washington DC, the Grand Ballroom, 8120 Wisconsin Avenue, Bethesda, Maryland.

Topic: The committees discussed new drug application (NDA) 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 who are at risk of developing severe hyperbilirubinemia.

These summary minutes for the May 3, 2018 joint meeting of the joint Gastrointestinal Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration were approved on June 10, 2018.

I certify that I attended the May 3, 2018, joint meeting of the Gastrointestinal Drugs Advisory Committee and Pediatric Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jay R. Fajiculay, PharmD
Designated Federal Officer
Gastrointestinal Drugs Advisory Committee

/s/
F. Sessions Cole, MD
Acting Chairperson
Pediatric Advisory Committee

Summary Minutes of the
Joint Gastrointestinal Drugs Advisory Committee and Pediatric Advisory Committee Meeting
May 3, 2018

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research and the Pediatric Advisory Committee (PAC) of the Food and Drug Administration, Office of the Commissioner, met on May 3, 2018 at the DoubleTree by Hilton Hotel Bethesda – Washington DC, the Grand Ballroom, 8120 Wisconsin Avenue, Bethesda, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from the FDA and InfaCare Pharmaceutical Corporation. The meeting was called to order by F. Sessions Cole, MD (Acting Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD (Designated Federal Officer). There were approximately 60 people in attendance. There were seven Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committees discussed new drug application (NDA) 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 who are at risk of developing severe hyperbilirubinemia.

Attendance:
GIDAC Members Present (Voting): David N. Assis, MD; Linda A. Feagins, MD, AGAF; Joy McVey Hugick, BA (Consumer Representative); Sandeep Khurana, MBBS; Jean-Pierre Raufman, MD; Rachel L. Rosen, MD, MPH; Lisa L. Strate, MD, MPH

GIDAC Members Not Present (Voting): Lin Chang, MD; Christopher S. Coffey, PhD, MS; Benjamin Lebwohl, MD, MS; Darrell S. Pardi, MD, MSc

GIDAC Member Present (Non-Voting): Douglas Levine, MD (Industry Representative)

PAC Members Present (Voting): Danielle Boyce, MPH (Patient-Family Representative); David J. Callahan, MD; Mary Cataletto, MD, MMM; Robert A. Dracker, MD, MHA, MBA, CPI; Peter L. Havens, MD, MS; K. Sarah Hoehn, MD, MBe; Wael N. Sayej, MD; Kelly C. Wade, MD, PhD, MSCE, FAAP; Michael White, PhD, MD, FACC

PAC Members Not Present (Voting): Avital Cnaan, PhD; Melody Cunningham, MD; Mark Hudak, MD (Chairperson); Bridgette Jones, MD (Pediatric Health Organization Representative); Christy Turer, MD, MHS, FAAP, FTOS

PAC Member Present (Non-Voting): Ronald Portman, MD, FAAP (Industry Representative)

Temporary Members (Voting): Heather R. Adams, PhD; Hany Aly, MD, FAAP; F. Sessions Cole, MD (Acting Chairperson); Annie Ellis (Patient Representative); Charleta Guillory, MD, MPH, FAAP; Sally Hunsberger, PhD; Thomas B. Newman, MD, MPH; P. Brian Smith, MD, MPH, MHS

FDA Participants (**Non-Voting):** Julie Beitz, MD; Jessica J. Lee, MD, MMSc, Stephanie O. Omokaro, MD, Y. Veronica Pei, MD, MEd, MPH; Gerri R. Baer, MD; Jamie Wilkins Parker, PharmD

Designated Federal Officer (Non-Voting): Jay R. Fajiculay, PharmD

Open Public Hearing Speakers: Warren Rosenfeld, MD (South Nassau Communities Hospital); Lauren Buck; Margaret Conway-Orgel, DNP, NNP-BC (Medical University of South Carolina); Gavin Clingham (National Coalition for Infant Health); Sonja Ferguson (Hand to Hold; statement read by Margaret Conway-Orgel); Carol L. Wagner, MD (Medical University of South Carolina); Thomas F. Nealon III (American Liver Foundation)

The Agenda was as follows:

Call to Order and Introduction of Committee	**F. Sessions Cole, MD** Acting Chairperson, Pediatric Advisory Committee (PAC)
Conflict of Interest Statement	**Jay R. Fajiculay, PharmD** Designated Federal Officer Division of Advisory Committee and Consultant Management (DACCM), CDER, FDA
FDA Introductory Remarks	**Stephanie O. Omokaro, MD** Lead Medical Officer Division of Gastroenterology and Inborn Errors Products (DGIEP) Office of Drug Evaluation (ODE) III Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**InfaCare Pharmaceutical Corporation**
Introduction	**Lawrence A. Hill, PharmD, MBA** Vice President, Clinical Development Mallinckrodt Pharmaceuticals
Unmet Need	**Jeffrey Maisels, MD, DSc** Chair Emeritus and Professor Department of Pediatrics Oakland University William Beaumont School of Medicine

Clinical Pharmacology, Efficacy and Safety	**Nancy Ruiz, MD** Senior Medical and Clinical Advisor InfaCare, A Mallinckrodt Pharmaceuticals Company
Long-Term Neurodevelopmental Safety	**Dawn Phillips, PT, MS, PhD** Research Scientist, Outcomes Research Evidera
Risk Management Considerations	**Lawrence A. Hill, PharmD, MBA**
Benefit-Risk / Clinical Perspective	**Jeffrey Maisels, MD, DSc**

Clarifying Questions

BREAK

FDA PRESENTATIONS

Clinical Pharmacology Findings of Stannsoporfin	**Shen (Steven) Li, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology III Office of Clinical Pharmacology Office of Translational Sciences (OTS), CDER, FDA
Analyses of Efficacy Data	**Feiran Jiao, PhD** Mathematical Statistician Division of Biostatistics III, Office of Biostatistics (OB), OTS, CDER, FDA
Summary of Findings from Nonclinical Safety Studies in Neonatal Animals	**David Joseph, PhD** Lead Pharmacologist DGIEP, ODE III, OND, CDER, FDA
Focused Safety Evaluation	**Y. Veronica Pei, MD, MEd, MPH** Medical Officer DGIEP, ODE III, OND, CDER, FDA
Proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 209904 Stannsoporfin	**Charlotte Jones, MD, PhD, MSPH** Medical Officer Office of Medication Error Prevention and Risk Management Office of Surveillance and Epidemiology, CDER, FDA

Clarifying Questions

LUNCH

Clarifying Statements from Industry

OPEN PUBLIC HEARING

Questions to the Committee and Committee Discussion

BREAK
Questions to the Committee and Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** The Applicant has submitted a single, adequate, and well-controlled study (Study 64,185-204) as evidence to support the approval of stannsoporfin.

    a. Please discuss the clinical meaningfulness of the primary endpoint of "percent change from baseline in total serum bilirubin (TSB)" at 48-hours post-treatment with stannsoporfin.

Committee Discussion: *Some of the panel members stated that the change in TSB is not clinically meaningful, as this can vary per individual patient based on where the starting point of observation occurs. Additionally, it was discussed that the proposed endpoint was limited in that it did not pre-specify an estimated value range which could be considered clinically significant. However, one panel member stated that in the intended infant population where it is important to bring down TSB levels to prevent negative complications, percent change from baseline in TSB can be clinically meaningful. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please discuss your recommendations for dosing (3 mg/kg or 4.5 mg/kg single dose) based on the available information.

Committee Discussion: *The committee did not reach a general consensus of recommending either the 3 mg/kg single dose or 4.5 mg/kg single dose based on the available information. It was stated that based on the data from both the sponsor and FDA, both the 3 mg/kg single dose and 4.5 mg/kg single dose were equivalent in terms of efficacy. However, across the panel, concerns of inadequate data due to a small study population were discussed.*

Those in favor of the 3 mg/kg single dose stated that since both doses were statistically significant regarding effectiveness, the lower dose has a benefit of containing a lower amount of tin to be introduced into the infant. Those in favor of the 4.5 mg/kg single dose stated that although both doses were statistically significant regarding effectiveness, only the higher dose achieved secondary endpoint significance. Please see the transcript for details of the committee discussion.

3. **VOTE:** 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 (AAP) criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia?

Vote Result: **Yes: 6** **No: 17** **Abstain: 1**

Committee Discussion: *The majority of the committee agreed that the Applicant did not provide substantial and persuasive evidence of effectiveness for stannsoporfin for the proposed indication. The committee discussed various reasons regarding whether the Applicant provided substantial and persuasive evidence of effectiveness for stannsoporfin for the proposed indication.*

Those who voted YES stated that based on the strict wording of the question and the data provided by the FDA, stannsoporfin was shown to be effective in decreasing TSB in neonates. One committee member also stated that since this was not a phase 3 trial, there is time to discuss future steps.

Those who voted NO stated that the sample size was too small to confirm effectiveness, and that the study may not have used a clinically relevant endpoint to determine effectiveness. Before moving forward, one committee member stated that it would be beneficial to discuss what types of endpoints may be considered clinically meaningful. One member was concerned that data regarding infants between 35-37 weeks of gestational age were missing in the studies to support the indication. Another committee member stated they had many unanswered questions, and with the provided data and small population size, cannot calculate the number needed-to-treat or number needed-to-harm.

One committee member abstained, stating that they were uncertain whether the drug reduced TSB; or if so, in a clinically meaningful way. Please see the transcript for details of the committee discussion.

4. **VOTE:** Are the submitted data on long-term safety assessments adequate to characterize the potential risk of stannsoporfin-related adverse neurodevelopmental outcomes?

Vote Result: **Yes: 3** **No: 21** **Abstain: 0**

Committee Discussion: *The majority of the committee agreed that the submitted data on long-term safety assessments are not adequate to characterize the potential risk of stannsoporfin-related adverse neurodevelopmental outcomes. The committee discussed various reasons whether the submitted data on long-term safety assessments are adequate to characterize the potential risk of stannsoporfin-related adverse neurodevelopmental outcomes.*

Those who voted YES stated that kernicterus is a disaster for the brain. It was further stated that if a drug can decrease the rate of this complication from occurring, although the potential outcome may be the same, it is worth studying.

Those who voted NO stated that the small sample size made it difficult to identify potential safety signals of this product. Although there were lots of historical data provided, patients were not randomized and the investigators switched between measures across the different studies. Some committee members stated they would like to see long term follow-up data to study 205, as well as data regarding oxidative stress. One committee member stated that when neurotoxicity as a complication is the outcome, correctly identifying potential risks of adverse neurodevelopmental outcomes are very important. Please note that one committee member voted NO, but intended to vote YES, who stated that the submitted data were adequate to identify potential risks, neurodevelopmental outcomes (hearing, language), seizures, death in premature infants, thrombocytopenia, and infection. Please see the transcript for details of the committee discussion.

5. **VOTE:** Does the long-term and short-term safety profile of stannsoporfin in the proposed indicated population support approval?

Vote Result: **Yes: 2** **No: 21** **Abstain: 1**

Committee Discussion: *The majority of the committee agreed that the long-term and short-term safety profile of stannsoporfin in the proposed indicated population does not support approval. The committee stated that building on the previous discussions, there are inadequate data to support the long-term and short-term safety profile of stannsoporfin. One committee member who ABSTAINED stated that they were unable to decide. Please note that one committee member who voted YES stated he intended to vote NO. Please see the transcript for details of the committee discussion.*

6. **DISCUSSION:** Please discuss whether additional interventions beyond FDA-approved labeling, such as a Risk Evaluation and Mitigation Strategy (REMS), are necessary to ensure that the drug's benefits outweigh its risks.

    a. Please discuss the REMS proposed by the FDA, which consists of health care setting certification (for dispensing and administration), safe use conditions, and a registry.

Committee Discussion: *The committee discussed that since this drug is to be used in a very narrow patient population, it might be beneficial to focus a REMS based on the studied population. Additionally, it was stated that a REMS should be based upon a phase 3 study and recommended the Applicant to continue development in the standard phase 3 format.*

Regarding the REMS proposed by FDA, the committee discussed that a REMS program where providers are uncertain of all the potential risks, might transpose to public uncertainty. One committee member stated that a registry may be a good idea for patients who experience a rare drug-related adverse outcome that does not occur often; however, for outcomes that happen in many patients even without the drug being administered, it might be difficult to relate the outcome to the drug. It was also discussed that further study is needed, and one committee member proposed that a post-approval control group could include: (1) standardized performance on treated group versus a normal standard of care therapy group, or (2) post-approval follow-up of those who elect not to receive the treatment. Please see the transcript for details of the committee discussion.

7. **VOTE:** Does the overall risk-benefit profile of stannsoporfin support approval?

   A. Yes without a REMS
   B. Yes with a REMS
   C. No

   Vote Result: **A: 0** **B: 3** **C: 21**

   Committee Discussion: *The majority of the committee agreed that the overall risk-benefit profile of stannsoporfin does not support approval. The committee discussed both the benefits and limitations of approval of this product for the proposed indication.*

   Those who voted B (Yes with a REMS) stated that for providers who are treating infants at a high risk of developing kernicterus, they would like to have this option available. It was further stated that this product might also be an option for families who refuse blood products or exchange transfusion. One committee member stated that if approved, the REMS needs to be clearly specified, and only available at appropriately licensed facilities. Another committee member stated that some aspects of a REMS they would like to see include neonates 38 weeks of gestational age and older, level 3 NICU, and neonates who had failed phototherapy.

   Those who voted C (NO) stated that there is not enough clinical data to support approval of this drug. One committee member stated that there is a group of patients who may benefit from this drug, but that the specific population needs to be more clearly identified and studied. Another committee member stated that the use of biomarkers to identify risks earlier would be beneficial. It was also discussed that the harm versus benefit cannot be mitigated by a REMS. Please see the transcript for details of the committee discussion.

8. **DISCUSSION:** Please discuss the necessity of additional studies (clinical or nonclinical) with stannsoporfin to assess the potential for adverse neurodevelopmental outcomes. Comment on potential design elements.

   Committee Discussion: *The committee discussed the necessity of additional studies regarding the next steps of the development program. One committee member stated that it*

might be beneficial to look back retrospectively into the data that are currently available, or to look at existing data in different ways. Regarding timing of follow up studies, it was discussed that annual follow-ups are not necessarily required, but that follow-ups at milestone ages of 2, 5, and 8 years of age during an annual exam can decrease the burden of multiple office visits.

Several committee members stated that it may be beneficial to hold a workshop with various focus-groups to identify the types of data that can be considered clinically meaningful. Some focus-group ideas included parent groups to identify what level of risk they are willing to take regarding the potential safety issues of this drug versus phototherapy and the impact on bonding time, or mothers to identify differences in breastfeeding with and without the use of the drug. Another committee member stated that follow-up in other countries might be an option, or the use of monozygous twins. One member also stated that pre-clinical animal and primate models may be beneficial. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 3:50 p.m.