Temporary Compliance Waiver Notice

At the time of initial posting on May 1, 2018, the attached PDF document may not be fully accessible to readers using assistive technology. A fully accessible version of the document is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

In the event you are unable to read this document or portions thereof, please contact Division of Drug Information in Office of Communications at 301-796-3634 or email druginfo@fda.hhs.gov.

FDA Briefing Document

JOINT MEETING of the

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE and the PEDIATRIC ADVISORY COMMITTEE

May 3, 2018

Stannsoporfin

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

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this application for stannsoporfin 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 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

TABLE OF CONTENTS

LISTING OF TABLES

LISTING OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term or Definition
AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration vs time curve from time 0 to infinity
$AUC_{0\text{-}48h}$	Area under the plasma concentration vs time curve from time 0 to 48 hours
BIND	Bilirubin-induced neurologic dysfunction
BLA	Biologics license applications
BSID	Bayley Scales of Infant [and Toddler] Development
CBCL	Child Behaviour Checklist
CBE	Chronic bilirubin encephalopathy
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CYP	Cytochrome P450
DAT	Direct antiglobulin test
ECG	Electrocardiogram
ECRS	Early Childhood Rating Scale
EOP2	End-of-Phase 2
ET	Exchange transfusion
ETCO	End-tidal carbon monoxide
ETASU	Elements to assure safe use
FDA	Food and Drug Administration
FDAA	Food Drug Administration Amendments Act
FDCA	Food, Drug, and Cosmetic Act
G6PD	Glucose-6-phosphate dehydrogenase

Abbreviation	Term or Definition
GA	Gestational age
GCP	Good Clinical Practices
GIDAC	Gastrointestinal Drugs Advisory Committee
HCS	Health care settings
hr	Hour
IND	Investigational New Drug
ITT	Intent-to-treat
IVH	Intraventricular hemorrhage
IVIG	Intravenous immunoglobulin
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean platelet volume
MSEL	Mullen Scales of Early Learning
ND	Neurodevelopmental
NDA	New Drug Application
NEC	Necrotizing Enterocolitis
OR	Operating room
ORL	Operating room light
PK	Pharmacokinetic
PPI	Patient package insert
PT	Phototherapy
RDS	Respiratory Distress Syndrome
REEL	Receptive-Expressive Emergent Language test
REMS	Risk Evaluation and Mitigation Strategy
Rh	Rhesus
SAE	Serious adverse event
SD	Standard deviation
SIDS	Sudden Infant Death Syndrome
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event

Abbreviation	**Term or Definition**
T_{max}	Time of maximum concentration
TSB	Total serum bilirubin
US	United States
VABS	Vineland Adaptive Behavior Scale
WIPPSI	Wechsler Preschool and Primary Scale of Intelligence

1. EXECUTIVE SUMMARY

The Joint Gastrointestinal Drugs Advisory Committee and Pediatric Advisory Committee will be meeting on May 3, 2018, to discuss the adequacy of data submitted by the Applicant, InfaCare Pharmaceutical Corporation (a legal entity under Mallinckrodt Public Limited Company as of September 25, 2017), to support the safety and efficacy of stannsoporfin for the treatment of neonates who are at high risk for developing serious complications related to severe hyperbilirubinemia. The Committee includes experts in gastroenterology/hepatology, pediatrics and sub-specialties including neonatology and neurology, as well as biostatistics, and representatives from the patient community. The Applicant is seeking approval for stannsoporfin 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. In such patients, inhibition of heme oxygenase may decrease the production of bilirubin which may lead to a clinical benefit when administered in conjunction with phototherapy (PT).

Stannsoporfin, a tin metalloporphyrin that inhibits the rate-limiting enzyme in the catabolism of heme, is manufactured as a 30 mg/1.5 mL (20 mg/mL) injection. The Applicant is proposing a dosing regimen of 4.5 mg/kg of body weight, administered intramuscularly (IM) as a single dose.

One pivotal study (Study 64,185-204) in 91 neonates was submitted to establish the safety and efficacy of stannsoporfin. Study 64,185-204 was a phase 2b multicenter, double-blind, randomized, placebo-controlled trial of stannsoporfin, administered as a single IM injection in conjunction with phototherapy, in neonates greater than or equal to 35 weeks to less than or equal to 43 weeks gestational age with hyperbilirubinemia and indicators of ongoing hemolysis due to ABO or rhesus (Rh) incompatibility, or glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency. The primary objective of this study was to evaluate the safety and efficacy of two dose levels, the higher of which is proposed for approval, of stannsoporfin (3 mg/kg [n=30] and 4.5 mg/kg [n=31]) compared to placebo (n=30) as an adjunct to phototherapy.

The primary endpoint was the percent change from baseline in total serum bilirubin (TSB) at 48 hours post-treatment. The mean differences for percent change in TSB at 48 hours after treatment are statistically significant for both the 3 mg/kg and 4.5 mg/kg doses (LSM differences are -31.64 and -27.40 using the Applicant's intent-to-treat population, respectively, with both p-values < 0.0001), compared with placebo. The clinical meaningfulness of such a reduction at the selected time of 48 hours is uncertain as there are many other factors such as gestational age, hour of life, and comorbidities that contribute to the risk of developing complications from severe hyperbilirubinemia. To better understand how reduction in TSB might be translated into a clinical benefit in the target population, the following three pre-specified secondary endpoints were sequentially tested to control the overall Type I error rate:

- First secondary endpoint: time at which TSB crossed at or below the defined PT threshold
- Second secondary endpoint: PT failure (defined as re-start of PT > 6 hours after stopping, re-hospitalization for hyperbilirubinemia, use of intravenous immunoglobulin [IVIG], and/or need for exchange transfusion)
- Third secondary endpoint: incidence of rebound hyperbilirubinemia

After excluding 11 neonates whose TSB levels at enrollment were below the defined PT threshold, 15 neonates whose estimated time at which TSB crossed the threshold was prior to study medication injection, and 1 neonate with a baseline TSB that exceeded the threshold for exchange transfusion (ET) at enrollment and received ET during the trial, the difference between the stannsoporfin treatment arms (n=22 for the 3 mg/kg arm; n=23 for the 4.5 mg/kg arm) and placebo (n=19) for the 1st secondary endpoint was statistically significant only for the 4.5 mg.kg arm, precluding further hierarchical testing of additional endpoints. The results of the remaining protocol-specified secondary endpoints are discussed descriptively for their clinical interest. While the study was not powered to detect differences in each subcategory of PT failure (i.e., re-start of PT > 6 hours after stopping, re-hospitalization for hyperbilirubinemia, use of intravenous immunoglobulin [IVIG], need for exchange transfusion), PT failure was observed to occur at a more frequent rate in the placebo arm (n=8) compared to neonates in the stannsoporfin 3 mg/kg (n=3) and 4.5 mg/kg (n=1) arms. Three neonates in the placebo arm experienced rebound hyperbilirubinemia within 54 hours of discontinuing PT compared to 1 neonate in the 4.5 mg/kg stannsoporfin arm and none in the 3 mg/kg stannsoporfin arm.

Two supporting studies (Study 64,185-202 [n=58] and Study 64,185-06 [n=55]) were also submitted; however, the trial designs and enrolled populations differed from that of the pivotal study. The findings from these two supportive studies were not internally consistent, and interpretability was limited by lack of a placebo for one of the studies and observed treatment effects only at doses lower than those evaluated in the pivotal study (Study 64,185-204).

Nonclinical data suggest that brain, liver, and thyroid are potential target organs for exposure-related toxicity with repeated doses of stannsoporfin. The extent to which tin, a heavy metal, contributes to the observed findings is unclear. Given that stannsoporfin is administered as a single dose, the direct relevance of the nonclinical findings to human neonates is unknown. Of note, exposure to operating room light within 120 hours after a single administration of stannsoporfin resulted in phototoxicity leading to death in neonatal guinea pigs.

A total of 1430 neonates were included in the stannsoporfin safety population: 543 controls (received placebo with or without phototherapy) and 887 exposed to different doses of stannsoporfin (including neonates from the pivotal Study 64,185-204). The safety data available to directly support the proposed indication in the target population is limited because of the heterogeneous population and varying doses of stannsoporfin. There were no deaths or serious adverse events (SAEs) leading to study discontinuation in the pivotal study; however, there were 12 deaths reported during the overall development program, 10 of which occurred in the stannsoporfin treatment group which were assessed as not related to treatment. There were 27 neonates who developed SAEs that were assessed as not related to stannsoporfin and considered consistent with adverse events expected in neonates with hyperbilirubinemia. The major safety concerns based on FDA review are phototoxicity, thrombocytopenia and the potential for adverse neurodevelopmental (ND) outcomes.

The long-term ND database for the follow-up study to the pivotal trial (Study 64,185-205; stannsoporfin and placebo) is small. For example, only 34 pediatric patients had completed a one-year ND assessment and only 7 pediatric patients had completed a 2-year ND assessment, which is insufficient to characterize the potential risk of long-term neurodevelopment outcomes

related to stannsoporfin. There is some evidence to suggest that neurodevelopmental toxicity may be possible in pediatric patients exposed to stannsoporfin. Preliminary data from the pooled long-term extension studies showed that there is a numerically higher rate of both speech and hearing adverse events in stannsoporfin-treated pediatric patients.

Regulatory Considerations

FDA requires that drug manufacturers provide substantial evidence to establish a drug's effectiveness (i.e., "…evidence consisting of adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling…").

Generally, two or more adequate and well-controlled trials, each convincing on its own, are required to establish effectiveness. In certain circumstances, FDA will consider a single highly persuasive positive trial combined with independent findings that substantiate efficacy to support approval; however, it is critical to consider the possibility of an incorrect outcome which requires that all the available data be examined for their potential to either support or refute reliance on a single trial. Some of the characteristics of a single highly persuasive trial intended to support a marketing application include data from a large multicenter study, internal consistency across study subsets, multiple studies within a study, evidence of an effect on multiple endpoints evaluating different events, and statistically very persuasive findings.

The safety of a drug is considered in the context of its benefit and must provide an adequate number and duration of patient exposures to characterize the risks. FDA will consider the serious and life□threatening nature of the condition when determining the minimum number and duration of exposures required to adequately assess safety. Drugs shown to provide an important clinical benefit to address an unmet medical need may require less safety data to provide adequate assurance that risks are commensurate with benefits.

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical Applicants to develop and comply with a Risk Evaluation and Mitigation Strategies (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In general, these assessments are prepared by the Applicant and reviewed by FDA.

FDAAA also authorizes FDA to require post-approval studies or clinical trials:

- To assess a known serious risk related to the use of the drug;
- To assess signals of serious risk related to the use of the drug; or
- To identify an unexpected serious risk when available data indicates the potential for a serious risk.

2. POINTS TO CONSIDER FOR THE COMMITTEE

This background document is presented to facilitate the Committee's discussion and recommendations on whether data submitted by the Applicant adequately support the proposed indication of treatment of hyperbilirubinemia in neonates greater than or equal to 35 weeks of gestational age with indicators of hemolysis who are at risk of developing severe hyperbilirubinemia.

As you review the briefing information, consider the following:

1. A single adequate and well-controlled study (Study 64,185-204) was submitted. Consider whether the Applicant:
    a. assessed the appropriate primary endpoint to demonstrate a clinically meaningful outcome,
    b. conducted adequate dose exploration in the development program to determine the lowest effective dose, and
    c. provided substantial and highly persuasive evidence of effectiveness of 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 AAP criteria for phototherapy for developing complications associated with severe hyperbilirubinemia.

2. Based on the Applicant's characterization of the safety profile of stannsoporfin to date in the proposed population, consider:
    a. the adequacy of the overall and short-term safety assessment,
    b. the adequacy of the long-term safety assessment and database to characterize the risk of the potential for stannsoporfin-related adverse neurodevelopmental outcomes.

3. Discuss whether a Risk Evaluation and Mitigation Strategy (REMS) is needed to ensure the benefits of stannsoporfin outweigh the potential risks, if the drug is approved.
    a. If you believe a REMS is needed, discuss the merits of the REMS proposed by the FDA, which consists of restricted distribution, health care setting certification, safe use conditions and a registry.

4. Consider whether the risk-benefit profile of stannsoporfin supports approval.

5. If approval is supported, discuss the trial design for a post-approval study to assess the potential for adverse neurodevelopmental outcomes.

3. BACKGROUND

3.1. Drug Overview

Stannsoporfin is a first-in-class new chemical entity heme oxygenase inhibitor intended for the treatment of severe neonatal hyperbilirubinemia. In contrast to current available therapies, which reduce unconjugated bilirubin levels by increasing excretion, stannsoporfin inhibits the

production of bilirubin.

3.2. Neonatal Hyperbilirubinemia

Neonatal hyperbilirubinemia (elevated serum bilirubin concentration) results from a higher rate of bilirubin production in newborn infants and their limited ability to conjugate and excrete bilirubin. Neonatal jaundice (yellow staining of the skin and sclerae (the whites of the eyes)) resulting from hyperbilirubinemia occurs in up to 84% of term newborns.[1] In most cases, such jaundice is a self-limiting condition referred to as "physiologic jaundice" and is not considered harmful.[2-4] Hyperbilirubinemia associated with physiologic jaundice usually peaks at age 72-120 hours, and resolves by age 2-3 weeks.[5] However, significant hyperbilirubinemia that reaches a threshold for intervention occurs in 8-11% of infants and is the most common cause of hospital readmission in the neonatal period.[6]

The definition of severe hyperbilirubinemia varies in the literature. Severe, or extreme, hyperbilirubinemia has been used to describe TSB ≥25 mg/dL (425 μmol/L) or ≥30 mg/dL (513 μmol/L) in term and late-preterm neonates. The estimated incidence of neonatal severe hyperbilirubinemia in developed countries outside the U.S. since 2000 has varied widely from 7 to 40 per 100,000 live births (Table 1).[7-16] After a statewide quality improvement initiative in California in 2012, the rate of TSB ≥25 mg/dL decreased from 19.5/100,000 live births in 2007 to 13.3/100,000 live births, and the rate of TSB ≥30 mg/dL decreased from 3.6 to 1.9/100,000 live births.[17] Previous data from California suggest that the incidence of TSB ≥30 mg/dL during the years 1995-2011 was 8.6 per 100,000 live births.[18, 19] Based on available information, the incidence of severe hyperbilirubinemia appears to be decreasing. While estimates of the incidence of severe hyperbilirubinemia with TSB ≥ 25 mg/dL remain variable, an upper limit estimate would be 800 U.S. neonates per year (assuming an incidence rate of ~20/100,000 based on U.S. and developed countries' data since 2007).

Table 1: Literature-Based Incidence of Severe Hyperbilirubinemia in Late-Preterm and Term Neonates

	Region	Time Period		Peak TSB		Incidence (of live births)	Comment
			GA (weeks)	SI	Conventional		
Ebbesen, et al.	Denmark	2000-07	≥ 35	≥450µmol/L[a]	≥26 mg/dL	45/100,000	CBE[b] in 3 (all > 30) ABE[c] in 2 (resolved)
Sgro, et al.	Canada	2002-04	>36	≥428µmol/L	≥25 mg/d[a]	~40/100,000	2007 Canadian Pediatric Society guidelines implemented
		2011-13	>36	≥428µmol/L	≥25 mg/d[a]	12/100,000	
McGillivray, et al.	Australia	2010-13	>34	≥450µmol/L[a]	≥26 mg/dL	9.4/100,000	
Bhutani, et al.	U.S./California	2007-12	≥35	≥425µmol/L	≥25 mg/d[a]	19.2/100,000	Estimates decreased from 2007-2012
			≥35	≥510µmol/L	≥30 mg/d[a]	3.8/100,000	
Zoubir, et al.	Switzerland	2007-08	≥35	≥425µmol/L[a]	≥25 mg/dL	17/100,000	
			≥35	≥500µmol/L[a]	≥29 mg/dL	2/100,000	
Manning, et al.	UK and Ireland	2003-05	≥35	≥510µmol/L[a]	≥30 mg/dL	7.1/100,000	
Gotink, et al.	Netherlands	2005-09	≥37	≥500µmol/L[a]	≥29 mg/dL	10.4/100,000	
Kuzniewicz, et al.	U.S./California	1995-2011	≥35	≥510µmol/L	≥30 mg/dL[a]	8.6/100,000	

TSB = Total serum bilirubin; GA = Gestational age; SI=International System of Units; CBE = Chronic bilirubin encephalopathy; ABE = Acute bilirubin encephalopathy
[a] Actual value reported in the study.
[b] Chronic Bilirubin Encephalopathy.
[c] Acute Bilirubin Encephalopathy.

3.3. Predicting Risk and Prevention of Neurotoxicity

Neonatal hyperbilirubinemia in infants greater than or equal to 35 weeks gestational age (GA) is defined as total serum or plasma bilirubin (TB) greater than 95th percentile on the hour-specific Bhutani nomogram (Appendix 1). The primary goal of treatment of hyperbilirubinemia is preventing neurotoxicity. The decision to treat an infant who has hyperbilirubinemia is conventionally based on multiple factors including TSB, gestational age at birth, postnatal age in hours, and other clinical risk factors.

Major risk factors for development of severe hyperbilirubinemia in infants 35 or more weeks of gestation include [20]:

1) Pre-discharge TSB in the high-risk or high-intermediate risk zone of the Bhutani nomogram (Appendix 1)
2) Jaundice in the first 24 hours
3) Isoimmune or other hemolytic disease (e.g., G6PD deficiency), or elevation of end-tidal carbon monoxide (ETCO)
4) Gestational age 35 to 36 weeks
5) A previous sibling who received phototherapy
6) Cephalohematoma or significant bruising,
7) Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
8) East Asian race

Because bilirubin-induced neurologic dysfunction can result in significant morbidity and mortality, the American Academy of Pediatrics (AAP) has recommended universal screening through clinical exam and/or laboratory testing on every newborn infant.

One population-based study of over 525,000 newborns in California identified 47 patients with TSB >30 mg/dL, and of those, 4 patients developed chronic bilirubin encephalopathy (CBE/kernicterus).[18] The 4 patients with CBE were Coombs negative. One had sepsis, and 3 had decreased G6PD activity. Other literature suggest that hyperbilirubinemia-related neurotoxicity occurs primarily in infants with additional risk factors, and there is considerable uncertainty regarding the correlation of TSB level and the development of bilirubin toxicity.[21-24] No specific TSB threshold coincides with onset of acute or chronic bilirubin encephalopathy. There are infants with TSB <25 mg/dL, most often preterm or with additional risk factors, who have developed kernicterus.[11, 20, 25]

In summary, individual risk factors are of limited use as predictors of significant hyperbilirubinemia, and there is a range of outcomes at TSB levels thought to convey significant risk of disability. There is no ideal prognostic indicator for patients who will develop bilirubin toxicity. Despite the lack of clear correlation between TSB levels and the development of kernicterus, TSB remains an important biomarker used for determining whether an infant requires treatment. However, there are many other factors such as gestational age, hour of life, and comorbidities that contribute to the risk of developing complications from severe hyperbilirubinemia. It is not clear how bilirubin levels alone can translate into a clinically-meaningful endpoint. Since TSB measures the bilirubin not in the brain but in the blood, the overwhelming majority of which is bound to albumin, it is difficult to accurately determine a ‘‘safe’’ level of TSB at which kernicterus or bilirubin induced brain injury will not occur.

3.4. Currently Available Treatments for Neonatal Hyperbilirubinemia

As discussed in Section 4.2, many neonates will not require treatment for hyperbilirubinemia. The TSB level will not reach a threshold of concern and will decrease spontaneously over hours to days. Clinicians also typically evaluate nutrition and hydration status in jaundiced neonates, as dehydration and increased enterohepatic circulation may inhibit bilirubin excretion. Interventions

such as more frequent breastfeeding or supplementation with infant formula may be used in attempts to avoid reaching the treatment threshold. Patients who approach the phototherapy threshold using the nomogram in the 2004 AAP Clinical Practice Guideline (Appendix 2) are considered candidates for treatment. Current practices for screening and treating neonatal hyperbilirubinemia have been successful in lowering the incidence of exchange transfusions. Although the development of bilirubin encephalopathy is rare, intensive PT and exchange transfusion (ET) are the two primary interventions used to treat hyperbilirubinemia in the neonate.

3.4.1. Phototherapy

Phototherapy (PT) is the first line standard-of-care treatment for neonates who are approaching or who have crossed the threshold for treatment on the PT nomogram (Appendix 2). The neonate's bare skin is exposed to light in order to photoisomerize unconjugated bilirubin into forms that are more water-soluble and can be excreted rapidly by the liver and kidney. Phototherapy lamps predominantly provide light in the 460-490 nm blue region, which is most effective for treating hyperbilirubinemia. In addition to blue fluorescent lights, light-emitting diode or filtered halogen lights have been used. The effectiveness of the light source is related to its irradiance (energy output), measured in microwatt (μW) per square centimeter per nanometer.

PT is initiated based on the TSB, chronologic age and gestational age, as well as the presence or absence of risk factors (Appendix 2). "Intensive PT" is defined by the AAP as a spectral irradiance of at least 30 $\mu W/cm^2/nm$ delivered to as much body surface as possible. When the TSB reaches the hour-specific threshold on the Bhutani nomogram, the AAP Guidelines recommend the initiation of intensive PT. At a TSB level below the PT threshold, "standard PT" at an irradiance of 8-10 $\mu W/cm^2/nm$ may be delivered. Preterm neonates are treated with PT at lower TSB levels, but there are no widely accepted treatment threshold guidelines below 35 weeks gestation.

PT has been used for over four decades and has proven to be a generally safe procedure, although complications can occur. Short-term adverse effects may include interference with maternal-infant bonding and temperature instability.[26, 27] Case-control studies in large populations have suggested PT may be a risk factor for asthma and type 1 diabetes; however, the evidence is conflicting and inconclusive. Based on epidemiologic studies, there is no clear link between neonatal phototherapy and the development of melanocytic nevi, melanoma, or childhood cancer.

Literature Review on Neurodevelopmental Outcomes Associated With Phototherapy

As stannsoporfin is indicated as an adjunct therapy to phototherapy treatment, it is important to understand if phototherapy exposure alone may increase the risk of neurodevelopmental complications. To inform the Committee, the FDA performed a systematic literature review. PubMed and EMBASE databases were searched for published epidemiological literature that investigated the association between phototherapy exposure and neurocognitive-related outcomes. The search was limited to literature published in English from January 1, 1998 through February 15, 2018. The search resulted in 1,453 entries. Any abstract that mentioned the use of phototherapy exposure for the treatment of hyperbilirubinemia and the assessment of any neurodevelopmental outcome was considered for full text review. Only studies with full text

were included. In addition, the search aimed to identify 1) hypothesis testing epidemiological study designs that included a comparison group and 2) studies that evaluated study populations that corresponded to the proposed indication for stannsoporfin (specifically, study populations comprised of neonates born ≥35 weeks of gestational age and with normal birth weight). This resulted in 11 publications that met the pre-specified inclusion criteria for full text review. Most of the studies were published in the past 5 years (7/11, 63%) and were conducted in study populations outside of the United States (9/11, 82%).

The neurodevelopmental outcomes ranged from measurements of auditory and ocular findings, autism and attention deficit hypersensitivity disorder, measurements of psychological and learning development and movement disorders, including epilepsy. The study findings and corresponding barriers to interpretation are discussed in Appendix 3. The term 'healthy' refers to study neonates that did not have any evidence of jaundice or hyperbilirubinemia.

There are additional shortcomings beyond the study specific limitations that should be considered. Patient selection varied across studies, limiting the ability to make comparisons. Differences by source populations and small sample sizes also limit the interpretability of the study findings. For the studies with larger sample sizes and multivariate analyses, detailed information on the statistical methods employed to generate effect estimates are lacking to help interpret the validity of the findings observed.

There are also limitations to the systematic search methods. Articles were limited to English. Exclusions included studies that were not published in peer-reviewed articles and that evaluated subclinical neurocognitive outcomes (such as MRIs, cerebral vascular flow to brain, neurocognitive biomarkers); evidence from such studies could allude to underlying biological mechanisms that may serve as future biomarkers.

Taken together, the dearth of epidemiological evidence and the limitations of the existing studies, precludes any definitive conclusions regarding the independent risk of phototherapy treatment exposure on neurodevelopmental complications in neonates with hyperbilirubinemia. Subsequently, based on this review, it remains unknown whether phototherapy exposure has the potential to modify the theoretical risk of stannsoporfin exposure on neurodevelopmental complications. Long-term follow-up of patients from the 64,185-204 study might help ascertain potential differences in risk.

3.5. Clinical Consequences of Hyperbilirubinemia

Severe hyperbilirubinemia is associated with an increased risk for neurodevelopmental complications, also referred to as bilirubin-induced neurologic dysfunction (BIND). BIND can occur in the form of acute bilirubin encephalopathy (ABE) that may progress to kernicterus (chronic bilirubin encephalopathy [CBE]) resulting in permanent irreversible neurological dysfunction.

ABE refers to the development of acute manifestations of BIND that may be seen in the first few weeks after birth. Clinical presentation is characterized by apnea, inability to feed, fever, seizures, and a semi-comatose state that can progress to coma. Death may result from respiratory

failure or intractable seizures. In a report based on prospective data from the voluntary Canadian Paediatric Surveillance Program (2002-04), 32 of 258 (12.4%) infants with severe hyperbilirubinemia (defined as TSB >24.8 mg/dL [424 µmol/L]) were diagnosed with ABE. An additional 20 (7.8%) of these infants had non-specific neurological findings that were not considered sufficient to be definitively diagnosed with ABE.[28]

Kernicterus, or CBE, is characterized by choreoathetoid cerebral palsy, abnormalities in gaze, sensorineural hearing loss and some level of intellectual disability. Long-term follow-up studies in infants with severe hyperbilirubinemia have estimated the incidence of kernicterus in developed nations to be in the range of 0.44 to 2.3 per 100,000 live births.[18, 25, 29, 30] There are no true incidence data available for the U.S. The rate of kernicterus in a group of term and late-preterm patients with TSB ≥ 30 mg/dL may be as low as 1% or as high as 10%.[29] In a population of 106,627 children born term and late-preterm in California between 1995-98, there were 140 children who had peak TSB >25 mg/dL, including 10 children who had peak TSB >30 mg/dL. All but 4 were treated with PT or PT and ET. On 2-year follow-up of 94% of the patients, none had kernicterus, and the proportion of children with neurodevelopmental disabilities was not different from matched controls.[24] Active surveillance in Canada between 2007-09 produced a conservative estimate of 1 in 41,000 live births.[31]

Table 2: Estimated Incidence of Severe Hyperbilirubinemia and Clinical Consequences (based on the incidence data in Table 1)

	Incidence (from Table 1)	Estimated # in U.S. per Year	Comment
Estimated Incidence of Severe Hyperbilirubinemia			
Bilirubin ≥25mg/dL	10-40/100,000 live births	400-1600	Including years 2000-2013
Bilirubin ≥30 mg/dL	2-10/100,000 live births	80-400	Including years 1995-2012
Clinical Consequences of Severe Hyperbilirubinemia			
Kernicterus	No U.S. incidence data[a] 1/41,000 live births (Canada)	98	2007-09 Canadian Surveillance Data
Risk of kernicterus with bilirubin > 25 mg/dL	Ebbesen (0/149 who were <30) 5.7% in Canada (2006)		Denmark, Canada
Risk of kernicterus with bilirubin > 30 mg/dL	Ebbesen 3/75 (4%) Kuzniewicz 4/47 (8.5%)		Denmark, U.S.
Risk of Cerebral Palsy/kernicterus with ≥1 TSB > ET threshold	Wu [32] 0.4% (Overall 0.57/100,000)		

[a] Refer to text in paragraph above.

3.5.1. Exchange Transfusion (ET)

Exchange transfusion involves replacing the infant's blood with donor blood typically via a central venous access. This procedure is generally reserved when phototherapy fails to keep TSB below levels at which kernicterus has been reported. The 2004 AAP Clinical Practice Guideline provides a nomogram (Appendix 4), to guide clinicians regarding when to consider exchange transfusion. Because exchange transfusion is used uncommonly in the U.S. (3 per 100

000 live births) [19], it is difficult to determine the long-term risks. Adverse events of exchange transfusion reported in the literature include a 1-5% mortality risk and a 5-10% risk of significant morbidity including: apnea, bradycardia, cyanosis, thrombocytopenia, portal vein thrombosis, necrotizing enterocolitis, electrolyte imbalance, graft-versus-host disease, and infection.[33-35]

3.5.2. Other Therapies

The 2004 AAP Clinical Practice Guideline recommends the use of intravenous immunoglobulin (IVIG) 0.5-1 g/kg IV over 2 hours in patients with isoimmune hemolytic disease if the TSB is rising despite intensive PT or if the TSB is within 2-3 mg/dL of the ET level. IVIG treatment is thought to reduce the need for ET, particularly in the case of hemolysis from ABO or Rh-incompatibility, but placebo-controlled trials have not clearly demonstrated a benefit.[36] Of note, IVIG is not FDA-approved for this indication.

Intravenous fluids and/or supplemental oral fluids or feedings are frequently used in clinical practice to improve hydration in neonates with hyperbilirubinemia. The AAP Guideline emphasizes ensuring adequacy of feeding and hydration, including breastfeeding 8-12 times daily, as both preventive measures and for patients under intensive phototherapy. The overall evidence is weak, but intravenous fluid and feeding supplementations may reduce bilirubin levels and the need for ET, without altering bilirubin-related neurological outcomes in otherwise healthy term newborns on phototherapy.[37]

Clofibrate, a lipid-lowering agent, has been studied for treatment of hyperbilirubinemia outside the U.S., and appears to decrease bilirubin and duration of phototherapy; however, studies did not report rate of bilirubin encephalopathy or mortality. The compound is not approved in the U.S. for this use.

Serum bilirubin is highly bound to albumin, with low levels of unbound bilirubin in plasma. Low albumin levels are thought to convey higher risk of neurologic sequelae in neonates with hyperbilirubinemia,[38, 39] although treatment with albumin has not been widely accepted nor is it recommended in the 2004 AAP Guideline.[40] Animal studies as well as small clinical studies have shown reduction in bilirubin and neurological dysfunction, including improved auditory brainstem response testing, when neonates with high unbound bilirubin are treated with albumin, in particular, prior to ET.[38, 41-46] There are several albumin products indicated for neonatal hyperbilirubinemia, but there are no supporting data in the product labels.

3.6. Regulatory History

Clinical studies of stannsoporfin were initiated in 1987 by Dr. Attallah Kappas at Rockefeller University, New York, under a research Investigational New Drug Application (IND) 29,462 for the prevention and treatment of hyperbilirubinemia in several populations including term and near-term infants, patients with porphyria, and patients with Crigler-Najjar syndrome. Rights to the drug were acquired by Roberts Pharmaceutical Corporation who met with the Division in July 1997 to discuss the development of stannsoporfin but did not initiate studies. Development rights were subsequently acquired by Wellspring Pharmaceutical Corporation who opened a second IND (64,185) on February 15, 2002 with the intention to develop and market stannsoporfin as a treatment for hyperbilirubinemia in neonates. On June 1, 2005, WellSpring

transferred sponsorship of IND 64,185 to InfaCare Pharmaceutical Corporation.

The development program for stannsoporfin has raised several concerns including, the appropriateness of the target population that should be studied, selection of efficacy endpoints, and various clinical trial design features. These concerns were addressed at two previous FDA Advisory Committee Meetings summarized in Appendix 5.

The Pediatric Subcommittee of Anti-Infective Drugs Advisory Committee held an open session on June 11, 2003 to discuss the current state of medical management of neonatal hyperbilirubinemia. The Committee was asked to discuss specific questions, including whether drugs should be developed to prevent severe hyperbilirubinemia in newborns and if so, what safety information should be required. The Committee supported conducting studies to provide an alternative therapy to exchange transfusion to prevent kernicterus, but emphasized the importance of identifying a target study population of infants who would benefit most from treatment. The Committee also emphasized the importance of assessing both acute and long-term safety of therapies in clinical trials. Committee did not favor prevention of hyperbilirubinemia as the initial focus of clinical development.

In 2008, InfaCare proposed a new clinical development program to evaluate stannsoporfin as a treatment to be initiated prior to PT rather than as an adjunct to PT. Study 64,185-202 was a phase 2, multicenter, multinational, randomized, placebo-controlled, dose-escalation study in newborns with Coombs positive isoimmune hemolytic disease. The study objective was to evaluate safety and pharmacokinetics (PK) of stannsoporfin at 1.5 mg/kg, 3 mg/kg, and 4.5 mg/kg. The Division had concerns about the specific design of this study, including the proposed study population, the study endpoints, and the proposed long-term follow-up of enrolled patients. Ultimately, the study was allowed to proceed, with modifications to the protocol that included specific qualifying TSB levels for study entry (i.e., within 1 mg/dL of the threshold for PT based on 2004 AAP guidelines for neonates up to 12 hours of age, or within 2 mg/dL of the PT threshold for neonates > 12 to 48 hours of age).

During trial 64,185-202, the Applicant modified the enrollment criteria to allow Coombs (direct-antiglobulin test) negative ABO-incompatible infants to be enrolled and to allow enrollment and initiation of treatment when the TSB level was 2-3 mg/dL below the threshold for PT. The Division noted that the broadened enrollment criteria allowed enrollment of neonates that would otherwise not likely require PT. For those neonates who did not need any treatment for their hyperbilirubinemia, the administration of stannsoporfin presented an unreasonable and significant risk of illness or injury (21 CFR 312.42b) and was a violation of the Division's interpretation of CFR 50.52 (Subpart D). Under 21 CFR 50.52, the risk of administering stannsoporfin must be justified by the anticipated direct clinical benefit to the enrolled neonate, and the relation of the anticipated direct benefit to the risk must be at least as favorable to the enrolled neonate as that presented by available alternative approaches. Based on these concerns, Study 64,185-202 was placed on Partial Clinical Hold and was subsequently not completed.

On March 13, 2012, the Gastrointestinal Drugs Advisory Committee (GIDAC) convened an open session meeting to discuss and provide general advice on the appropriateness of target populations, objective and trial designs intended to evaluate products for the treatment of

hyperbilirubinemia in newborn infants. The Committee recommended that neonates with the most severe levels of hyperbilirubinemia at the highest risk of complications be included in the study population, including those with Rh incompatibility with a positive Coombs test and G6PD deficiency with no access to intensive phototherapy. The Committee also voted in support of drug development as an adjunct to phototherapy in the treatment of significant hyperbilirubinemia, rather than head-to-head comparison with phototherapy or to prevent significant hyperbilirubinemia.

Subsequent to the Advisory Committee meeting, the Division met with InfaCare to discuss the use of stannsoporfin as an adjunctive therapy in neonates with isoimmune hemolytic disease receiving PT. The Division emphasized that the Applicant should limit the study population to patients who are actively hemolyzing and should study stannsoporfin as an adjunct to PT and the Applicant should identify a window of time after phototherapy has been initiated to administer stannsoporfin. The Applicant submitted the protocol for Study 64,185-204 as a Complete Response to Clinical Hold on August 9, 2012. The Division noted that while the protocol did not address how patients will be assessed for evidence of hemolysis, the proposed study population was acceptable and the protocol was deemed adequate to support removal of Partial Clinical Hold.

At the End-of-Phase 2 (EOP2) meeting on July 19, 2016, the Applicant stated their intention to submit a New Drug Application (NDA) based on their completed studies 64,185-202 and 64,185-204 for the proposed indication of "stannsoporfin inhibits bilirubin production and is indicated when intervention is being considered for the treatment of neonates greater than or equal to 35 weeks of gestational age with hyperbilirubinemia". The Division emphasized that the proposed indication was too broad and did not accurately reflect the population studied in the pivotal trial (Study 64,185-204). Additionally, the Division questioned the likelihood that "percent change from baseline TSB" will predict clinical benefit in high risk neonates and informed the Applicant that they will need to provide evidence from their clinical development program, and any other available sources that support the conclusion that changes in this biomarker confer clinical benefit. The Division indicated it was acceptable for InfaCare to present neurocognitive data at age 3 years as a minimum length of neurocognitive follow-up. Due to the complexities of the scientific issues raised and the novelty of the indication sought, the Division also informed the Applicant of the intention to convene an Advisory Committee meeting to discuss their application.

On January 29, 2016, the Applicant submitted a request for Breakthrough Therapy Designation for stannsoporfin for treatment of "hyperbilirubinemia in healthy near-term and term infants". The Division denied this request because the Applicant did not adequately define a population of infants at high risk for progression to serious adverse outcomes and, therefore, stannsoporfin did not qualify as a drug product intended to treat a serious or life-threatening condition.

On December 15, 2016, the Division concluded that the data submitted were adequate to support a Fast Track Designation for stannsoporfin as an "adjunct therapy to phototherapy (PT) in neonates of ≥35 weeks gestational age with laboratory evidence of hemolysis and hyperbilirubinemia meeting the AAP criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia." The "at risk" population specified

infants meeting the following criteria "1) age = 0 to 48 hours; 2) presence of ABO/Rh incompatibility; 3) direct antiglobulin test (DAT) positive or if DAT negative, with reticulocytes >6%; 4) serum total bilirubin meeting criteria for phototherapy."

The Pre-NDA meeting was held on March 7, 2017. Upon review of the meeting package, it was apparent that the long-term follow-up study (64,185-205) to the pivotal trial would be incomplete at the time of the planned NDA submission. The Division accepted InfaCare's plan to submit the NDA as proposed, but expressed concerns regarding the incomplete long-term follow-up Study 64185-205 and the limited long-term neurodevelopment follow-up data that would be provided at the time of NDA submission. The Division also recommended that the Applicant modify the protocol for long-term neurodevelopment follow-up in Study 64,185-205 to include a global measure of intellect (e.g., the Wechsler Preschool and Primary Scale of Intelligence [WPPSI]) and a global measure of development (e.g., the Vineland Adaptive Behavior Scale [VABS]) at the year 3 and 4 visits.

On September 25, 2017, InfaCare Pharmaceutical Corporation was acquired by Mallinckrodt Public Limited Company, however InfaCare Pharmaceutical Corporation continues as a legal entity in the Mallinckrodt Pharmaceuticals corporate structure. The Applicant completed their submission of a New Drug Application (NDA) on December 22, 2017 and the NDA was filed and granted priority review status on February 20, 2018.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

4.1. Pharmacology

Stannsoporfin (tin-mesoporphyrin) is a metalloporphyrin that acts as a competitive inhibitor (K_i = 14 nM) of heme oxygenase (HO), the rate-limiting enzyme in the catabolism of heme to bilirubin and carbon monoxide. HO is expressed in the liver, spleen, brain, kidney, and testis. Studies in adult and neonatal rats showed that subcutaneous administration of stannsoporfin decreased HO activities in liver, kidney, and spleen. Stannsoporfin, administered subcutaneously to newborn rats at a single dose of 1 μmol/kg (754 μg/kg), prevented the increase in serum bilirubin which routinely occurs in neonatal rats, shortly after birth. Heme oxygenase activity in liver, kidney, and spleen was decreased.

The cardiac electrophysiological effects of stannsoporfin were evaluated in two *in vitro* studies, to evaluate the potential for delayed ventricular repolarization (i.e., QT interval prolongation). In an assay that measures potassium current mediated by the hERG (human ether-a-go-go related gene) channel, stannsoporfin inhibited the K^+ tail currents in transfected CHO-K1 cells, albeit with low potency (IC_{50} = 200 μM). In a study using a rabbit Purkinje fiber preparation, stannsoporfin increased the action potential duration at 50% and 90% repolarization (APD_{50} and APD_{90}). However, the QT_c interval was unaffected in a cardiovascular safety study in dogs (study is described below).

Single intravenous administration of stannsoporfin produced effects in studies to evaluate central nervous system (CNS) function in mature rats (e.g., decreased activity and hypothermia) and cardiovascular function in mature dogs (e.g., small and/or transient decreases in heart rate, left

ventricular pressure, left ventricular end-diastolic pressure, and maximum rate of pressure change [dP/dt max]). However, these effects occurred at high dose multiples relative to the proposed dose of 4.5 mg/kg in human neonates. Furthermore, the use of intravenous administration in these animal studies likely produced extremely high plasma drug levels, which may further diminish the relevance to safety risk in humans, where intramuscular administration is used. The CNS-related effects in mature rats occurred at 17 times the proposed dose in human neonates, and the slight changes in heart function parameters in mature dogs occurred at 9 times the proposed dose in human neonates. No effects occurred in rats or dogs at lower doses (3.3 and 4.4 times the proposed dose in human neonates, respectively). The dose comparisons between animals and human neonates are based on body surface area (mg/m^2). Stannsoporfin had no effects on respiratory function in mature rats at intravenous doses up to 3.3 times the proposed dose in human neonates.

4.2. Pharmacokinetics/Toxicokinetics

Maximum drug levels in blood and plasma occurred at one hour after intramuscular administration of ^{119m}Sn-stannsoporfin in neonatal dogs. The blood and plasma concentrations were below the limit of quantification at 168 and 24 hours, respectively. The highest level of radioactivity was observed in the GI tract, followed by liver, lymph node (inguinal), and kidney. Terminal elimination half-lives ($t_{1/2}$) for kidney, liver, and spleen were 30.5 days, 34.8 days, and 24.4 days, respectively. Radioactivity was also detected in cerebrospinal fluid. Unchanged drug was the major radioactive component in plasma (95.9% of radioactivity). Excretion of radioactivity derived from ^{119m}Sn-stannsoporfin occurred in urine and feces, with most of the radioactivity recovered in feces. In the pivotal toxicology studies using repeated intramuscular injection for 28 days, the plasma $t_{1/2}$ values were 2-12 hours in neonatal rats and 1-4 hours in neonatal dogs. Systemic exposure (AUC and C_{max}) was approximately dose-proportional in both species. Accumulation in plasma was observed in neonatal rats, but not in neonatal dogs.

4.3. Toxicology

4.3.1. Pivotal Toxicology Study in Neonatal Rats:

Neonatal rats were treated with 0 (vehicle), 1, 4.5, or 20 mg/kg (intramuscular) stannsoporfin daily for 28 days, starting on postnatal day 5 (49-51 rats per sex per dose group; [rats/sex/group]). The main study animals were sacrificed on study day 29 (~20 rats/sex/group), followed by sacrifice of recovery groups at 1 month, 3 months, and 6 months after the end of treatment (~10 rats/sex/group for each recovery sacrifice). The systemic exposure (AUC) achieved with the daily doses used in this study (1, 4.5, and 20 mg/kg) was 0.06, 0.39, and 1.9 times the AUC at 4.5 mg/kg (the proposed dose) in human neonates. However, when the cumulative exposure over the 28-day treatment period in neonatal rats is considered, the multiples of the human AUC increase to 1.7, 10.9, and 53.2.

No treatment-related deaths occurred. Discolored urine (orange or red) occurred in animals receiving 4.5 or 20 mg/kg/day. This observation was attributed to excretion of the test article. At the end of the treatment period, bodyweight was reduced by 5.2% and 6.3% in the 20 mg/kg/day males and females, respectively, compared to bodyweight in the control group. These

effects were associated with reductions of 7.7% and 7% in weight gain. The effects on body weight were reversed during the recovery period. At the end of the dosing period, hematology evaluation showed small but significant decreases in MCV (3.9%, 4.9%), MCH (6.2%, 7.6%), and MCHC (2.3%, 2.5%) in male rats receiving doses of 4.5 and 20 mg/kg/day, respectively.

During the lactation period of the study (days 1-17), stannsoporfin had no effects on physical development or reflexes in the rat pups. However, behavioral effects were noted during the post-weaning period (study days 18 and beyond). Male rats in the 4.5 and 20 mg/kg/day groups showed a significant decrease in motor activity on study day 18 (i.e., total time in motion during a 1.5-hr observation period was decreased 47% and 45% at 4.5 and 20 mg/kg/day, respectively). The human age equivalent on the day of this test was approximately two years. The effect on motor activity in males was reversed by the 14th day of the recovery period. Females showed no changes in motor activity at any time-point.

The acoustic startle habituation test was conducted on study days 19 and 43 (age of rats on testing days was equivalent to human ages of approximately two years and 12 years, respectively). The acoustic startle response is mediated through a multi-synaptic pathway in the lower brainstem which activates spinal and cranial motor neurons. A key part of this pathway is the caudal pontine reticular nucleus, which receives input from various brain nuclei involved in modulation of the acoustic startle response (e.g., fear-potentiation, sensitization, habituation, prepulse inhibition, and pleasure attenuation). This test is proposed to evaluate sensorimotor-motivational information processing at the behavioral and neurophysiological level in mammals.[47] Females in the 20 mg/kg/day group exhibited a decrease in startle response magnitude on both days of the test (i.e., ↓31.2% and 19.5% on study days 19 and 43, respectively). The response in males was unaffected.

The passive avoidance test was performed on study day 20 (±1) and at one week thereafter, to evaluate learning, short-term memory, and long-term memory (age of rats was equivalent to human ages of approximately two years and five years on testing days). The results showed no impairment in any of the study parameters. Males and females in the 20 mg/kg/day group showed a slight delay in sexual maturation (i.e., onset of preputial separation and vaginal patency, respectively).

Minimal to moderate necrosis of individual hepatocytes was observed in 9/10 males and 4/10 females in the 20 mg/kg/day treatment group at the end of the treatment period. This change was associated with small but significant increases in ALT, AST and total bilirubin (1.3, 1.8, and 1.9 times the control values in males, respectively, and 1.5, 1.6, and 1.9 times the control values in females, respectively). Small reductions in albumin (up to 11% decrease) occurred in the 4.5 and 20 mg/kg/day group at the end of treatment. Single cell (hepatocyte) necrosis was no longer present at the end of one month of recovery.

At the injection sites, a dose-dependent increase in focal degeneration of muscle fibers was observed (5/20, 7/20, 15/20, and 19/20 rats in the vehicle, 1, 4.5, and 20 mg/kg/day groups, respectively). Multifocal mixed inflammatory infiltrations were seen in 4/20, 3/20, 11/20, 17/20 rats in the vehicle, 1, 4.5, and 20 mg/kg/day groups, respectively. The incidence and severity of various changes at the injection sites, including necrosis of muscle fibers, regeneration of muscle

fibers, pigmented macrophages, and microgranulomas, was increased in the 4.5 and 20 mg/kg/day groups. The effects at the injection sites were reversed after one month of recovery.

The major effects in this study were indicative of neurotoxicity (e.g., reduced motor activity in mid- and high-dose males, decreased response in acoustic startle test in high-dose females) and liver toxicity (single hepatocyte necrosis in high-dose group, completely reversed in recovery). In a distribution study in neonatal rats, low levels of radioactivity were detected in brain and cerebrospinal fluid following intramuscular injection of ^{119m}Sn-stannsoporfin. Therefore, it is possible that the changes in CNS function parameters in the toxicology study were mediated by direct drug effects on brain development. The target of drug action, HO, is expressed in brain. Therefore, the CNS effects of stannsoporfin may be target related, although off-target mechanisms are also possible.

The overall toxicity profile in this repeat-dose study may not present a major concern for the intended use of stannsoporfin that involves only a single administration, although the totality of the data suggests that stannsoporfin has the potential to produce developmental neurotoxicity. The initial notable reduction in bodyweight (6.4% decrease in the high-dose females relative to controls) was not observed until the 18th day of treatment.

4.3.2. Pivotal Toxicology Study in Neonatal Dogs:

Neonatal dogs were treated with 0 (vehicle), 1, 4.5, or 20 mg/kg/day stannsoporfin (intramuscular) daily for 28 days, starting on postnatal day 5 (16 dogs/sex/group). The main study animals were sacrificed on study day 29, followed by sacrifice of recovery groups at 1 month, 3 months, and 6 months after the end of treatment (4 dogs/sex/group for each sacrifice). The systemic exposure (AUC) achieved with the daily doses used in this study (1, 4.5, and 20 mg/kg) was 0.01, 0.04, and 0.16 times the AUC at 4.5 mg/kg (the proposed dose) in human neonates. However, when the cumulative exposure over the 28-day treatment period is considered, the multiples of the human AUC increase to 0.28, 1.1, and 4.5.

Two animals in the 20 mg/kg/day group were found dead on days 21 and 23 of treatment, and these deaths are considered drug-related. The animal that died on day 23 showed clinical signs of toxicity, including hypoactivity, thinness, red material on the anogenital area and hind limbs, and green discharge from the right eye. These clinical observations were preceded by four consecutive days of body weight loss. No clinical signs were observed in the animal that died on day 21.

The findings of urine and feces containing red material, red anal discharge, and red material on various body surfaces in the high-dose group was likely due to the color of the test article. A dose-dependent increase in the incidence of redness and/or swelling at the injection sites were noted in the treatment groups. At the end of the treatment period, bodyweight was decreased by 14.8% and 13.5% (not significant) in the 4.5 and 20 mg/kg/day males, respectively, and by 10.2% and 9.1% (not significant) in the 4.5 and 20 mg/kg/day females, respectively, compared to bodyweight in the control group. Mean body weight gains at the end of the dosing period were reduced by 21.5% and 20.8% in the 4.5 and 20 mg/kg/day male groups, respectively, and by 16% and 14.6% in the 4.5 and 20 mg/kg/day female groups, respectively. The decrease in bodyweight in males persisted throughout the 6-month recovery period, with only a partial

reversal. The bodyweights at the end of recovery in the 4.5 and 20 mg/kg/day male groups were 20% and 12.4% lower, respectively, than the control male value. No effects were observed in developmental landmarks, neurobehavioral tests, respiration, or cardiovascular parameters (including ECG). Changes in hematology parameters (e.g., reductions in hematocrit, reticulocytes, and lymphocytes) were observed in the 4.5 and 20 mg/kg/day groups at the end of the treatment period. These changes were completely or partially reversed after the 6-month recovery period.

In the groups sacrificed at the end of the 28-day treatment period, the major finding was the presence of pigment in liver, which occurred in all drug-treated animals with a dose-dependent severity. The liver pigment persisted in all treated animals through the end of the 6-month recovery period, with decreased severity observed at the 6-month sacrifice. The composition of the liver pigment was not evaluated, but the Applicant proposed two possible explanations for this finding: 1) deposition of stannsoporfin and/or its metabolites resulting from its mesoporphyrin structure, which may predispose it for storage in liver; and 2) accumulation of heme in hepatocytes. Based on the high distribution and the long half-life (34.8 days) in liver in neonatal dogs, the liver pigment was likely the result of accumulated stannsoporfin and/or metabolites. Thyroid atrophy was observed in the 20 mg/kg/day group, but was reversed after one month of recovery.

Although adverse effects occurred in this study (e.g., growth impairment, death), the overall toxicity profile is of minimal concern for the intended use of stannsoporfin, where only a single administration will be used. The initial notable reduction in bodyweight (↓5% in the high-dose males relative to controls) did not occur until the 6th day of treatment, and deaths did not occur until day 21. Thus, the most concerning findings were clearly associated with repeated administration. Although the accumulation of liver pigment could be considered as adverse, given that this change persisted through the 6-month recovery period, it is unlikely to have clinical relevance in the context of single administration use in patients. It should be noted that no growth impairment was observed at the low dose.

4.3.3. 7-Day Intramuscular Toxicity Study in Neonatal Dogs:

In a 7-day toxicity study in neonatal beagle dogs (1-day old), intramuscular injection of stannsoporfin was administered at doses of 0, 4.7, 18.8 and 75.4 mg/kg/day. Hepatic vacuolation was observed at 4.7, 18.8 and 75.4 mg/kg/day (1/8, 4/8, and 4/8 dogs, respectively). The effects observed at 18.8 and 75.4 mg/kg/day included renal tubule dilatation (3/8 and 7/8 dogs, respectively) and thymus atrophy (4/8 dogs in both groups). Drug-related effects that occurred only in the 75.4 mg/kg/day group included increased alkaline phosphatase (~2.5-fold), increased GGT (↑1.3-fold females, 1.8-fold in males), RBC casts in renal tubules (males only), increased proportion of early-stage (immature) granulocytic and erythroid cells in bone marrow, and increased myeloid:erythroid (M:E) ratio. The increase in M:E ratio was mainly due to an increase in the number of myeloblasts. A low incidence of multifocal hemorrhage and focal necrosis at the site of injection occurred in all drug-treated groups. The maximum tolerated dose was considered to be 18.8 mg/kg/day, at which the daily AUC was 0.18 times the AUC at 4.5 mg/kg (the proposed dose) in human neonates (cumulative AUC over the 7-day treatment period was 1.3 times the human AUC). The highest dose tested (75.4 mg/kg/day) produced changes in liver, thymus, kidneys, and bone marrow, which were associated with a human AUC multiple of

2 (cumulative AUC over the 7-day treatment period was 14 times the human AUC).

4.3.4. Phototoxicity Study in Neonatal Guinea Pigs:

Because of the known photo-reactivity of metalloporphyrins, a study was conducted in neonatal albino hairless guinea pigs to evaluate the phototoxicity of stannsoporfin in response to exposure to operating room light (ORL). Neonatal guinea pigs were administered stannsoporfin at 20 mg/kg IM and exposed to ORL at 30 minutes post-dose. The administered dose was 1.5 times the proposed dose in humans, based on a mg/m^2 comparison. A high incidence of mortality (11/12) was observed in neonatal guinea pigs treated with stannsoporfin followed by 6 hours of ORL exposure, as compared to the control group treated with vehicle and ORL exposure (1/12).

Mortality due to stannsoporfin administration and ORL exposure was reduced by ORL filtration, reduction in the duration of ORL exposure, and extension of the time interval between stannsoporfin administration and ORL exposure. No mortality was observed after exposure to ORL at 120 hours after stannsoporfin administration. Erythema grade 1 (i.e., barely perceptible light redness) in skin occurred in all drug-treated animals exposed to ORL at 30 minutes post-dose. Wrinkling was observed in some animals when ORL exposure was initiated at 2 or 12 hours post-dose. Interventions which decreased the incidence of erythema grade 1 in skin included ORL filtration, extension of the time interval between stannsoporfin administration and ORL exposure, and reduction in the duration of ORL exposure. Therefore, stannsoporfin was determined to be phototoxic in the presence of ORL. Treatment-related clinical signs at 20 mg/kg with 6-hour exposure to ORL included: dehydration, cold to touch, loss of righting reflex (return from a supine position to prone), vocalization, emaciation, lying on side and labored breathing, red ears, hind limbs or hind paws splayed, prostrate position, back ulceration, lacrimation, and opisthotonos (spasm of muscles causing backward arching of head, neck spine, and legs). The incidence of adverse clinical signs was reduced by filtration of ORL, extension of the time interval between stannsoporfin administration and ORL exposure, and shortened ORL exposure time. Stannsoporfin administration with ORL exposure increased creatinine, BUN, triglycerides, and decreased glucose (on Day 2). The most severe microscopic changes (dermal and epidermal necrosis and inflammation) occurred mostly in the non-surviving guinea pigs that were given stannsoporfin with six hours of ORL exposure initiated at approximately 30 minutes after dosing. The incidence and severity were reduced by shortened ORL exposure duration but not by ORL filtration. Increased incidence of diffuse or periportal hepatocellular vacuolation was observed in neonatal guinea pigs that were treated with stannsoporfin followed by ORL exposure. Filtration of ORL, shortening of ORL exposure, and increasing the time interval between stannsoporfin injection and ORL exposure to 120 hours reduced the incidence of liver damage induced by stannsoporfin with ORL exposure. These results suggest that stannsoporfin has the potential to produce systemic toxicity if administered to a patient who is subsequently exposed to ORL.

4.3.5. Other Toxicology Studies:

Stannsoporfin toxicity was also evaluated in mature (adolescent) rats and dogs in acute studies (single intravenous administration) and 1-month repeat-dose studies (intravenous). The target organs of toxicity in these studies included liver and kidney, and the nature of the microscopic changes were generally similar to those reported in neonatal animals. In the 1-month intravenous toxicity studies in both species, the maximum dose tested was 10 mg/kg/day. The

minor differences in toxicity profiles between neonatal and mature animals may be attributed to the use of intravenous dosing in mature animals, as compared to intramuscular dosing in neonatal animals.

Stannsoporfin tested negative in all genotoxicity studies conducted, which comprise the standard regulatory test battery.

5. CLINICAL PHARMACOLOGY

5.1. Clinical Pharmacokinetics

The pharmacokinetics of stannsoporfin were studied in healthy male adults (Study 64,185-02) and neonates (Study 64,185-202).

5.1.1. PK in Healthy Adults

Following a single intramuscular injection to healthy adults at 20, 40, and 80 mg (N=10, 10, and 12, adults respectively), peak plasma concentrations of stannsoporfin are achieved between 1 and 3 hours post-dose and increase 3-fold with an increase in dose from 20 to 80 mg. Mean $AUC_{0\text{-}48h}$ increases 4.8-fold over this dose range. Stannsoporfin is >99% bound to human plasma proteins at concentration of 5,000 – 50,000 ng/mL.

The metabolism of stannsoporfin is not well characterized in humans. *In vitro* studies suggest that cytochrome P450 (CYP) enzymes are not involved in the metabolism of stannsoporfin. In healthy adults, the percent of stannsoporfin dose recovered as stannsoporfin over the first 48 hours ranged from 0.22% to 9.85% in urine, and from 0% to 13.32% in feces. In adults, stannsoporfin was detectable in plasma at the last sampling time of 48 hours after a single 80 mg intramuscular injection. The major elimination pathway is unclear. The effects of hepatic or renal impairment on the PK of stannsoporfin have not been studied.

5.1.2. PK in Neonates with Hyperbilirubinemia

Following a single intramuscular injection in neonates with a gestational age greater than or equal to 35 weeks, mean peak plasma concentrations of stannsoporfin are achieved within 1.5 to 2.3 hours post-dose and increase 3.2-fold with an increase in dose from 1.5 to 4.5 mg/kg (Table 3). Mean $AUC_{0\text{-}inf}$ increases 5.4-fold over this dose range. Based on the population PK analysis, the apparent volume of distribution is estimated to be 0.97 L for a neonate weighing 3.5 kg, around 3-fold of the typical blood volume (0.3 L) suggesting extravascular distribution of stannsoporfin.

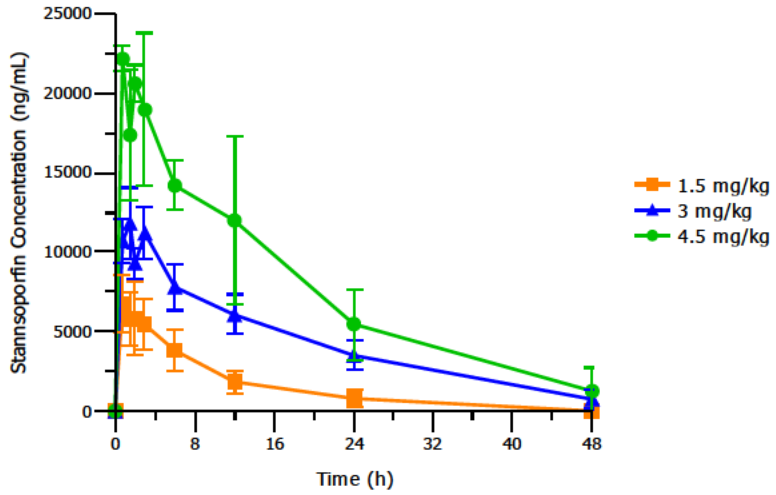
The mean apparent terminal half-life ($t_{1/2}$) is 5.5 hours following the 1.5 mg/kg dose and approximately 10-11 hours following the 3 and 4.5 mg/kg doses in neonates. Plasma stannsoporfin concentrations were still quantifiable at the last sampling time of 48 hours after dosing at the 3 and 4.5 mg/kg doses (see Figure 1).

Table 3: Pharmacokinetic Parameters following a Single Intramuscular Injection of Stannsoporfin in Neonates

PK Parameter [a]	1.5 mg/kg (N=15)	3 mg/kg (N=15)	4.5 mg/kg (N=7)
T_{max} (hr)	1.87 (0.83 - 6.08)	1.52 (0.75 - 3.08)	2.30 (0.75 - 6.18)
C_{max} (ng/mL)	6445 (1792)	11531 (1577)	20414 (4074)
AUC_{0-t} (ng·h/mL)	67995 (22050)	191873 (35361)	352971 (76903)
AUC_{0-inf} (ng·h/mL)	70338 (21141)	206393 (46826)	377571 (106856)
$t_{1/2}$ (hr)	5.46 (2.98 - 9.99)	10.7 (5.64 - 18.0)	9.86 (6.59 - 14.7)

[a] Presented as mean (SD), except for T_{max} presented as median (min-max) and $t_{1/2}$ presented as mean (range).
Source: Results were extracted from Table 12 and post-text Table 3 in the Applicant's PK Report for Study 64,185-202.

Figure 1: Mean (SD) Plasma Stannsoporfin Concentration-Time Profile following a Single Intramuscular Injection of Stannsoporfin in Neonates



Note: Patients were stratified into two PK sampling groups during the first 3 hours post-dose: group 1, PK blood sampling at 0.75 and 2 hours and group 2, PK blood sampling at 1.5 and 3 hours post-dose. All patients had PK samples collected at 6, 12, 24, and 48 hours post-dose.
Source: Reviewer's plot based on data extracted from post-text Table 2 in the Applicant's PK Report for Study 64,185-202

5.2. Dose/Exposure-Response Relationship for Total Serum Bilirubin Change

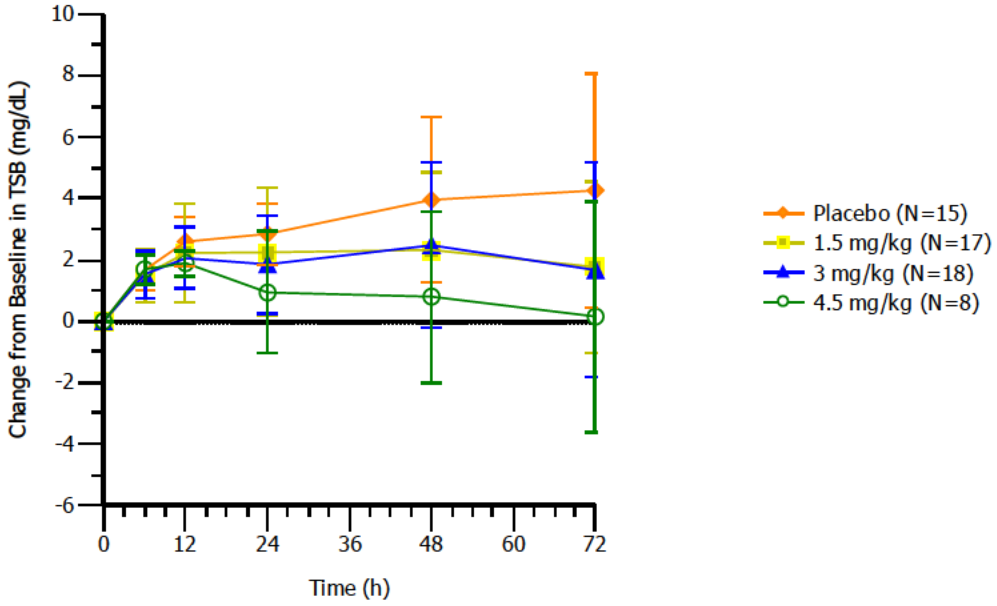
The Applicant explored the dose (exposure)-response relationship in the supportive Study 64,185-202 and the pivotal Study 64,185-204 using the absolute change and percent change from baseline in TSB, respectively, as the primary endpoint. Selection of the 3 mg/kg and 4.5 mg/kg doses for the pivotal Study 64,185-204 was based on the dose/exposure-response relationship for the change from baseline in TSB in a placebo-controlled study 64,185-202.

The effects of a single intramuscular dose of 1.5, 3, and 4.5 mg/kg of stannsoporfin on the change in TSB was evaluated in neonates with hyperbilirubinemia in Study 64,185-202. Phototherapy (PT) was administered if the neonate's TSB reached or exceeded the threshold to initiate PT based on the 2004 AAP Clinical Practice Guideline.

In Study 64,185-202, 3 of 17, 6 of 18, 2 of 8, and 8 of 15 neonates received PT in the 1.5, 3, 4.5

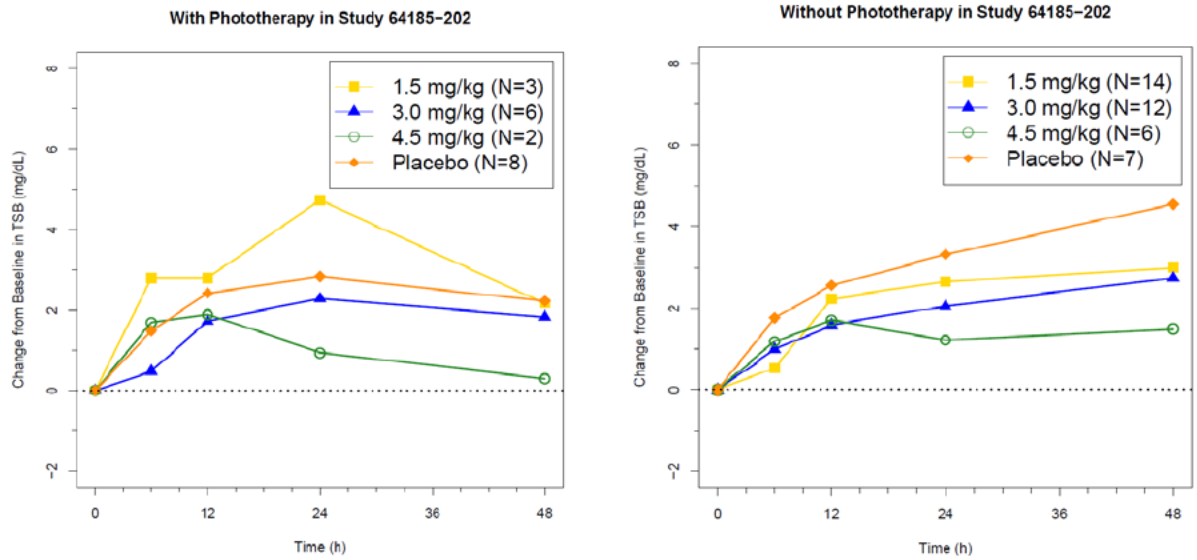
mg/kg stannsoporfin, and placebo arms, respectively. The mean change from baseline in TSB over time for all neonates, and stratified by PT treatment in Study 64,185-202 is presented in the figures below (Figure 2 and Figure 3). Stannsoporfin 4.5 mg/kg appeared to attenuate the rise in TSB over time in neonatal patients compared to placebo treatment, regardless of PT treatment. Two lower doses, 1.5 and 3 mg/kg also appeared to attenuate the rise in TSB compared to placebo in neonates without PT treatment (Figure 3, right panel). Due to the small number of neonates who received PT in this study, a definitive conclusion regarding dose-response in patients receiving PT could not be drawn although the effect of the 4.5 mg/kg dose on TSB appeared to be greater than two lower doses.

Figure 2: Mean (SD) Change from Baseline in Total Serum Bilirubin over Time for all Neonates in Study 64,185-202



Source: Reviewer's plot based on data extracted from Table 14.2.3.2 in Applicant's Clinical Study Report for Study 64,185-202.

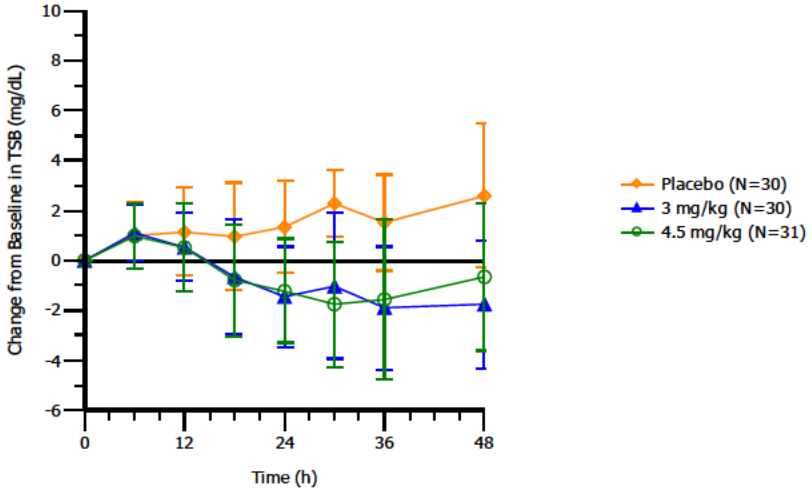
Figure 3: Mean Change from Baseline in Total Serum Bilirubin over Time Stratified by Phototherapy Treatment in Study 64,185-202



Source: Reviewer's plot based on the dataset for Study 64,185-202 (i.e., data202.xpt) submitted in the amendment (Sequence 0045) dated 4/2/2018.

Subsequently, stannsoporfin doses of 3 and 4.5 mg/kg were evaluated in neonates with hyperbilirubinemia in Study 64,185-204. In this study, stannsoporfin was administered within 30 minutes before or after initiating phototherapy treatment. The mean change from baseline in TSB over time profiles from Study 64,185-204 are presented in Figure 4. Both the 3 mg/kg and 4.5 mg/kg doses decreased TSB over time in neonates compared to placebo treatment. There was no apparent difference between the 3 mg/kg and 4.5 mg/kg doses in the change from baseline in TSB. Of note, the dose-response relationship for the percent change from baseline in TSB showed similar trends to that for the absolute change from baseline in TSB in both Studies 64,185-202, and 64,185-204 (graphs not presented).

Figure 4: Mean (SD) Change from Baseline in Total Serum Bilirubin over Time in Study 64,185-204

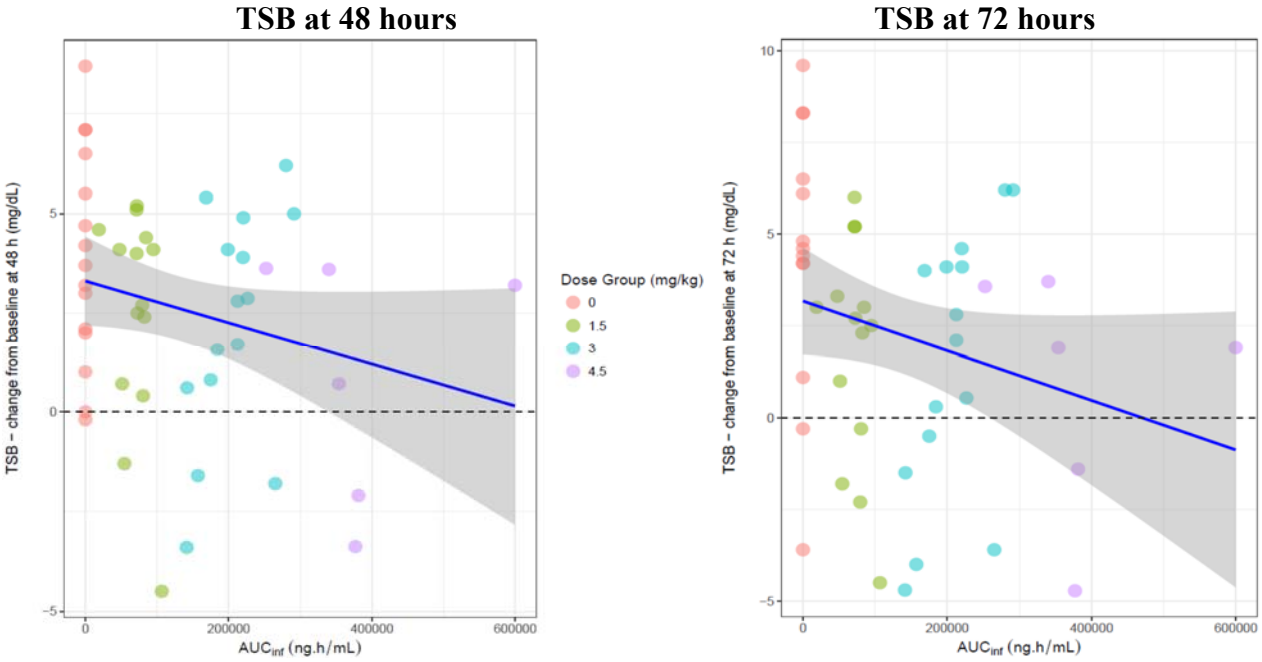


Source: Reviewer's plot based on data extracted from Table 14.3.3.1.1 in Applicant's Clinical Study Report for Study 64,185-204

Considering the mean change from baseline in TSB, stannsoporfin dosed at 4.5 mg/kg appeared to decrease TSB over time in neonates compared to placebo treatment in the pivotal efficacy Study 64,185-204 and the supportive Study 64,185-202. As noted above, the effect observed in the 3 mg/kg dose was not consistent between Studies 64,185-204 and 64,185-202.

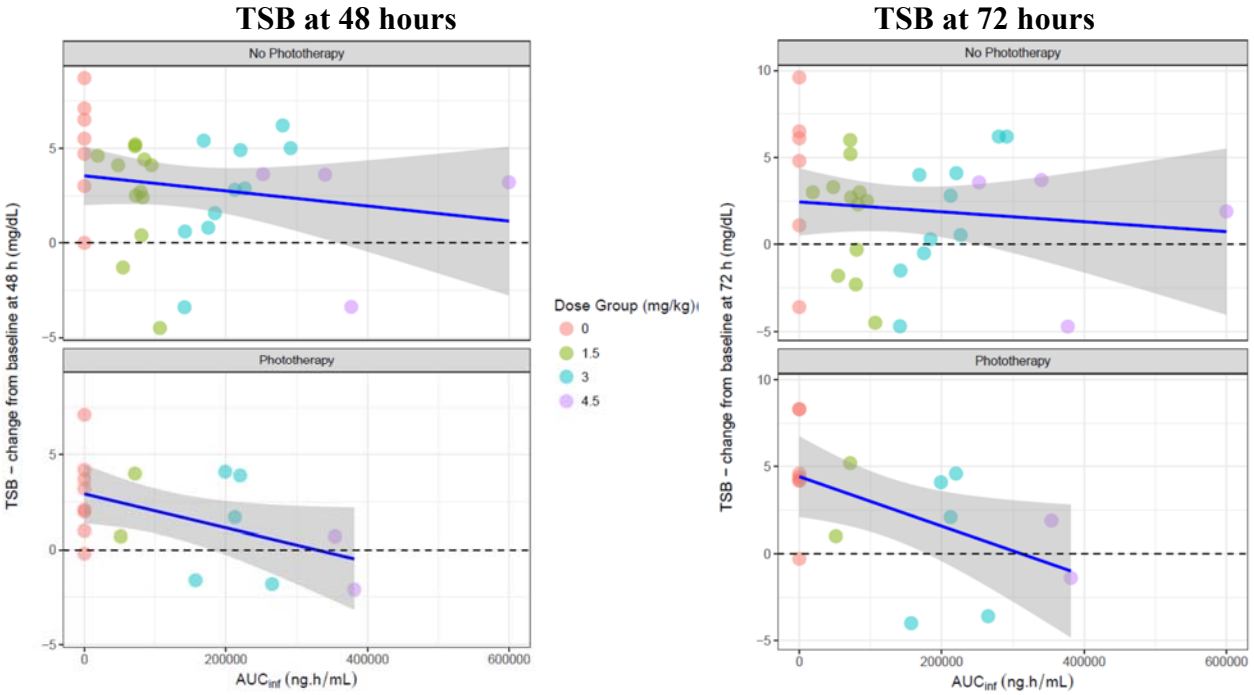
In addition, the exposure-response relationships for change from baseline in TSB were assessed in Study 64,185-202 based on 1) individual stannsoporfin AUC values in neonatal patients and 2) change from baseline in TSB at 48 and 72 hours. Exposure-response analyses conducted with the PK and PD data collected from Study 64,185-202 are shown in Figure 5 and Figure 6.

Figure 5: Exposure-Response Relationship for Change from Baseline in Total Serum Bilirubin Concentrations at 48 and 72 hours for all Patients in Study 64,185-202



TSB = Total serum bilirubin
Source: Reviewer's plots based on data provided by Applicant for Study 64,185-202.
Note: Blue line represents the linear regression line with its 95% confidence intervals (shaded area). Black dashed line is the reference line at 0.

Figure 6: Exposure-Response Relationship for Change from Baseline in Total Serum Bilirubin Concentrations at 48 and 72 hours Stratified by Phototherapy Treatment (Upper panel: without PT; Lower panel: with PT) for Study 64,185-202



TSB = Total serum bilirubin
Source: Reviewer's plots based on data provided by Applicant for Study 64,185-202.
Note: Exposure-response relationship is presented for patients who did not receive phototherapy (top panel) and who received phototherapy (lower panel). Blue line represents the linear regression line with its 95% confidence intervals (shaded area). Black dashed line is the reference line at 0.

Overall, graphical assessment of the exposure-response relationship in Study 64,185-202 indicates that there is a shallow inverse relationship between increasing systemic exposure and change from baseline at 48 and 72 hours in TSB in neonates regardless of PT treatment, which is consistent with the observed dose-dependent attenuation of TSB rise. Individual response was highly variable among patients without PT treatment and in patients with PT treatment to a lesser degree. Again, the apparent relationship in neonates who received PT treatment should be interpreted with caution due to the small sample size.

The Applicant also conducted an exposure-response analysis for the percent change from baseline in TSB at 48 hours across three studies: the pivotal Study 64,185-204 and two legacy Studies 29,462-04 and 29,462-08 that included preterm neonates with GA less than 35 weeks. In these three studies, PK blood samples were not collected, and individual AUC values were predicted based on a population PK model developed from different populations, i.e., adults and full-term neonates. Therefore, exposure-response analysis across these three studies is not considered appropriate.

6. EFFICACY

6.1. Overview of the Clinical Development Program

The Applicant conducted 18 clinical studies under two INDs (064185 and 029462) that included pediatric and adult populations (Appendix 6). A total of 911 neonates have been exposed to stannsoporfin in studies of various designs and in heterogenous populations. Nine studies (8 completed, 1 ongoing) have been conducted under IND 064185 and were compliant with Good Clinical Practices (GCP):

- Pivotal efficacy and safety study (Table 4):
  a) Study 64,185-204 (N=91)
     - Follow-up long-term safety extension Study 64,185-205 (ongoing)

- Applicant proposed efficacy and safety studies to support pivotal study:
  a) Study 64,185-202 (N=58; early termination due to the Division's concern about enrollment of less "at risk" population and preventative trial design rather than adjunct to PT)
     - Follow-up long-term safety extension Study 64,185-203 (N=52)
  b) 64,185-06 (N=55)
     - Follow-up long-term safety extension study 64,185-06LT (N=55)
     - Based on prior agreement between the Applicant and the Division, results from this study will not be used to support efficacy or safety given that this study was conducted in Vietnam (with the exception of 1 US neonate) and it is not possible to verify whether the clinical evaluations and long-term neurological assessments were performed using validated translated assessment tools.

- Other studies compliant with GCP:
  a) Study 64,185-013W (N=176; prematurely discontinued because it was placed on Clinical Hold due to the Division's concern about enrollment of neonates without evidence of hemolysis)
     - Follow-up long-term safety extension Study 64,185-01C3W (N=117)
  b) Study 64,185-02-01W (N=12; PK study conducted in healthy adults)

The other 9 studies under IND 029462 were not compliant with GCP standards. Six of these studies enrolled neonates, while the remainder enrolled adults and children. GCP provides public assurance that the rights, safety and well-being of human subjects involved in research are protected and ensures quality, reliability and integrity of the data collected. Additionally, these non-compliant GCP studies were of various designs and enrolled heterogenous populations that differed from the pivotal study population and are not suitable for inclusion in the efficacy analyses.

Table 4: Summary of Stannsoporfin Pivotal and Supportive Studies

Study # Country	Population	N and Treatment Arms	Efficacy Endpoints
Pivotal Study			
64,185-204 Multi-center U.S.	• ≥35 to ≤ 43 weeks GA • Risk factors for severe hyperbilirubinemia • Meeting criteria for PT[a]	• N=30 (3 mg/kg) • N=31 (4.5 mg/kg) • N=30 (Placebo)	**Primary:** • Percentage reduction from baseline in TSB at 48 hours **Secondary:** • Time to TSB crossing below age specific PT threshold • PT failure defined as one of: o Restart of PT >6 h after stopping o Re-hospitalization for hyperbilirubinemia o Use of IVIG o Need for ET • Incidence of rebound hyperbilirubinemia[b]
Supportive Studies			
64,185-202[b] Multi-center U.S. and Europe	• ≥35 to < 43 weeks GA • Risk factors of hemolysis • TSB within 2 mg/dL below criteria for PT	• N=17 (1.5 mg/kg) • N=18 (3 mg/kg) • N=8 (4.5 mg/kg) • N=15 (Placebo)	**Primary:** • Change from baseline in adjusted TSB[d] at 48 hours **Secondary:** • Change from baseline unadjusted TSB at 48 hours. • Proportion of subjects who required PT or ET • Duration of PT
64,185-06 Vietnam (1 subject from U.S.) Uncontrolled[e]	• ≥35 weeks GA • Hospitalized for hyperbilirubinemia • TSB within 2-3 mg/dL of the threshold for ET	• N=19 (0.75 mg/kg) • N=18 (1.5 mg/kg) • N=18 (Placebo)[e]	**Endpoints:** • Need for exchange transfusion. • TSB concentration • Jaundice • Incidence and duration of phototherapy • Duration of hospital stay

Source: Reviewer generated based on information submitted by the Applicant for NDA 209904.
[a] Protocol modified during trial to allow enrollment when baseline TSB is within 2 mg/dl below criteria for PT.
[b] Defined as an increase in TSB above the age-specific threshold for initiating PT following the discontinuation of the initial PT.
[c] Early termination and incomplete enrollment due to Division's concern with less at-risk enrollment population. Study was placed on Clinical Hold.
[d] Adjusted TSB = [(TSB − PT threshold/ PT threshold] x 100%.
[e] Placebo group was added mid-trial.

6.2. Pivotal Trial: Study 64-185-204

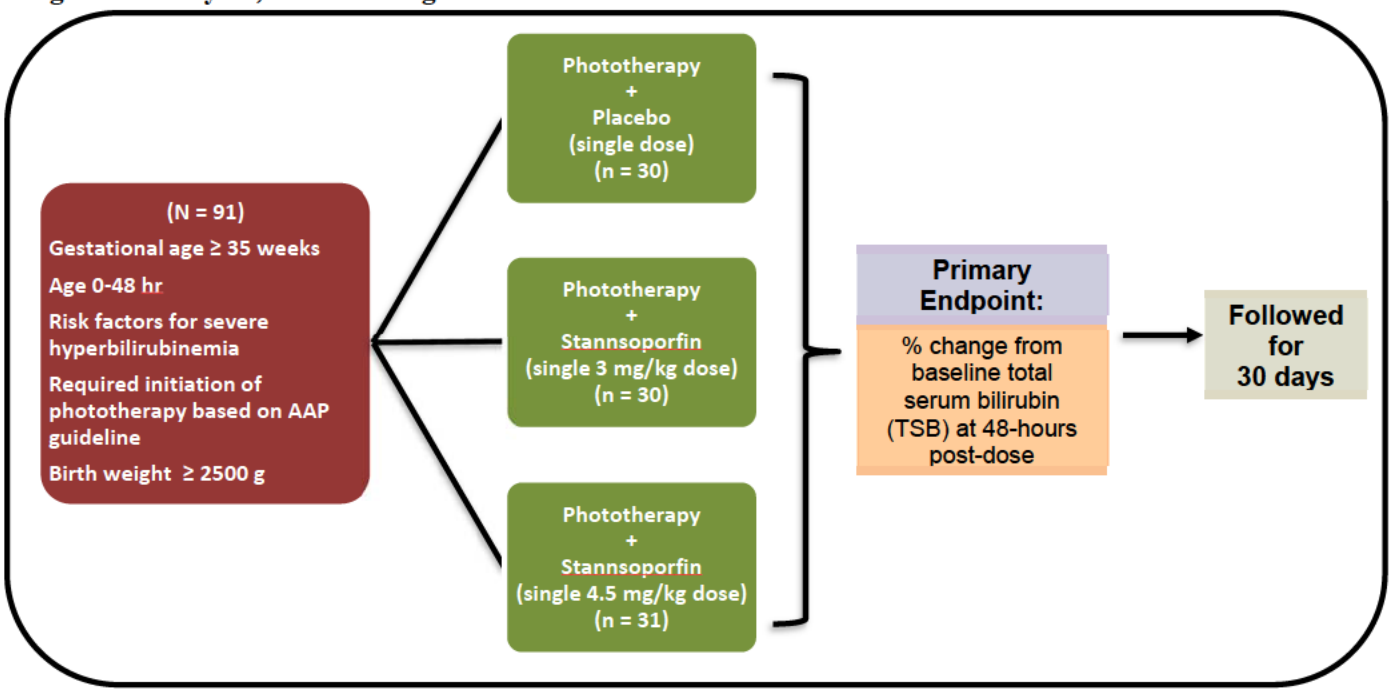
6.2.1. Trial Design and Objectives

Study 64,185-204 was a phase 2b multicenter, double-blind, randomized, placebo-controlled trial of stannsoporfin administered as a single IM injection in conjunction with PT in neonates greater than or equal to 35 weeks to less than or equal to 43 weeks gestational age (GA) with hyperbilirubinemia and indicators of ongoing hemolysis due to ABO or rhesus (Rh) incompatibility, or G6PD deficiency (Figure 7). The primary objective of this study was to assess the safety and efficacy of two dose levels of stannsoporfin (3.0 mg/kg and 4.5 mg/kg) as an adjunct to phototherapy.

Ninety-one neonates were randomized in a 1:1:1 ratio to phototherapy in conjunction with stannsoporfin 3 mg/kg, 4.5 mg/kg, or placebo within the first 48-hours of life. All neonates required concomitant PT based on the 2004 AAP Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation.[48] The requirement for PT was based on gestational age and risk level defined as:

- Medium-risk: Term (≥ 38 weeks gestation) with risk factors (isoimmune hemolytic disease); or near-term infants (≥ 35 to 37 and 6/7 weeks gestation) without risk factors
- High-risk: Near-term infants (≥ 35 to 37 and 6/7 weeks gestation) with risk factors (iso-immune hemolytic disease) for an exchange transfusion

Figure 7: Study 64,185-204 Design Scheme



Source: Reviewer generated based on information submitted by the Applicant for NDA 209904.

Phototherapy with eye protection was standardized per protocol and planned to be started within a window of no more than 30 minutes before or after stannsoporfin administration. The use of bili blankets or home PT was not permitted. TSB measurements were performed at 6, 12, 18, 24,

30, 36 ±2 hours, and 48 ±6 hours after stannsoporfin administration. If the neonate continued PT beyond 48 hours, the TSB measurements were obtained every 12 ± 6 hours.

The criteria for discontinuing PT were standardized for the trial and based on crossing the threshold for PT as outlined in the AAP guidelines. For example, if a TSB measurement was below the age-specific threshold for PT, PT was to be discontinued. Rebound hyperbilirubinemia was defined as an increase in TSB above the age-specific AAP threshold for initiating PT following discontinuation of PT. In cases of rebound hyperbilirubinemia, TSB collection occurred after initial discontinuation of PT, at 6-12 hours after discontinuation of PT and ≤54 hours posttreatment. PT re-initiation times that exceeded 54 hours posttreatment or occurred prior to 6 hours after initial PT discontinuation were not considered to meet the protocol definition of rebound hyperbilirubinemia.

Follow-up visits for all neonates occurred on Day 7 and Day 30. A visit on Day 14 was required if there were any clinically significant findings or events noted on Day 7. All neonates who received stannsoporfin could participate in the voluntary long-term follow-up study (64,185-205) to evaluate long-term neurocognitive and developmental outcomes.

6.2.2. Pivotal Study Population

Key Inclusion Criteria:

- ≥35 and ≤43 weeks GA
- Age 0-48 hours (at the time the qualifying TSB was drawn)
- ABO or Rh incompatibility (anti C, c, D, E, or e)
- One of the following indicators of hemolysis:
    - Direct agglutination test (DAT) positive or DAT-negative (or status unknown) with an elevated reticulocyte count (>6%).
    - Age 0-72 hours at the time the qualifying TSB was drawn, with confirmed G6PD deficiency
- TSB value at or above the age-specific threshold for initiating PT per AAP guidelines
- Birth weight ≥2500 grams

Key Exclusion Criteria:

- Direct (conjugated) bilirubin of ≥2 mg/dL or >20% of TSB
- Apgar score ≤6 at age of 5 minutes
- An unexplained existing rash or skin erythema
- Prior exposure to PT
- Electrocardiogram (ECG) finding of prolonged QT interval
- Use of intravenous immunoglobulin (IVIG) or albumin prior to study drug administration

6.2.3. Pivotal Study Endpoints

Primary efficacy outcome:

- Percent change from baseline in TSB (the baseline TSB is the TSB that qualifies for randomization) at 48 hours post-treatment

Secondary efficacy outcomes:

1. Time to TSB crossing at or below age-specific PT threshold
2. Phototherapy failure defined as:
   - Re-start of PT > 6 hours after stopping
   - Re-hospitalization for hyperbilirubinemia
   - Use of IVIG
   - Need for exchange transfusion
3. Incidence of rebound hyperbilirubinemia (i.e., increase in TSB above the age-specific threshold for initiating PT following the discontinuation of the initial PT) ≤54 hours after discontinuation of PT

Other secondary endpoints (not discussed further in this document):

- Percent change from baseline in TSB (the baseline TSB is the TSB that qualifies for randomization) at 6, 12, 18, 24, 30 and 36 hours post-treatment
- TSB area under the curve (AUC) above the baseline TSB (0 to 48 hours post-treatment)
- Peak serum bilirubin
- Duration of clinical requirement for PT defined as the interval between the initiation of PT and the time the serum bilirubin level crosses below the age-specific threshold for PT

The selection of percent change from baseline in TSB as the primary outcome in high risk neonates was questioned by the FDA because of the uncertainty in published literature and expert consensus guidelines of the clinically meaningfulness of this endpoint. While TSB is routinely used in clinical practice to guide the need for treatment and is included in widely accepted clinical guidelines, such as the AAP guidelines, for initiation of PT and ET, it is the level of free, unbound bilirubin that may more accurately predict the risk of bilirubin toxicity since only free bilirubin can cross the blood-brain barrier.[49-51] During the EOP2 meeting, the Division expressed concern over the choice of the endpoint and communicated to the Applicant "we question the likelihood that 'percent change from baseline TSB' will predict clinical benefit in high risk neonates" and indicated that these concerns would be review issues. As noted in Section 3.3, there are many other factors such as gestational age, hour of life, and comorbidities that contribute to the risk of developing complications from severe hyperbilirubinemia.

6.2.4. Statistical Methods

The Applicant's primary efficacy analysis was the analysis of covariance (ANCOVA) model, with treatment as a factor and baseline TSB value as a covariate. For the treatment difference of each active stannsoporfin dose vs. placebo, the LS mean difference, SE, p-value, and two-sided 95% CI were reported. Missing visit data were imputed using last observation carried forward (LOCF). The majority of the neonates with missing visit data were discharged from the hospital before 48 hours post treatment.

6.2.5. **Study Results**

Study 64,185-204 enrolled 151 neonates and randomized 91 neonates who were 35 to 41 weeks GA (30 in placebo group; 31 in 4.5 mg/kg group; 30 in 3 mg/kg group) across 22 sites in the U.S. Demographic characteristics were similar across treatment arms with the exception of race, with slightly higher proportions of Black or African American neonates enrolled in stannsoporfin treatment arms compared to placebo (Table 5).

Table 5: Demographic Characteristics (Study 64,185-204)

	Placebo N=30 n (%)	Stannsoporfin	
		4.5 mg/kg N=31 n (%)	3 mg/kg N=30 n (%)
SEX			
F	13 (43.3%)	15 (48.4%)	15 (50%)
M	17 (56.7%)	16 (51.6%)	15 (50%)
GESTATIONAL AGE			
≥38 weeks (AAP medium risk)	25 (83.3%)	28 (90.3%)	25 (83.3%)
41 weeks	2 (6.7%)	1 (3.2%)	3 (10%)
40 weeks	5 (16.7%)	11 (35.5%)	7 (23.3%)
39 weeks	16 (53.3)	11 (35.5%)	10 (33.3%)
38 weeks	2 (6.7%)	5 (16.1%)	5 (16.7%)
35 and <38 weeks (AAP high risk)	5 (16.7%)	3 (9.7%)	5 (16.7%)
37 weeks	5 (16.7%)	2 (6.5%)	5 (16.7%)
36 weeks	0 (0%)	0 (0%)	0 (0%)
35 weeks	0 (0%)	1 (3.2%)	0 (0%)
DIRECT AGGLUTINATION TEST (DIRECT COOMBS TEST)			
Negative	3 (10%)	2 (6.5%)	1 (3.3%)
Positive	27 (90%)	29 (93.5%)	29 (96.7%)
RACE			
Asian	1 (3.3%)	0 (0%)	0 (0%)
Black or African American	9 (30%)	13 (41.9%)	16 (53.3%)
Other	8 (26.7%)	5 (16.1%)	4 (13.3%)
White	12 (40%)	13 (41.9%)	9 (30%)
ETHNICITY			
Hispanic or Latino	15 (50%)	9 (29%)	7 (23.3%)
Not Hispanic or Latino	15 (50%)	22 (71%)	23 (76.7%)
COUNTRY			
USA	30 (100%)	31 (100%)	30 (100%)

Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

In the protocol, the Applicant defined the intent-to-treat (ITT) population (N = 91) as all randomized neonates who received an injection of placebo or stannsoporfin, have a baseline TSB, and at least one post-baseline TSB value.

Although the enrollment criteria stated TSB must be at or above the age-specified threshold for PT, the protocol allowed investigators to follow the AAP guidelines, which stated that phototherapy can be provided at TSB levels 2 to 3 mg/dL below the age-specified

thresholds.[48] In this study, 11 neonates (12.1%) had an enrollment TSB that was 2-3 mg/dL below the age-specific threshold for initiation of PT (Table 6).

Table 6: Baseline TSB Values for Neonates Enrolled in Study 64,185-204

	Placebo N=30 n (%)	Stannsoporfin	
		4.5 mg/kg N=31 n (%)	3 mg/kg N=30 n (%)
Number of neonates with baseline TSB value at or above the age-specific PT threshold	25 (83.3%)	29 (93.5%)	26 (86.7%)
Number of neonates with baseline TSB value below the age-specific PT threshold	5 (16.7%)	2 (6.5%)	4 (13.3%)

Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

Additionally, 15 neonates (3 in the 3 mg/kg stannsoporfin arm, 6 in the 4.5 mg/kg stannsoporfin arm and 6 in placebo; 13 AAP medium risk and 2 AAP high risk neonates) had negative interpolated time values, suggesting the TSB values of these neonates had already fallen below the defined phototherapy threshold prior to stannsoporfin or placebo injection.

One neonate who received the 3 mg/kg dose had a baseline TSB that exceeded the threshold for exchange transfusion (ET) at enrollment and received ET during the trial almost 11 hours after the stannsoporfin injection at approximately 18 hours of life.

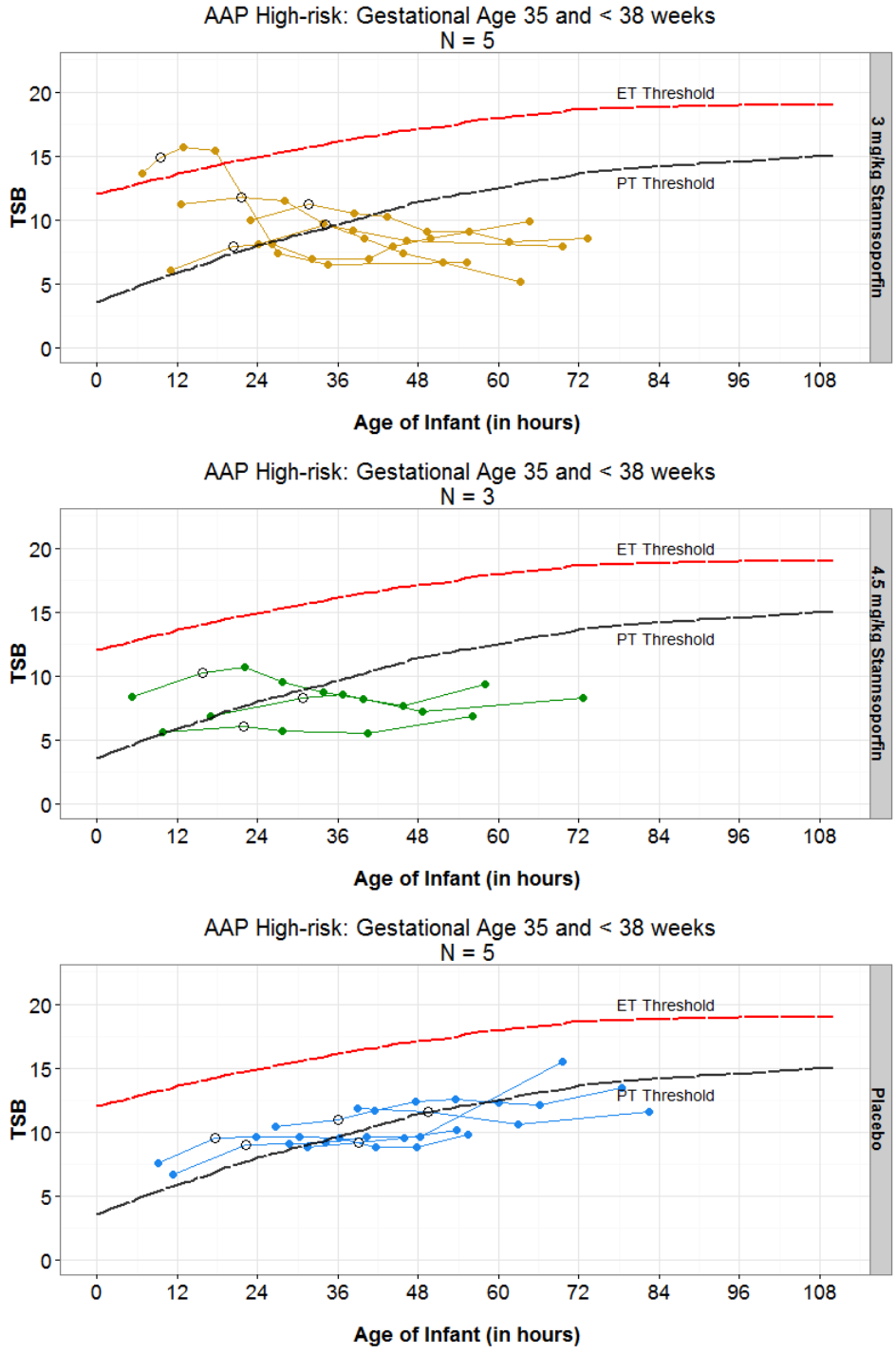
We performed analyses using both the N=91 and N=64 (91-11-15-1) populations.

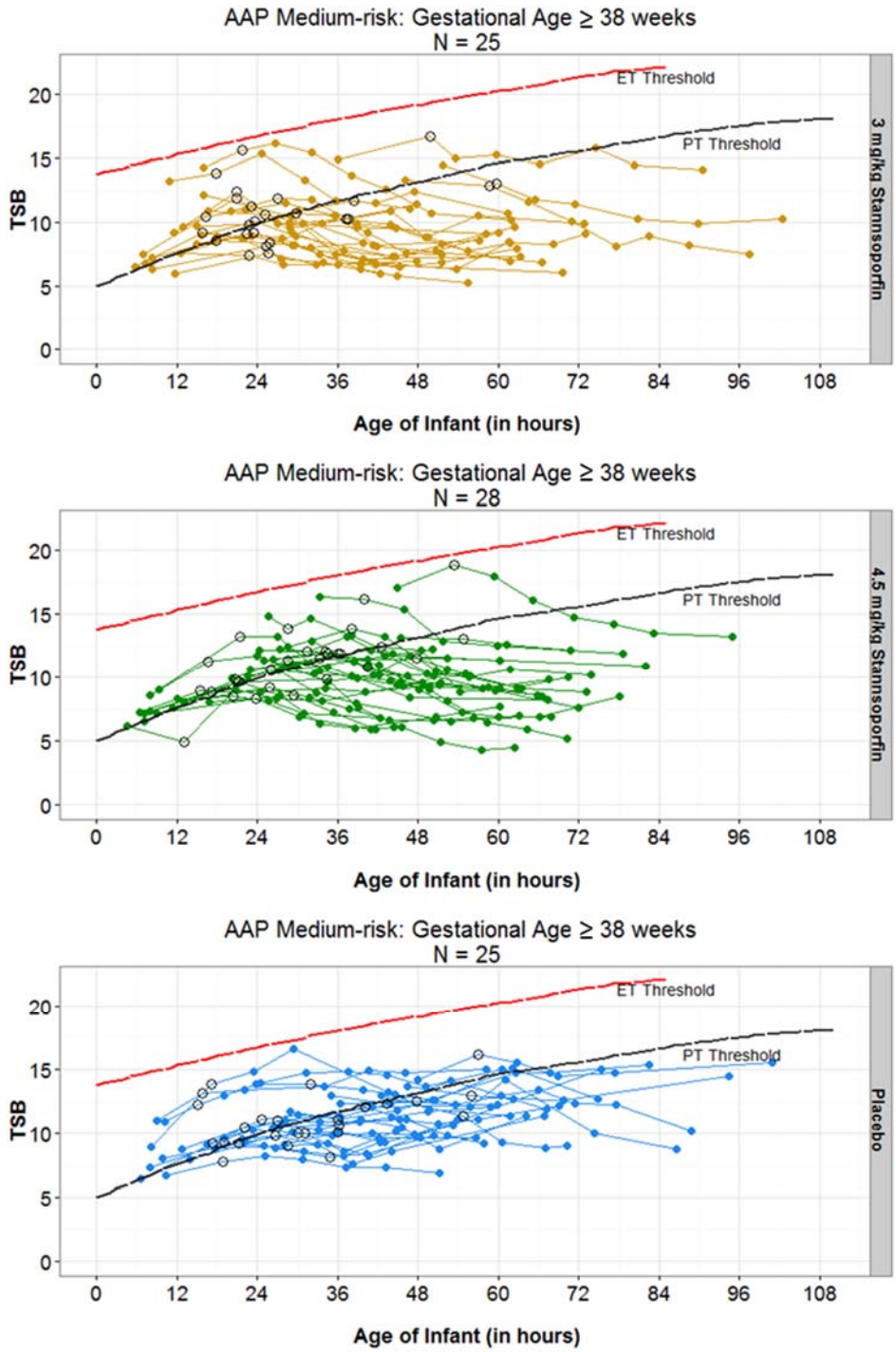
Individual Neonatal Subject Profiles

The panels in Figure 8 show the individual neonates' performance over time for Study 64,185-204, and the age-specific PT and ET thresholds. The majority of enrolled neonates had gestational age greater than 38 weeks, and as such, were considered to have AAP medium risk for developing complications from severe hyperbilirubinemia.

Differences in trajectories for the AAP high risk neonates were noted with stannsoporfin treatment. Although the numbers are small, the stannsoporfin-treated AAP high risk neonates have TSB levels that fall below the PT high risk threshold line, whereas the placebo treated AAP high risk neonates have levels that stay close to that line.

Figure 8: Individual TSB Trajectories Based on AAP Risk Designation (ITT, 91 Neonates; Study 64, 185-204)





TSB = Total serum bilirubin; AAP = American Academy of Pediatrics; PT = Phototherapy; ET = Exchange transfusion
Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204
Note: ○ identifies the first visit after the injection of the study medication. Of note, in ±30 minutes after injection, majority of the neonates were treated with phototherapy.

Primary Endpoint Results

The Applicant's analysis results for the primary endpoint based on the ITT population (N=91) are shown in Table 7. The mean differences for percent change in TSB at 48 hours after treatment

are statistically significant for both 3 mg/kg and 4.5 mg/kg stannsoporfin treatment arms compared with placebo (LS mean differences are -31.64 and -27.40, respectively, with both p-values < 0.0001). The results for the 64 neonates population are also statistically significant.

Table 7: Percent Change from Baseline in TSB at 48 Hours Post-Treatment (LOCF, Study 64,185-204)

	Statistic	Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
Baseline TSB (mg/dL)	Mean (SD)	9.92 (2.21)	9.97 (2.97)	9.82 (2.64)
Percent change from baseline at 48H post-dose *ITT, 91 neonates*[a]	N	30	31	30
	LS mean (95% CI)	22.10 (13.36, 30.84)	-5.30 (-13.90, 3.30)	-9.54 (-18.28, -0.80)
	LS mean diff vs placebo (95% CI) [p-value]		-27.40 (-39.66, -15.14) [<0.0001]	-31.64 (-44.00, -19.28) [<0.0001]
Percent change from baseline at 48H post-dose *64 neonates*[b]	N	19	23	22
	LS mean (95% CI)	27.44 (16.89, 38.00)	-2.77 (-12.37, 6.83)	-14.20 (-24.02, -4.38)
	LS mean diff vs placebo (95% CI) [p-value]		-30.21 (-44.47, -15.94) [<0.0001]	-41.64 (-56.06, -27.23) [<0.0001]

TSB = Total serum bilirubin; SD = Standard deviation; CI = Confidence interval
[a] Source: Results were extracted from Table 14.2.1.1 in the Applicant's Clinical Study Report
[b] Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

Secondary Endpoints Results

Three secondary endpoints were sequentially tested. The Applicant proposed testing the 4.5 mg/kg dose compared to placebo, followed by testing of the 3 mg/kg dose compared to placebo.

1st secondary endpoint: Time at which TSB crossed at or below the defined PT threshold

Time (in hours) at which TSB crossed at or below the AAP defined age-specific threshold was calculated as Date/Time [TSB first crossed at or below the defined threshold ≤ 54 hours post-treatment] minus Date/Time of injection of study medication. Two neonates in the placebo arm who never crossed the PT threshold prior to or at the 54 hours pre-specified post-treatment time were censored. Linear interpolation was used to estimate the time when the neonate's TSB value crossed the defined PT threshold line.

Table 8: Time (in Hours) at Which TSB Crossed at or Below the AAP Age-Specific Phototherapy Threshold (T_TSB) for Study 64,185-204

	Statistic	Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
Interpolated T_TSB[a] ***76 (= 91- 15) neonates***	N	24	25	27
	50th percentile (hr) (95% CI)	20.9 (9.2, 26.5)	10.6 (8.1, 16.4)	11.8 (8.2, 21.8)
	Log-rank p-value vs. placebo		0.003	0.23
Interpolated T_TSB[b] ***64 (=91-11-15-1) neonates***	N	19	23	22
	50th percentile (hr) (95% CI)	15.1 (6.9, 26.5)	9.4 (7.1, 13.9)	10.9 (7.6, 16.1)
	Log-rank p-value vs. placebo		0.014	0.16

TSB = Total serum bilirubin; CI = Confidence interval
[a] Results were extracted from Table 14.2.4.1 in the Applicant's Clinical Study Report.
[b] Reviewer's analysis based on data submitted by Applicant for Study 64,185-204. Removed 27 of the 91 randomized neonates from the Applicant's ITT population: 26 were below the defined threshold at randomization or prior to stannsoporfin injection; 1 additional neonate received ET in the 3 mg/kg treatment arm.
Note: Linear interpolation was used to obtain the interpolated T_TSB. To better understand this method of estimation, consider 2 timepoints, the first above and the second below the age-specific PT threshold connected by a straight line. Assume at the same 2 timepoints, the age-specific PT threshold TSB values are connected by another line. The intersection of these 2 lines provides an estimate of the time when the neonate's actual TSB values crossed the age-specific PT threshold (see the example graph in Appendix 7).

The Applicant claimed the 4.5 mg/kg dose was superior to placebo (log rank test p-value=0.003; Table 8) in reducing the time until bilirubin levels crossed the defined threshold for discontinuing PT. It should be noted that the Applicant conducted this analysis based on 76 neonates, after the 15 neonates who had negative interpolated T_TSB were automatically excluded from the Statistical Analysis System (SAS) implement.

Since the results of the first secondary endpoint for 3 mg/kg are not statistically significant, per the Applicant's testing hierarchy, testing the 2nd and 3rd secondary endpoints for either dose level is not allowed. However, given their clinical interest, we summarize the analysis results descriptively below.

2nd secondary endpoint: PT failure

PT failure was observed to occur more frequently in the placebo arm than in the stannsoporfin arms (Table 9).

Table 9: Phototherapy Failure (Study 64,185-204)

	Statistic	Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
PT failure[a] ***ITT, 91 neonates***	N	30	31	30
	Occurred n (%)	8 (27%)	1 (3%)	3 (10%)
PT failure[b] ***64 neonates***	N	19	23	22
	Occurred n (%)	7 (37%)	1 (4%)	2 (9%)

PT = Phototherapy
[a] Source: Results were extracted from Table 14.2.5.5 in the Applicant's Clinical Study Report
[b] Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

Subcategories of PT failure

The numbers of neonates within the subcategories of PT failure in each treatment group are shown in Table 10. The main numerical difference between treatment arms is seen in the restart of PT after 6 hours post-discontinuation. However, it is important to note the study was not powered to detect differences in each subcategory of PT failure.

Table 10: Summary of Phototherapy Failure (Study 64,185-204) for 91 Randomized Neonates

PT Failure	Placebo	Stannsoporfin	
		4.5 mg/kg	3 mg/kg
N=91	30	31	30
Any Neonate with PT Failure[a]	8 (26.7%)	1 (3.2%)	3 (10%)
Restart of PT > 6hr	7 (23.3%)	1 (3.2%)	1 (3.3%)
Re-hospitalization for hyperbilirubinemia	3 (10%)	1 (3.2%)	0 (0%)
Use of IVIG	1 (3.3%)	0 (0%)	1 (3.3%)
Need for exchange transfusion	0 (0%)	0 (0%)	1 (3.3%)
N=64	19	23	22
Any Neonate with PT Failure[a]	7 (36.8%)	1 (4.3%)	2 (9.1%)
Restart of PT > 6hr	6 (31.6%)	1 (4.3%)	1 (4.5%)
Re-hospitalization for hyperbilirubinemia	2 (10.5%)	1 (4.3%)	0 (0%)
Use of IVIG	1 (5.3%)	0 (0%)	1 (4.5%)
Need for exchange transfusion	0 (0%)	0 (0%)	0 (0%)

PT = Phototherapy; IVIG = Intravenous Immunoglobulin
Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204
[a] Any PT failure refers to the number of neonates who experienced at least one of the events listed. An individual neonate may experience more than one of the PT failure events listed.

3rd secondary endpoint: Rebound hyperbilirubinemia <54 hours after discontinuation of PT

Numerically, more neonates in the placebo arm experienced rebound hyperbilirubinemia compared to the stannsoporfin arms (Table 11).

Table 11: Incidence of Rebound Hyperbilirubinemia (ITT, Study 64,185-204)

	Statistic	Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
Rebound hyperbilirubinemia[a] ***ITT, 91 neonates***	N	30	31	30
	Occurred n (%)	3 (10%)	1 (3%)	0 (0%)
Rebound hyperbilirubinemia[b] ***64 neonates***	N	19	23	22
	Occurred n (%)	3 (16%)	1 (4%)	0 (0%)

ITT = Intent-to-treat
[a] Source: Results were from Table 14.2.5.7 in the Applicant's Clinical Study Report
[b] Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

6.2.6. Statistical Issues and Summary

Generally, two adequate and well-controlled trials are needed to provide substantial evidence of efficacy. The adequacy of a single trial to support approval will be determined by its ability to support the efficacy claim based on the strength of the results. If only one clinical trial is conducted (such as Study 64,185-204 in the current application), then internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will need to be considered in the evaluation.

For the protocol-specified primary endpoint of percent change from baseline in TSB, the stannsoporfin 3 mg/kg and 4.5 mg/kg doses exhibited a greater reduction compared to placebo, which was statistically significant. When the primary analysis was repeated by FDA based on 64 of 91 neonates (excluding 11 neonates who did not meet the age-specific threshold for initiation of PT, 15 neonates who had TSB values below the PT threshold prior to stannsoporfin or placebo injection, and 1 neonate with baseline TSB that exceeded the threshold for ET at enrollment and received ET during the trial), the primary endpoint results remained statistically significant. For the first secondary endpoint (time in hours when TSB fell below the age-specific PT threshold), stannsoporfin 4.5 mg/kg demonstrated statistical significance compared to placebo, based on the Applicant's analysis of 76 neonates (after excluding 15 neonates who had TSB values that fell below the defined PT threshold prior to stannsoporfin injection). When this analysis was repeated by FDA based on 64 neonates, the nominal p-value was 0.014 for the 4.5 mg/kg dose. The 3 mg/kg dose did not show a statistically significant difference on this endpoint compared to placebo.

Study 64,185-204 is the only pivotal study. The first secondary endpoint (time at which TSB crossed the age-specific AAP PT threshold), a clinical outcome of importance, supports the primary endpoint results for the 4.5 mg/kg dose. Overall interpretation of the results is limited by the small sample size and inclusion in the study of neonates who would otherwise not receive the drug.

6.3. Supportive Studies

6.3.1. Study 64,185-202

Study 64,185-202 was a multicenter, multinational, randomized, placebo-controlled, dose-escalation study that evaluated the safety and efficacy of stannsoporfin in neonates ≥35 weeks to <43 weeks GA with risk factors of hemolysis, including Coombs positive neonates who had TSB levels within 1-2 mg/dL below the AAP guideline age-specific threshold for the initiation of PT. Neonates were randomized to stannsoporfin or placebo in a 3:1 ratio at each dose level (1.5 mg/kg, 3 mg/kg, or 4.5 mg/kg). Neonates were assessed for the need for PT after receiving the investigational drug product. If required, phototherapy was standardized across all study sites. Key differences between Studies 64,185-202 and Study 64,184-204 are:

- Not all neonates in Study 64,185-202 received PT.
- In Study 64,185-202, neonates received stannsoporfin prior to reaching a PT threshold and, the TSB level required for enrollment was temporarily relaxed from 1-2 mg/dL below PT initiation to 2-3 mg/dL below PT initiation.

Given the differing TSB requirements for enrollment and administration of stannsoporfin in advance of reaching a threshold for initiating PT, the populations enrolled in the two studies are not comparable.

The primary efficacy endpoint was change in adjusted TSB, which takes into account the AAP guideline on age-defined PT threshold [(TSB − PT threshold/ PT threshold) x 100%], at 48 hours after study treatment. During enrollment of the 4.5 mg/kg treatment arm, the study was placed on Partial Clinical Hold due to FDA's concern about the appropriateness of the study population and design (refer to Section 3.6). Thus, the protocol-intended number of neonates at the 4.5-mg/kg dose level was not met.

A total of 58 neonates received treatment with either stannsoporfin (1.5 mg/kg (n=17); 3 mg/kg (N=18); 4.5 mg/kg (n=8)) or placebo (n=15). Fifty-six neonates completed the study, and 2 neonates were voluntarily withdrawn by their parents/guardians after receiving treatment. While the mean percent change in adjusted TSB at 48 hours decreased in all stannsoporfin treatment arms compared to placebo (p=0.040 for 1.5 mg/kg, p=0.117 for 3 mg/kg and p=0.057 for 4.5-mg/kg group), p-value <0.05 was only achieved for the lowest dose (1.5 mg/kg) arm (Table 12).

Table 12: Percent Change from Baseline in Adjusted TSB at 48 Hours Post-Treatment (Study 64,185-202)

	Statistic	Placebo N=15	Stannsoporfin		
			4.5 mg/kg N=8	3 mg/kg N=18	1.5 mg/kg N=17
Percent change from baseline at 48H post-dose *ITT, 58 neonates*	LS Mean (hr) (SEM)	-1.58 (5.05)	-16.51 (6.93)	-11.60 (5.61)	-15.03 (5.27)
	LS Mean Diff Vs. Placebo (95% CI)		-14.93 (-30.31, 0.44)	-10.02 (-22.61, 2.58)	-13.45 (-26.27, -0.62)
	p-value		0.057	0.117	0.040

LS = Least squares; SEM = Standard error of mean; ITT = Intent-to-treat;
Source: Reviewer generated based on data submitted by Applicant for Study 64,185-202

Percent change in (unadjusted) TSB from Baseline at 48 hours post-dose was a secondary endpoint for Study 64,185-202. While all arms showed an increase in TSB from baseline, neonates in all three arms of stannsoporfin had a smaller increase in TSB at 48 hours compared to those in placebo.

None of the neonates in any of the treatment arms including placebo required exchange transfusion. Phototherapy was only administered for 32.8% of the neonates (n=19). This contrasts with the population of the pivotal study 64,185-204 in which 100% of the neonates received phototherapy, suggesting enrollment of a less at risk population for complications related to severe hyperbilirubinemia in Study 64,185-202. While not statistically significant, a lower proportion of neonates in each stannsoporfin arm required phototherapy compared to placebo. This pattern was also seen in the duration of phototherapy. Across stannsoporfin treatment arms, the LS mean differences for PT duration were 5 to 6 hours shorter compared to placebo (314 minutes shorter in the 1.5 mg/kg arm, 254 minutes shorter in the 3 mg/kg arm, and 313 minutes shorter in the 4.5 mg/kg group).

6.3.2. Study 64,185-06

Study 64,185-06 was an open-label, non-randomized, ascending-dose, sequential-cohort (enrolled lowest dose first), dose exploration study of stannsoporfin at 0.75 mg/kg (Cohort 1) and 1.5 mg/kg (Cohort 2), designed to evaluate the safety of stannsoporfin and its effect in reducing the need for ET in neonates ≥35 weeks GA with TSB within 2-3 mg/dL of the age-specific threshold for exchange transfusion, which implied a more severe at-risk population for complications related to severe hyperbilirubinemia compared to the pivotal study.

Fifty-five neonates were enrolled to receive treatment with either stannsoporfin (0.75 mg/kg, n=19; 1.5 mg/kg, n=18) or placebo (n=18). All but one neonate were enrolled from a single Vietnam site. Twelve neonates required ET (0.75 mg/kg (n=1); 1.50 mg/kg (n=2); placebo (n=9)) post-study treatment. Both stannsoporfin treatment arms had statistically significantly fewer neonates requiring ET compared to the placebo group (0.75 mg/kg, p=0.003; 1.5 mg/kg, p=0.027). All neonates received PT, and the duration of PT was not significantly different

between arms (85.2, 60.8 and 68.7 hours for the stannsoporfin 0.75 mg/kg, 1.5 mg/kg and placebo arms, respectively). There were no statistically significant differences between the stannsoporfin and placebo arms in the mean duration of hospital stay from time of drug administration to hospital discharge (0.75 mg/kg, 191 hours; 1.5 mg/kg, 126 hours; and placebo, 141 hours).

While Study 64,185-06 enrolled a higher risk population for developing clinical consequences related to severe hyperbilirubinemia, there were multiple limitations to the study design significantly limiting the interpretability of the study results. The lack of blinding, randomization, and control group (placebo group was added mid-trial) all contribute to potential bias in the study results. The significance of the apparent longer PT duration and the duration of hospital stay observed in the 0.75 mg/kg arm compared to placebo is unclear and may be related to the small sample size. There were also a significant proportion of neonates with protocol violations: 94.7% in the 0.75 mg/kg arm (n=18); 94.4% in the 1.5 mg/kg arm (n=17); and 100% in the placebo arm (n=19). The large number of protocol violations underscores FDA's concerns about the reliability and validity of the study findings and would not consider this study to be an adequate and well-controlled study to support efficacy.

7. SAFETY EVALUATION

7.1. Safety Analysis Summary

The safety profile of stannsoporfin is notable for photosensitivity reactions, thrombocytopenia, hearing and speech related disorders, as well as the potential for long-term effects on neurodevelopment outcomes. FDA seeks input from the Committee regarding whether the long-term effects of stannsoporfin have been sufficiently characterized to date.

Review of the short-term safety data (within 30 days from the date of randomization or treatment) from the pivotal trial 64,185-204 (N=91) and pooled short-term follow-up studies (64,185-013W, 64,185-202, and 64,185-204; N=325) identified that the potential short-term risks related to stannsoporfin exposure include, but were not limited to, skin erythema and thrombocytopenia. Both of these adverse events (AEs) were reported at higher frequencies in Study 64185-204 and the pooled short-term follow-up studies.

The potential for neurodevelopmental adverse outcomes was assessed through evaluation of AEs in selected body systems (neurologic, psychiatric, auditory, and motor) and neurodevelopmental assessments performed during the long-term follow-up studies (64,185-01C3W, 64,185-203, and 64,185-205). A higher incidence of deafness and speech disorder was reported in pediatric patients in the 4.5 mg/kg arm; however, the small number of events limit the interpretability of these results. While the scores obtained across neurodevelopment assessments in the long-term follow-up studies were comparable between stannsoporfin and placebo arms, the results are difficult to interpret given the small sample size, the mixed population studied, and the variation in the type of assessments used longitudinally across studies. Moreover, the long-term extension trial to the pivotal trial (Study 64,185-205) is ongoing with only very limited 2-year neurodevelopment testing data in a small number of pediatric patients (n=7) currently available for review. Given these limitations, we do not believe the potential for long-term

neurodevelopmental adverse outcomes related to stannsoporfin exposure have been adequately assessed or characterized.

7.2. Safety Analysis Methodology

7.2.1. Safety Database:

The clinical review of safety of stannsoporfin in neonates at risk for developing complications due to severe hyperbilirubinemia is focused on Study 64,185-204 and its long-term extension trial (Study 64,185-205). The safety database was pooled based on three areas of interest: short-term safety (up to 30 days post-dose); long-term safety (up to 6 years depending on the individual trial); and long-term neurodevelopmental safety.

Safety data were pooled into a total of 4 datasets:

1. Short-term safety data provided information (within 30 days from the date of randomization or treatment) from randomized, double-blind, placebo-controlled studies (Studies 64,185-013W, 64,185-202, and 64,185-204) conducted under IND 064185 in neonates of similar GA (range ≥35 and ≤43 weeks).
2. Long-term safety data provided information on long-term safety (up to 6 years) in Studies 64,185-01C3W, 64,185-203, and 64,185-205 conducted under IND 064185.
3. Long-term neurodevelopmental assessments were compiled from 2 datasets which provide summary evaluation of the neurological and neurodevelopmental assessments in studies conducted under 2 separate INDs. These datasets are presented separately because different assessments were performed for studies conducted under IND 029462 and did not meet GCP standards:
    a. IND 064185 (GCP) – 3 studies (64,185-01C3W, 64,185-203, and 64,185-205)
    b. IND 029462 (not GCP) – 6 studies (29,462-04, -05, -06, -07, -08, and -09)

7.2.2. Overall Exposure:

A total of 1430 neonates were included in the stannsoporfin safety population (Table 13): 887 received doses of stannsoporfin ranging from 0.75 to 4.5 mg/kg and 543 as controls (placebo, no treatment, or PT only). An additional 18 neonates received stannsoporfin under compassionate use or emergency INDs. Forty-four adult and pediatric patients also received stannsoporfin in studies for other indications that do not directly support the proposed indication and, therefore, were not included in the safety population.

Table 13: Safety Population (Neonates) for Stannsoporfin

Safety Database for Stannsoporfin Neonates Exposed to Study Medication (Drug or Placebo) N= 1430 (N is the sum of all available numbers from the columns below)							
Study No.		Stannsoporfin N=887[a]					Control[d] N=543
		0.75 mg/kg	1.5 mg/kg	2.25 mg/kg	3 mg/kg	4.5 mg/kg	
GCP[b]	64,185-013w					87	89
	64,185-06-2ISNHP	19	18				18
	64,185-202		17		18	8	15
	64,185-204				30	31	30
Total GCP = 380		19	35		48	126	152
Not- GCP[c]	29,462-04	50	59	32	59	61	202
	29,462-05					48	44
	29,462-06					205	20
	29,462-07					35	12
	29,462-08					30	27
	29,462-09					80	86
Column Total = 1430		69	94	32	107	585	543

GCP = Good clinical practice
Source: Reviewer generated based on Module 2.7.4: Summary of Clinical Safety Table 20 submitted by Applicant.
[a] 18 neonates enrolled via compassionate use are not included in the analysis of overall safety database and will be discussed separately
[b] Studies conducted under IND 64185 were conducted under current good clinical practice (GCP) standards.
[c] Studies conducted under IND 29,462 did not meet current good clinical practice (GCP) standards.
[d] Control population includes neonates receiving placebo or phototherapy alone.

7.2.3. Safety Review Approach

Potential safety concerns based on stannsoporfin's mechanism of action and nonclinical data are outlined below:

- Neurodevelopmental effects
- Photosensitivity
- Kidney, liver, and bone marrow toxicity
- Iron deficiency anemia from prolonged inhibition of heme oxygenase (extensive heme excretion due to inhibition of heme catabolism)

Categorization of Adverse Events

An adverse event (AE) is any medical event that is associated with the use of a drug in humans, whether or not it is considered to be related to the drug. For all AEs, the intensity of the event is assessed as mild, moderate, or severe based on the extent of interference with routine activities. A serious adverse event (SAE) is any untoward medical occurrence that results in death, a life-threatening event, or requires hospitalization or prolongation of hospitalization. It is important to note that a severe AE is not necessarily serious in nature and that an SAE is not by definition, severe. In all studies, treatment-emergent adverse events (TEAEs) were defined as AEs that

started or worsened in intensity during or after the injection of study drug.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.0. To facilitate the safety review of the adverse events, events were recoded by grouping together terms for similar events as shown in Table 14:

Table 14: Recoding Scheme of MedDRA Level Preferred Terms During Review

Proposed AEDECOD[a]	Existing AEDECOD (Preferred Term)
Anemia	Anemia, Red blood cell count decreased, Hemoglobin/hematocrit decreased, Hemolytic anemia
Anxiety	Anxiety, Anxiety disorder
Deafness	Conductive deafness, Deafness, Deafness bilateral, Hypoacusis
Erythema	Erythema, Photosensitivity reaction (red rash when exposed to light), Rash erythematous, Generalized erythema
Feeding disorder	Feeding disorder, Feeding intolerance
Hyperbilirubinemia	Hyperbilirubinemia, Blood bilirubin increased, Bilirubin conjugated increased, Jaundice, Jaundice neonatal, Ocular jaundice
Oral candidiasis	Oral candidiasis, Candida infection (thrush)
Leukocytosis	Leukocytosis, WBC count increased
Meningitis	Bacterial meningitis, viral meningitis
Rash	Rash, Rash macular, Rash papular, Rash maculo-papular, Exfoliative rash, Seborrheic dermatitis, Seborrhea, Dermatitis contact
Rash neonatal	Rash neonatal, Erythema toxicum neonatorum, Millia, Acne infantile, Transient neonatal pustular melanosis, Candida nappy rash, Dermatitis diaper
Sepsis	Sepsis, Bacterial sepsis
Speech Disorder	Speech disorder, Speech disorder developmental, Speech sound disorder, Dysarthria, Dysphemia
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Vomiting	Vomiting, Infantile vomiting, Vomiting projectile

[a] AEDECOD refers to the dictionary derived text description of the adverse events; equivalent to the Preferred Term in MedDRA hierarchy.

7.2.4. Limitations to the Safety Analysis

There are limited safety data from the long-term extension of the pivotal study (Study 64,185-205). The applicant submitted an interim study report (with a data cut-off date of January 8, 2017), which included 34 pediatric patients with Year 1 and 7 pediatric patients with Year 2 neurodevelopmental testing results.

7.3. Key Safety Results

7.3.1. Safety Summary of Pivotal Study 64,185-204

Ninety-one neonates were randomized to one of three treatment arms: stannsoporfin 3 mg/kg (n=30), stannsoporfin 4.5 mg/kg (n=31), or placebo (n=30). Eighty-three neonates completed the

study and 8 discontinued (6 were lost to follow-up and 2 were voluntarily withdrawn by the parent/guardian).

Death and SAEs in Study 64,185-204

There were no deaths or SAEs leading to study discontinuation within the pivotal study. Fifteen neonates experienced SAEs. No individual SAE occurred in more than one neonate except for hyperbilirubinemia in the placebo group (3 neonates) and medical observations (2 neonates: 1 observation for supraventricular tachycardia and 1 for sepsis) in the stannsoporfin 3 mg/kg arm. All SAEs had resolved except in two neonates: supraventricular tachycardia in a neonate in the 3 mg/kg arm with a congenital heart defect that was thought to have a re-entry accessory pathway, and decreased hematocrit and hemoglobin that was recoded by FDA as anemia in a neonate in the placebo arm.

Table 15: SAEs in Study 64,185-204

	Placebo N = 30 n (%)	Stannsoporfin	
		4.5 mg/kg N = 31 n (%)	3 mg/kg N = 30 n (%)
Any Neonate with SAE	6 (20%)	4 (12.9%)	5 (16.6%)
Hyperbilirubinemia	3 (10%)	1 (3.2%)	1 (3.3%)
Medical observation	0 (0%)	0 (0%)	2 (6.7%)
Sepsis	0 (0%)	2 (6.4%)	0 (0%)
ABO incompatibility	1 (3.3%)	0 (0%)	0 (0%)
Anemia	1 (3.3%)	0 (0%)	0 (0%)
Leukocytosis	0 (0%)	0 (0%)	1 (3.3%)
Meningitis viral	0 (0%)	1 (3.2%)	0 (0%)
Reticulocyte count increased	1 (3.3%)	0 (0%)	0 (0%)
Supraventricular tachycardia	0 (0%)	0 (0%)	1 (3.3%)
Tachypnea	0 (0%)	0 (0%)	1 (3.3%)
Thrombocytopenia	0 (0%)	0 (0%)	1 (3.3%)

SAE = Serious adverse event
Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204.

Adverse Events in Study 64,185-204

The majority of neonates (n=71, 78%) had at least one TEAE. The proportion of neonates who had TEAEs in the 4.5 mg/kg stannsoporfin arm was comparable to placebo (n=21, 67.7%, and n=22, 73.3% respectively). Neonates in the 3 mg/kg stannsoporfin arm had the highest rate of TEAEs (n=28, 93.3%). Most TEAEs were mild and moderate in severity. All of the TEAEs graded "severe" occurred in the 3 mg/kg arm (n=3, 10%) and included hyperbilirubinemia, hyperkalemia, and thrombocytopenia requiring transfusion.

TEAEs in Study 64,185-204

Common TEAEs occurring in ≥2 neonates in any treatment arm are summarized in Table 16. The most common TEAEs reported in ≥2 neonates in any treatment arm was "rash", which occurred at similar frequencies across treatment arms. Cardiac murmur, anemia,

hyperbilirubinemia, and increased reticulocyte were also commonly reported across treatment arms, which may be related to infancy and the underlying disease process in these neonates. In contrast, the TEAEs of "erythema" (18%) and "thrombocytopenia" (9.8%) only occurred in the stannsoporfin arms and were not observed in the placebo.

Table 16: Common TEAEs (≥2 Neonates in Any Treatment Group) in Study 64,185-204

	Placebo N = 30 n (%)	Stannsoporfin	
		4.5 mg/kg N = 31 n (%)	3 mg/kg N = 30 n (%)
Neonates with any TEAE	22 (73.3%)	21 (67.6%)	28 (93.3)
Rash	7 (23.3%)	6 (19.4%)	11 (36.7%)
Rash neonatal	8 (26.7%)	4 (12.9%)	6 (20%)
Cardiac murmur	4 (13.3%)	4 (12.9%)	5 (16.7%)
Erythema	0 (0%)	6 (19.4%)	5 (16.7%)
Anemia	3 (10%)	2 (6.5%)	5 (16.7%)
Dry skin	3 (10%)	3 (9.7%)	2 (6.7%)
Hyperbilirubinemia	4 (13.3%)	3 (9.7%)	3 (10%)
Reticulocyte count increased	1 (3.3%)	3 (9.7%)	2 (6.7%)
Thrombocytopenia	0 (0%)	3 (9.7%)	3 (10%)
Umbilical hernia	0 (0%)	1 (3.2%)	4 (13.3%)
Congenital nevus	2 (6.7%)	2 (6.5%)	0 (0%)
Vomiting	1 (3.3%)	1 (3.2%)	2 (6.7%)
Aspartate aminotransferase increased	0 (0%)	1 (3.2%)	1 (3.3%)
Cough	0 (0%)	1 (3.2%)	1 (3.3%)
Gamma-glutamyl transferase increased	0 (0%)	0 (0%)	2 (6.7%)
Leukocytosis	0 (0%)	1 (3.2%)	1 (3.3%)
Medical observation	0 (0%)	0 (0%)	2 (6.7%)
Nasal congestion	0 (0%)	1 (3.2%)	1 (3.3%)
Scratch	2 (6.7%)	0 (0%)	0 (0%)
Sepsis	0 (0%)	2 (6.5%)	0 (0%)

TEAE = Treatment emergent adverse event
Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

Adverse Events of Special Interest (AESI) in Study 64,185-204:

Dermatologic AEs:

Forty-eight neonates experienced 77 dermatologic AEs. No dermatologic AE was considered an SAE and none of the neonates had mucous membrane involvement (Table 17). All of the AEs were mild (n=44, 91.7%) and moderate (n=4, 8.3%) in severity. Most did not require additional treatment (n=44, 91.7%). Common dermatologic AEs (≥2 neonates in any arm) included "rash", "rash neonatal", "erythema", and "dry skin". As previously noted (TEAEs in in Study 64,185-204), "erythema" was only observed in the stannsoporfin treatment arms. All the neonates who developed "erythema" did so by study Day 6. The majority (n=9, 81.8%) of erythema AEs occurred within the first 2 days with a median duration of 8 days. None of the neonates required additional treatment, and "erythema" resolved in all but one neonate at the end of the study follow-up (Day 30). The remainder of common dermatologic AEs occurred with similar frequencies across all treatment arms.

Table 17: Dermatologic Adverse Events in Study 64,185-204

	Placebo N = 30 n (%)	Stannsoporfin	
		4.5 mg/kg N = 31 n (%)	3 mg/kg N = 30 n (%)
Any Neonate with Dermatologic AE	14 (46.7%)	13 (41.9%)	20 (66.7%)
Rash[a]	7 (23.3%)	6 (19.4%)	11 (36.7%)
Rash neonatal[b]	8 (26.7%)	4 (12.9%)	5 (16.7%)
Erythema[c]	0 (0%)	6 (19.4%)	5 (16.7%)
Dry skin	3 (10%)	3 (9.7%)	2 (6.7%)
Cafe au lait spots	1 (3.3%)	0 (0%)	0 (0%)
Ecchymosis	0 (0%)	1 (3.2%)	0 (0%)
Melanosis	0 (0%)	0 (0%)	1 (3.3%)
Papule	0 (0%)	1 (3.2%)	0 (0%)
Skin disorder	1 (3.3%)	0 (0%)	0 (0%)
Skin hyperpigmentation	0 (0%)	0 (0%)	1 (3.3%)
Skin sensitization	0 (0%)	0 (0%)	1 (3.3%)

AE = Adverse event

[a] Included rash, rash macular, rash papular, rash maculo-papular, exfoliative rash, seborrheic dermatitis, seborrhea, dermatitis contact

[b] Included rash neonatal, erythema toxicum neonatorum, millia, acne infantile, transient neonatal pustular melanosis, candida nappy rash, dermatitis diaper

[c] Included erythema, photosensitivity reaction (red rash when exposed to light), rash erythematous, generalized erythema

Source: Reviewer generated based on data submitted by Applicant for Study 64,185-204

Laboratory Studies Study 64,185-204:

To evaluate potential effects of stannsoporfin on the bone marrow as indicated by the findings in the nonclinical toxicology studies, we evaluated mean change from baseline in hematologic parameters including hemoglobin (Hgb) and hematocrit (HCT), leukocytes (WBC) and platelets for each treatment arm. While the mean change from baseline shows a downward trend for Hgb and HCT, this effect was observed across all treatment arms including placebo and may be

related to ongoing evidence of hemolysis. Evaluation of platelets will be discussed separately below within the adverse events of special interest (AESI) section for thrombocytopenia. Serum chemistry values were also evaluated for abnormalities suggestive of acute kidney or liver injury. The mean change from baseline values did not suggest kidney or liver toxicity. Isolated elevations were observed but did not suggest any dose-related organ toxicity.

Thrombocytopenia:
In Study 64,285-204, thrombocytopenia was reported as an AE for 6 neonates in the stannsoporfin arms [n=3 (3 mg/kg); n=3 (4.5 mg/kg)] and none in the placebo. No posttreatment bleeding events were reported. The onset of the AE of thrombocytopenia was reported between study Days 1-2 and resolution was reported by study Day 5 through 19. One neonate in the 3 mg/kg arm experienced thrombocytopenia considered to be an SAE. This neonate had mild thrombocytopenia at screening (101 x $10^3/\mu L$) that decreased significantly to 30 x $10^3/\mu L$ on Study Day 3 and required a platelet transfusion. The event resolved on Day 5 and the platelet count was within normal limits at follow-up on Day 16.

In evaluating laboratory studies, 33 of the 91 neonates had serum platelet counts below the referenced normal range. Numerically more neonates from the stannsoporfin arms [n=16 (51.6%) in 4.5 mg/kg and n=12 (40.0%) in 3 mg/kg] reported platelet values below the normal reference range compared to the placebo [n=5 (16.7%)] with a possible dose-dependent trend. The majority of the thrombocytopenia events were noted at the 48 hours visit and resolved between Day 7 and Day 30 visits.

The Applicant explored possible mechanisms that could potentially explain a decrease in platelet count (decreased production, increased destruction, and sequestration), including the addition of mean platelet volume (MPV) in the safety assessments. Results of MPV measurements performed 7 days after drug administration in Study 64,185-204 were normal (low MPV may indicate decreased bone marrow production and high MPV may indicate increased destruction). The average life span of circulating platelets is 8 to 9 days, which suggests that the stannsoporfin-related effects are occurring much earlier than physiologic clearance. No plausible explanation for the observation of thrombocytopenia could be deduced at this time based on the clinical presentation.

7.3.2. Integrated Summary of Short-term Safety from Pooled Studies (64,185-013W, 64,185-202, 64,185-204)

The pooled short-term studies submitted by the Applicant to support short-term safety contained a heterogeneous population. It is important to note that Study 64,185-013W enrolled a healthy population which was different from Studies 64,185-202 and 64,185-204 which enrolled neonates with risk factors for severe hyperbilirubinemia and evidence of hemolysis. Therefore, the population of the pooled studies may not be fully representative of the targeted population for the proposed indication. In contrast, the gestational age of neonates in the pooled short-term follow-up studies are comparable to the population enrolled in the pivotal trial 64,185-204. The majority of neonates (82.1%, 82.5%, 89.6%, and 88.2% in placebo, 4.5 mg/kg, 3 mg/kg, and 1.5 mg/kg, respectively) were ≥38 weeks GA.

Deaths
The Applicant reported a total of 12 deaths across studies in the stannsoporfin development

program (Table 18) including 10 deaths that occurred in pre-term infants (i.e., GA <35 weeks) and 2 deaths that occurred from compassionate use and emergency INDs. All but one of the deaths occurring in pre-term infants were thought to be related to complications associated with prematurity. Two deaths were attributed to sudden infant death syndrome (SIDS)occurred under IND 64,185. One neonate in the 4.5 mg/kg stannsoporfin treatment arm died at age 4.5 months of SIDS in the long-term extension trial (Study 64,185-01C3W). The infant was found lying prone in the crib by his mother. An autopsy was performed and the cause of death was determined to be SIDS by exclusion. The death was judged by the investigator to be unrelated to study drug. The second SIDS death was a female infant who was screened but never randomized and never treated with stannsoporfin (Table 18). One additional SIDS death occurred at age 5 months in a 30 week 1/7 GA infant with Rh incompatibility who received stannsoporfin under an emergency IND. Although 10 of the deaths occurred in the stannsoporfin treated arms, none of the 12 neonatal deaths were considered by the Applicant to be treatment-related. However, it may be challenging to accurately attribute causality in a setting confounded by underlying co-morbidities of prematurity.

Table 18: Death in the Stannsoporfin Program (Under INDs 64,185 and 29,462)

Study No	Gender	Age at Death (days)	Description	Treatment Group
Acute Studies				
64,185-013W	F	20	SIDS (on autopsy)	Screened, not enrolled
29,462-04	M	15	Severe RDS, IVH	Stannsoporfin 1.5 mg/kg
29,462-04	F	3	RDS, pneumothorax, massive IVH	Stannsoporfin 3 mg/kg
29,462-04	F	5	Severe RDS, pneumothorax	Stannsoporfin 3 mg/kg
29,462-04	M	9	Severe RDS, pneumothorax, IVH	Stannsoporfin 4.5 mg/kg
29,462-04	F	16	RDS, IVH, seizures, multiple pneumothoraxes	Placebo
29,462-04	F	3	Pulmonary interstitial emphysema and pneumothorax	Tin protoporphyrin 0.75 mg/kg
Long-term Extension Studies				
64,185-01C3W	M	126	SIDS (on autopsy)	Stannsoporfin 4.5 mg/kg
29,462-04	F	252	Short bowel syndrome secondary to extensive NEC	Stannsoporfin 1.5 mg/kg
29,462-04	F	90	RDS, bilateral pneumothorax	Placebo
Compassionate and Emergency Use				
63,248	M	160	SIDS	Stannsoporfin 4.5 mg/kg
63,289	M	49	Expired in surgery due to necrotic and perforated bowel, respiratory distress	Stannsoporfin 4.5 mg/kg

M = Male; F = Female; IVH = Intraventricular hemorrhage; NEC = Necrotizing enterocolitis; RDS = Respiratory distress syndrome; SIDS = Sudden infant death syndrome
Source: Reviewer generated based on Module 2.7.4 Summary of Clinical Safety, Table 34 and NDA submission.

Serious Adverse Events (SAEs)

SAEs were reported for 27 subjects in the pooled AE dataset for the 3 short-term follow-up studies (Table 19). In general, the pooled SAE profile is similar to that of the pivotal Study 64,185-204. The most common SAEs (occurring in ≥2 subjects in any arm) were "hyperbilirubinemia", "anemia", and "medical observation" for possible sepsis, "sepsis" and "meningitis" (subjects described previously in Section 7.3.1). All other SAEs occurred in single subjects.

Table 19: Common SAEs (≥2 Subjects in Any Treatment Arm) in Pooled Short-term Studies (64,185-013W, 64,185-202, 64,185-204)

	Placebo N=134 n (%)	Stannsoporfin		
		4.5 mg/kg N=126 n (%)	3 mg/kg N=48 n (%)	1.5 mg/kg N=17 n (%)
Any Subject with SAE	9 (6.7%)	10 (7.9%)	6 (12.5%)	0 (0%)
Hyperbilirubinemia	6 (4.5%)	1 (0.8%)	1 (2.1%)	0 (0%)
Anemia	1 (0.7%)	0 (0%)	1 (2.1%)	0 (0%)
Medical observation	0 (0%)	0 (0%)	2 (4.2%)	0 (0%)
Meningitis	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)
Sepsis	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)

SAE = Serious adverse event
Source: Reviewer generated based on Applicant submission NDA 209904.

Treatment Emergent Adverse Events (TEAEs)

Similar to the results from the pivotal Study 64,185-204, TEAEs were more commonly reported in the 3 mg/kg arm (82.3%) compared to placebo (35.8%), or 4.5 mg/kg (41.3%), and 1.5 mg/kg treatment arms (47.1%). The most common TEAEs reported in ≥5% of neonates in any treatment group was "rash neonatal", which occurred at a higher frequency in the 3 mg/kg treatment group. The TEAEs of "erythema" and "thrombocytopenia" occurred more frequently in neonates that received 3 mg/kg and 4.5 mg/kg of stannsoporfin compared to placebo.

Table 20: Common TEAEs (≥ 5% Neonate in Any Treatment Group) in Pooled Short-term Studies (64,185-013W, 64,185-202, 64,185-204)

	Placebo N=134 n (%)	Stannsoporfin		
		4.5 mg/kg N=126 n (%)	3 mg/kg N=48 n (%)	1.5 mg/kg N=17 n (%)
Any Subject with TEAE	49 (35.8%)	52 (41.3%)	39 (81.3)	8 (47.1%)
Rash neonatal	12 (9%)	7 (5.6%)	11 (22.9%)	3 (17.6%)
Erythema	1 (0.7%)	11 (8.7%)	7 (14.6%)	0 (0%)
Rash	9 (6.7%)	7 (5.6%)	11 (22.9%)	1 (5.9%)
Cardiac murmur	4 (3%)	5 (4%)	5 (10.4%)	0 (0%)
Hyperbilirubinemia	8 (6%)	4 (3.2%)	3 (6.3%)	7 (41.2%)
Anemia	3 (2.2%)	4 (3.2%)	5 (10.4%)	0 (0%)
Thrombocytopenia	0 (0%)	4 (3.2%)	3 (6.3%)	0 (0%)
Umbilical hernia	0 (0%)	1 (0.8%)	5 (10.4%)	0 (0%)

TEAE = Treatment emergent adverse event
Source: Reviewer generated based on Applicant submission NDA 209904.

Severe TEAEs

Most TEAEs in all arms were mild, and the frequency of mild TEAEs was similar in the 4.5 mg/kg (31.0%) and placebo (31.3%) arms. There were five neonates with severe TEAEs

(incorrect dose administered [4.5mg/kg], hyperbilirubinemia [3 mg/kg], contusion from forceps delivery [1.5 mg/mg], hyperkalemia [3 mg/kg], and thrombocytopenia [3 mg/kg]) and all 5 neonates received stannsoporfin. Two of the cases are associated with dermatologic AEs and are described below in more detail. All cases of severe TEAEs were reported to be resolved.

64,185-013W Case 1: A 1-day old female neonate received an accidental overdose of study drug (30 mg [6.4 mg/kg] instead of 21 mg [4.5 mg/kg] for a total overdose of 9 mg). On the same day, after receiving 7.9 hours of PT, the neonate developed an erythematous rash (moderate in intensity; no blistering or peeling) in the shape of the bili blanket. The lights used were of incorrect wavelength (not otherwise specified) and the light source was not the one specified in the protocol. The rash did not require treatment and resolved in 5 days.

64,185-204 Case 2: A 1-day old male neonate in the 3 mg/kg stannsoporfin treatment arm developed hyperbilirubinemia which necessitated treatment with a double volume exchange transfusion (ET) based on TSB above the level for which an ET is recommended according to the AAP guidelines. The neonate received stannsoporfin at 13:09 on study Day 1 and ET was initiated on the same day at 23:55. The neonate's medical history included positive anti-C antibody, positive anti-D antibody, positive Direct Coombs test, and neonatal anemia. The hyperbilirubinemia resolved on Day 2 but the neonate remained in the hospital due to feeding dysfunction. Other AEs reported post ET included thrombocytopenia requiring platelet transfusion for an extreme decrease in platelet count to 18 x $10^3/\mu L$ (baseline was 112 x $10^3/\mu L$), hypocalcemia, and rash.

7.3.3. Adverse Events of Special Interest (AESI)

Dermatologic Adverse Events

Pooled Short-term Follow-up Studies (64,185-013W, 64,185-202, and 64,185-204)

Skin related manifestations comprised 32.7% of the TEAEs. Seventy-three neonates reported skin-related AEs. Neonates in the 3 mg/kg group had more dermatologic AEs (n=28 [58.3%]) compared to placebo (n=20 [14.9%]) and other treatment arms (22 [17.4%] in the 4.5 mg/kg and n=3 [17.6%] in the 1.5 mg/kg). The most common dermatologic-related AEs were "rash neonatal", "rash", and "erythema". However, similar to results seen in Study 64,185-204, the AE of "erythema" occurred more frequently in the 4.5 mg/kg and 3 mg/kg arms compared to placebo.

Exposure to Operating Room Lights:

A total of 16 neonates (9 neonates under IND 29,462 and 4 neonates under IND 64,185) required a surgical procedure during the follow-up period. The mean and median days to surgery was 530 and 614 days respectively. While no neonate reported a photosensitivity related adverse event, none of the surgical procedures occurred within 7 days of receiving the study medication. Therefore, an assessment for the risk of skin reactions that may occur from exposure to operating room (OR) lights in the immediate period following exposure to stannsoporfin cannot be performed.

Long-term (LT) AEs Related to Motor, Neurological, Auditory, or Psychological Conditions

The ISS database containing long-term follow-up studies 64,185-01C3W, 64,185-203, and

64,185-205 was reviewed for AEs of special interest. AEs suggestive of neurodevelopmental abnormalities including those of the ear and labyrinth, nervous system, psychiatric disorders, as well as selected investigations (neuropsychological test abnormal) and musculoskeletal and connective tissue disorders abnormalities (e.g., muscle spasticity) were extracted for comparison between treatment arms.

The safety population consisted of 197 pediatric patients across 3 studies. Thirty-nine pediatric patients reported neurological, psychological, or hearing related adverse events (Table 21). The majority of the AEs were mild (n=40, 58.8%) or moderate in severity (n=27, 39.7%). One pediatric patient from Study 64,185-01C3W (placebo) was identified as having behavioral problems of severe intensity. There were three pediatric patients with SAEs; two pediatric patients (64,185-203; placebo and 64,185-203; 4.5 mg/kg) had speech and language delay and the third pediatric patient (64,185-203; 3 mg/kg) had developmental delay.

Pediatric patients in the 4.5 mg/kg group were found to have the highest number of nervous system disorders (n=14; 19.2%) compared to pediatric patients in the placebo (n=9; 11.8%) and lower doses of stannsoporfin [n=0 in 3 mg/kg; n=1 (9.1%) in 1.5 mg/kg] suggesting a dose-dependent pattern. Speech disorder was the most frequently reported neurological disorder and accounted for 71.4% (10 out of 14 pediatric patients) of the nervous system disorders observed in the 4.5 mg/kg group. Data from the National Health Survey, 2012 suggest that approximately 5% of children ages 3-17 in the U.S. have some form of speech disorder.[52] While this rate is comparable to the rate of speech disorder reported in the placebo group [n=4 (5.3%)], the rates of speech disorder observed in the 4.5 mg/kg and 1.5 mg/kg stannsoporfin groups [n=10 out of 73 (13.7%) and n=1 out of 11 (9.1%), respectively] are higher than expected. The difference in the ages of the reported population limits direct comparability with the generalized population.

Deafness was also reported more frequently in the 4.5 mg/kg treatment arm and overall was more common in the stannsoporfin arms compared to placebo. The reported rate of 6.8% (n=5 out of 73) in the 4.5 mg/kg arm is significantly higher than the 2 to 3 out of every 1,000 children in the United States reported by the Center for Disease Control.[53]

Because speech and hearing deficits are associated with bilirubin neurotoxicity as well as neurodevelopmental disorders [54-59], the significance of AEs related to hearing and speech in the high dose stannsoporfin group is unknown but concerning. The small number of AEs observed limits the interpretability and generalizability of these results. Additional long-term data are needed to adequately evaluate these potential signals.

Table 21: Summary of Adverse Events Related to Motor, Neurological, or Psychological Conditions (Pooled Long-term Extension Studies 64,185-01C3W, 64,185-203, 64,185-205)

	Placebo N=76 n (%)	Stannsoporfin		
		4.5 mg/kg N=73 n (%)	3 mg/kg N=37 n (%)	1.5 mg/kg N=11 n (%)
Nervous System Disorder	**9 (11.8%)**	**14 (19.2%)**	**0 (0%)**	**1 (9.1%)**
Speech disorder[a]	4 (5.3%)	10 (13.7%)	0 (0%)	1 (9.1%)
Febrile convulsion	2 (2.6%)	1 (1.4%)	0 (0%)	0 (0%)
Language disorder	1 (1.3%)	1 (1.4%)	0 (0%)	0 (0%)
Tremor	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Dyspraxia	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Muscle spasticity	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Seizure	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Ear and labyrinth Disorder	**0 (0%)**	**5 (6.8%)**	**1 (2.7%)**	**0 (0%)**
Deafness[b]	0 (0%)	5 (6.8%)	1 (2.7%)	0 (0%)
Psychiatric Disorder	**9 (11.8%)**	**8 (11%)**	**1 (2.7%)**	**0 (0%)**
Abnormal behavior	2 (2.6%)	2 (2.7%)	0 (0%)	0 (0%)
Anxiety	1 (1.3%)	1 (1.4%)	0 (0%)	0 (0%)
Psychomotor hyperactivity	0 (0%)	1 (1.4%)	1 (2.7%)	0 (0%)
Aggression	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Agitation	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Attention deficit/hyperactivity disorder	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Depression	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Disturbance in attention	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Learning disability	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Post-traumatic stress disorder	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Impulsive behavior	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Sleep terror	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Decreased activity	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)
General Disorders	**1 (1.3%)**	**3 (4.1%)**	**1 (2.7%)**	**0 (0%)**
Developmental delay	1 (1.3%)	2 (2.7%)	1 (2.7%)	0 (0%)
Neuropsychological test abnormal	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Social Circumstances	**0 (0%)**	**2 (2.7%)**	**0 (0%)**	**0 (0%)**
Social problem	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Parent-child problem	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)
Congenital, familiar and genetic disorders	**0 (0%)**	**1 (1.4%)**	**0 (0%)**	**0 (0%)**
Macrocephaly	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)

Source: Reviewer generated based on Applicant submission NDA 209904.
[a] Include speech disorder, speech disorder developmental, speech sound disorder, dysarthria, dysphemia
[b] Include conductive deafness, deafness, deafness bilateral, hypoacusis

Long-term (LT) Neurodevelopmental Assessments

Long-term follow-up studies conducted under IND 064185 (64,185-01C3W, 64,185-203, and 64,185-205) were performed under current GCP and have planned assessments up to 6 years. LT follow-up studies conducted under IND 029426 do not meet current GCP standards and are not discussed further in this AC briefing document.

The objective of the long-term studies was to assess the potential neurodevelopmental effects of stannsoporfin for up to 6 years. In addition to general physical examinations that include neurological exams, neurodevelopmental status of pediatric patients who participated in the stannsoporfin clinical trials were assessed using a number of developmental, behavioral, and psychological instruments as described below. Table 22 provides a summary of the LT neurodevelopmental instruments used in the follow-up studies along with the number of patients with available data.

General cognitive development

Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (designed for children ages 2 years and 6 months to 7 years and 3 months) provides scores that represent intellectual functioning in verbal and performance cognitive domains, as well as a composite score that represents a child's general intellectual ability, and can be used in several ways (e.g., as an assessment of general intellectual functioning, as part of an assessment to identify intellectual giftedness, and to identify cognitive delay and learning difficulties). The WPPSI was assessed at 3, 4, and 6 years. The WPPSI-III (edition 3) was used for the Years 3 and 4 assessments in Study 64,185-203 and for the Year 3 assessment in Study 64, 185-01C3W, while the WPPSI-IV (edition 4) was used for the Year 6 assessment in Study 64,185-01C3W.

General cognitive and motor development

Mullen Scales of Early Learning (MSEL) (designed for children ages 0 to 68 months) is a measure of cognitive and motor functioning for infants and preschool children. The MSEL was assessed at 3 and 6 months and 1 and 2 years in Study 64,185-203, and at 1 and 2 years in Study 64,185-205.

Bayley Scales of Infant Development edition 2 (BSID) (designed for children ages 1 to 42 months) is used to describe the current developmental functioning of infants and measures development in 3 domains: psychomotor, behavioral, and mental. The BSID was used at 18 months in Study 64,185-01C3W.

Single cognitive domain – language screening

Receptive-Expressive Emergent Language Test (REEL) (designed for children ages 0 to 3 years) is used as a screening tool to identify young children who are acquiring language at a significantly delayed pace and determine if there is a significant discrepancy between receptive and expressive processes of emergent language. The REEL is a parent-completed questionnaire, rather than a test administered to a child, that tests a single cognitive domain of language. The REEL was used at 18 months in Study 64,185-01C3W.

Indices of general behavior problems

Conners' Early Childhood Rating scale (ECRS) (designed for children ages 2 to 6 years) is a multi-setting assessment with subscales examining inattention, hyperactivity, defiance, aggression, social functioning, atypical behaviors, anxiety, mood and physical symptoms. This tool provides information that may be useful to consider when determining whether a child is eligible for early intervention or special education. The Conners' ECRS was assessed at 2, 3, and 4 years in Studies 64,185-203 and 64,185-205.

Child Behavior Checklist (CBCL) is a screening tool (age range for use unknown but preschool and school versions available) that parents or other individuals who know the child well can complete to rate a child's problem behaviors and competencies. The CBCL was assessed at 18 months, 3 and 6 years in Study 64,185-01C3W.

Table 22: Overview of Neurodevelopment Assessments in Pooled LT Studies (64,185-01C3W, 64,185-203)

	Months				Years			
	3	6	12	18	2	3	4	6
Indices of General Cognitive Development								
WPPSI **No pivotal study data currently available**						Study 01C3W (N=63) Study 203 (N = 12)	Study 203 (N = 17)	Study 01C3W (N=56)
Mullen	Study 203 (N = 37)	Study 203 (N = 33)	Study 203 (N = 32) *Study 205* (N = 34)*		Study 203 (N = 31) *Study 205* (N = 7)*			
BSID **No pivotal study data currently available**				Study 01C3W (N=55)				
Indices of General Behavioral Problems								
Conners'					Study 203 (N = 20) *Study 205 (N = 5)**	Study 203 (N = 15) *Study 205* (N=TBD)*	Study 203 (N = 22) *Study 205* (N=TBD)*	
Child behavior checklist **No pivotal study data currently available**				Study 01C3W (N=55)		Study 01C3W (N=63)		Study 01C3W (N=57)

WPPSI = Wechsler Preschool and Primary Scale of Intelligence; BSID = Bayley Scales of Infant Development; TBD = to be determined (study incomplete); Study 203 = Study 64,185-203; Study 205 = Study 64,185=205
* Study 205 (long-term follow-up for the pivotal study) is ongoing and the N reflects the number of pediatric patients with available data at the time of NDA submission.
Shaded cells in grey indicate ongoing study with limited or no data currently available.
Source: Reviewer generated based on Applicant submission NDA 209904.

The mean scores from the LT neurodevelopmental assessments were compared between

pediatric patients exposed to stannsoporfin and placebo. The inclusion of assessments from pediatric patients who received placebo provides important context, given that severe hyperbilirubinemia itself can be associated with adverse neurodevelopmental outcomes. Based on the limited data submitted by the Applicant, most scores obtained across neurodevelopment assessments were comparable between stannsoporfin and placebo arms. In the Mullen Scales of Early Learning (MSEL), the mean percentile rank[1] of the stannsoporfin group was lower than the mean of the placebo groups across all six scales (fine motor, gross motor, visual perception, receptive language, expressive language, and early learning composite) tested at Month 3. This trend was not observed consistently in the Month 6, Year 1 and Year 2 scores. The significance of these score differences between stannsoporfin and placebo is unclear due to the limitations described in the following paragraph.

There were several limitations to the available data from the LT follow-up studies (64,185-01C3W, 64,185-203, and 64,185-205) conducted to assess potential neurodevelopment effects for up to 6 years. The overall sample size with available LT neurodevelopment assessments is small, thereby limiting the comparability and the overall interpretability of these results. While study 64185-01C3W has follow-up data for up to 6 years, this study enrolled neonates with a relatively low risk for severe hyperbilirubinemia when compared to the target population studied for the intended indication. The LT extension trial to the pivotal Study 64,185-204 (Study 64,185-205) is ongoing and 2-year neurodevelopment assessment results were only available for 7 pediatric patients. The Applicant also used different neurodevelopment assessments across different trials rather than the preferred approach of using a single instrument longitudinally. It is important to note that while there is some overlap in the areas assessed by each individual instrument (i.e., cognitive, motor, language etc.), the variabilities between instruments limit the ability of data from individual instruments to be pooled for interpretation.

In general, for medical product development, FDA recommends selection of neurodevelopmental tools that can assess an age-appropriate spectrum and minimize the need to use multiple tools. The submission and review of the long-term safety data for cognitive development should typically be at the time of completion of the long-term study so that there is sufficient time and sample size to observe any detectable impact to the child's development. Early engagement with the FDA (e.g., Pre-IND) and throughout drug development to discuss the clinical outcomes assessment endpoint strategy is recommended to ensure the selected instruments are fit-for-purpose for the context of use prior to initiation of pivotal studies.

8. ADDITIONAL POSTMARKETING ACTIONS

8.1. Risk Evaluation and Mitigation Strategies

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical Applicants to develop and comply with a Risk Evaluation and Mitigation

[1] Percentile rank indicates the percentage of children in an age group who performed at or below the score of the child being tested. A girl of 36 months, who obtains a percentile rank of 66 on Fine Motor, for example performed as well or better than 66% of her age-mates on that Scale.

Strategies (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or PPI, a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under NDAs and BLAs have a timetable for submission of assessments of the REMS. These assessments are prepared by the Applicant and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug. Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid an Applicant's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

8.1.1. Risk Management Considerations

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies minimize risks in several ways. They can communicate specific risk

information, as well as information regarding optimal product use. In addition, they can provide guidance and encourage, remind, or support adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate patients where the benefits outweigh the risks.

The Committee will be asked whether a REMS is needed to ensure the benefits of stannsoporfin outweigh the potential risk of neurodevelopmental toxicity. If the Committee believes that a REMS is needed, we seek advice on FDA's proposed REMS which provides the following safeguards: 1) to ensure that dispensation and administration of the product is only to certain healthcare settings that are able to care for neonates and treat hyperbilirubinemia in infants who may require an exchange transfusion; 2) to ensure proper patient selection for the drug, and 3) to ensure that legal guardians are informed of the risks.

8.1.2. Applicant Proposed Risk Minimization Plan

The Applicant did not submit a proposed REMS. They submitted a risk minimization plan that includes restricting distribution of stannsoporfin to hospitals for use in the inpatient setting only. The Applicant states that these hospital settings will provide continuous care for neonates by health care providers who will closely monitor them for any safety issues. The commercial communication efforts would include educational and promotional materials that focus on appropriate patient selection, and the use of a hospital based sales force to disseminate these materials and promote use in the approved population.

8.1.3. FDA Proposed REMS Strategy

FDA is proposing that the REMS have the following goals:
To mitigate the potential risk of neurodevelopmental toxicity in neonates with the use of stannsoporfin by:

1. Ensuring that stannsoporfin is dispensed and administered in health care 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.
2. Ensuring that health care providers are educated about the approved indication and limitations of use for stannsoporfin, and the potential risk of long-term neurodevelopmental problems associated with its use.
3. Ensuring that legal guardians are informed about the potential long-term neurodevelopmental risk of stannsoporfin and the need for obtaining neurodevelopmental screenings.
4. Enrolling all patients in a registry to ensure the safe use of stannsoporfin and further support long-term safety.

FDA proposes the following components for the REMS:

1. Elements to assure safe use including:
    - Dispensation only in certain health care settings
    - Documentation of safe-use conditions
    - Each patient must be enrolled in the REMS registry
2. An implementation system
3. A timetable for submission of assessments

Dispensation Only in Certain Health Care Settings

Restricting the distribution of stannsoporfin to certain health care settings (HCS) would ensure that these sites have health care providers who are able to care for neonates with hyperbilirubinemia, and can treat or refer infants who may require an exchange transfusion to HCS that can provide such treatment. In order to become a certified, the HCS must attest that they are able to provide care for neonates, and have health care providers with expertise in the treatment of hyperbilirubinemia in infants who may require an exchange transfusion. Additionally, HCS must implement policies and procedures to ensure that the appropriate patients receive stannsoporfin, prescribers receive training, legal guardian counseling is completed, and patients are enrolled into the REMS.

Documentation of Safe Use Condition

The proposed safe use conditions for use of stannsoporfin include that legal guardians are provided with a Patient Fact Sheet, and complete a form indicating that they have received and read the fact sheet as well as received counseling regarding the potential risk of long-term neurodevelopmental toxicity. Use of this enrollment form will also enroll the patient into the REMS program. This will ensure that legal guardians are educated about the potential risk and are able to make an informed decision regarding treatment with stannsoporfin, and will enroll the patient into the REMS registry to further support the long-term safety assessment of stannsoporfin.

Patient Registry

The Applicant must maintain a registry of all patients who receive stannsoporfin who could be followed long-term in a postmarketing prospective observational study (see Section 8.2).

Discussion of the Agency Proposed REMS Strategy

In considering risk management strategies for stannsoporfin, the benefit of treatment must be weighed carefully against the seriousness of the potential risks associated with use, including the risk of long-term neurotoxicity. As detailed prior, the proposed elements of the REMS would provide greater assurance that by restricting dispensation and use of the product to certified HCS, prescribers will be educated on proper patient selection for the drug, and that legal guardians will be informed of and counseled on the potential risk of neurotoxicity. Via these restrictions the risk may be mitigated by ensuring that healthcare settings treating patients with stannsoporfin have expertise in, and are able to provide exchange transfusion, that prescribers of the drug are educated on proper patient selection, and that legal guardians are informed of the potential long-term risks, and will receive messaging regarding the importance for follow up neurodevelopmental screenings for their children. In conclusion, FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a risk management approach for stannsoporfin if approved, the FDA considered that this is a drug that provides a new treatment for hyperbilirubinemia, however it may expose neonates to a risk of long term neurotoxicity, which will be discussed by this Committee. The Committee additionally will be asked if the proposed REMS is necessary to ensure the safe use of stannsoporfin, and if so, will it ensure the benefits of the drug outweigh the potential risk of neurodevelopmental toxicity.

8.2. Postmarketing Requirements/Commitments

The major safety concerns thus far based on FDA review are increased risk of dermatologic adverse events (e.g., erythema), thrombocytopenia, speech disorder, and hearing deficits. Based on recommendations from the 2012 Advisory Committee that long-term neurocognitive outcomes should be assessed at preschool age (e.g., at 3 years of age) and again during primary school (e.g., at 7 years of age), the potential long-term neurodevelopmental adverse outcomes related to stannsoporfin may not be sufficiently characterized to date. Additionally, comparison of long-term neurodevelopmental outcomes for AAP high risk vs. AAP medium risk neonates will be of interest. Requirement of a post-approval prospective observational study to assess long-term neurodevelopmental outcomes is under consideration. FDA will seek input from the Committee regarding the types of post-marketing activities that are warranted, if approved.

9. REFERENCES

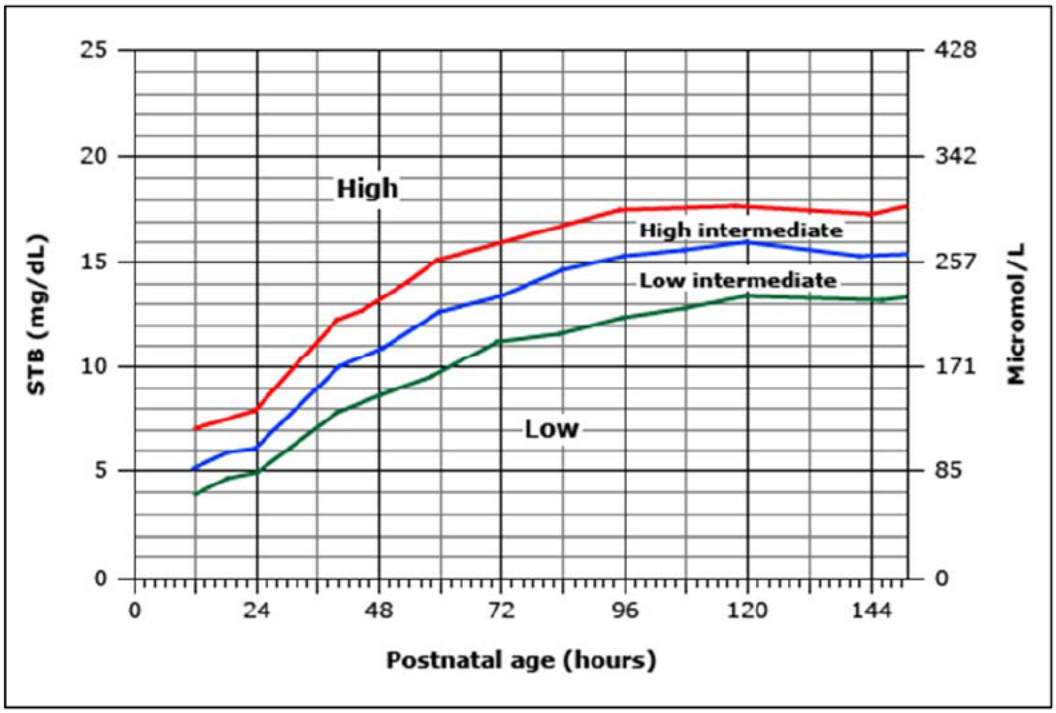
1. Bhutani VK, S.A., Lazzeroni LC, et al., *Initial Clinical Testing Evaluation and Risk Assessment for Universal Screening for Hyperbilirubinemia Screening Group. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy.* J Pediatr, 2013. **162**(3): p. 477-482.
2. Hintz, S.R., et al., *Serum bilirubin levels at 72 hours by selected characteristics in breastfed and formula-fed term infants delivered by cesarean section.* Acta Paediatr, 2001. **90**(7): p. 776-81.
3. Maisels, M.J., et al., *The Natural History of Jaundice in Predominantly Breastfed Infants.* Pediatrics, 2014. **134**(2): p. e340-e345.
4. Maisels, M.J. and E. Kring, *Transcutaneous bilirubin levels in the first 96 hours in a normal newborn population of > or = 35 weeks' gestation.* Pediatrics, 2006. **117**(4): p. 1169-73.
5. Smith, D. and T.R. Grover, *The Newborn Infant*, in *CURRENT Diagnosis & Treatment Pediatrics, 23e*, W.W. Hay, et al., Editors. 2016, McGraw-Hill Education: New York, NY.
6. Sgro, M., D. Campbell, and V. Shah, *Incidence and causes of severe neonatal hyperbilirubinemia in Canada.* CMAJ : Canadian Medical Association Journal, 2006. **175**(6): p. 587-590.
7. McGillivray, A., et al., *Prospective Surveillance of Extreme Neonatal Hyperbilirubinemia in Australia.* J Pediatr, 2016. **168**: p. 82-7.e3.
8. Bhutani, V.K., et al., *Extreme hyperbilirubinemia and rescue exchange transfusion in California from 2007 to 2012.* Journal Of Perinatology, 2016. **36**: p. 853.
9. Ebbesen, F., et al., *Extreme hyperbilirubinaemia in term and near-term infants in Denmark.* Acta Paediatr, 2005. **94**(1): p. 59-64.
10. Gotink, M.J., et al., *Severe neonatal hyperbilirubinemia in the Netherlands.* Neonatology, 2013. **104**(2): p. 137-42.
11. Johnson, L., et al., *Clinical report from the pilot USA Kernicterus Registry (1992 to 2004).* J Perinatol, 2009. **29 Suppl 1**: p. S25-45.
12. Kuzniewicz, M.W., et al., *Incidence, etiology, and outcomes of hazardous hyperbilirubinemia in newborns.* Pediatrics, 2014. **134**(3): p. 504-9.
13. Manning, D., et al., *Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland.* Arch Dis Child Fetal Neonatal Ed, 2007. **92**(5): p. F342-6.
14. McGillivray, A., et al., *Prospective Surveillance of Extreme Neonatal Hyperbilirubinemia in Australia.* The Journal of Pediatrics. **168**: p. 82-87.e3.
15. Sgro, M., D. Campbell, and V. Shah, *Incidence and causes of severe neonatal hyperbilirubinemia in Canada.* Cmaj, 2006. **175**(6): p. 587-90.
16. Zoubir, S., et al., *Incidence of severe hyperbilirubinaemia in Switzerland: a nationwide population-based prospective study.* Arch Dis Child Fetal Neonatal Ed, 2011. **96**(4): p. F310-1.
17. Bhutani, V.K., R.J. Wong, and D.K. Stevenson, *Hyperbilirubinemia in Preterm Neonates.* Clin Perinatol, 2016. **43**(2): p. 215-32.
18. Kuzniewicz, M.W., et al., *Incidence, Etiology, and Outcomes of Hazardous Hyperbilirubinemia in Newborns.* Pediatrics, 2014. **134**(3): p. 504-509.
19. Bhutani, V.K., et al., *Extreme hyperbilirubinemia and rescue exchange transfusion in California from 2007 to 2012.* J Perinatol, 2016. **36**(10): p. 853-7.
20. Maisels, M.J., et al., *Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications.* Pediatrics, 2009. **124**(4): p. 1193-8.
21. Gamaleldin, R., et al., *Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia.* Pediatrics, 2011. **128**(4): p. e925-31.

22. Oh, W., et al., *Influence of clinical status on the association between plasma total and unbound bilirubin and death or adverse neurodevelopmental outcomes in extremely low birth weight infants.* Acta Pædiatrica, 2010. **99**(5): p. 673-678.
23. Ahlfors, C.E., *Predicting bilirubin neurotoxicity in jaundiced newborns.* Current Opinion in Pediatrics, 2010. **22**(2): p. 129-133.
24. Newman , T.B., et al., *Outcomes among Newborns with Total Serum Bilirubin Levels of 25 mg per Deciliter or More.* New England Journal of Medicine, 2006. **354**(18): p. 1889-1900.
25. Ebbesen, F., J.V. Bjerre, and P.K. Vandborg, *Relation between serum bilirubin levels ≥450 µmol/L and bilirubin encephalopathy; a Danish population-based study.* Acta Paediatrica, 2012. **101**(4): p. 384-389.
26. Munchowski, K., *Evaluatio and Tretment of Neonatal Hyperbilirubinemia.* American Family Physicians, 2014. **89**(11): p. 873-8.
27. Finn, E., H. Thor Willy Ruud, and M.J. Maisels, *Update on Phototherapy in Jaundiced Neonates.* Current Pediatric Reviews, 2017. **13**(3): p. 176-180.
28. Sgro, M., et al., *Acute neurological findings in a national cohort of neonates with severe neonatal hyperbilirubinemia.* J Perinatol, 2011. **31**(6): p. 392-396.
29. Manning, D., et al., *Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland.* Archives of Disease in Childhood - Fetal and Neonatal Edition, 2007. **92**(5): p. F342-F346.
30. Brooks, J.C., et al., *Evidence Suggests There Was Not a "Resurgence" of Kernicterus in the 1990s.* Pediatrics, 2011. **127**(4): p. 672-679.
31. Sgro, M., et al., *Kernicterus - January 2007 to December 2009.*, in *Canadian Paediatric Surveillace Program 2009 Results.*
32. Wu, Y.W., et al., *Risk for cerebral palsy in infants with total serum bilirubin levels at or above the exchange transfusion threshold: a population-based study.* JAMA Pediatr, 2015. **169**(3): p. 239-46.
33. Jackson, J.C., *Adverse events associated with exchange transfusion in healthy and ill newborns.* Pediatrics, 1997. **99**(5): p. E7.
34. Hakan, N., et al., *Exchange transfusion for neonatal hyperbilirubinemia: an 8-year single center experience at a tertiary neonatal intensive care unit in Turkey.* J Matern Fetal Neonatal Med, 2015. **28**(13): p. 1537-41.
35. Patra, K., et al., *Adverse events associated with neonatal exchange transfusion in the 1990s.* J Pediatr, 2004. **144**(5): p. 626-31.
36. Zwiers, C., et al., *Immunoglobulin for alloimmune hemolytic disease in neonates.* Cochrane Database of Systematic Reviews, 2018(3).
37. Lai, N.M., et al., *Fluid supplementation for neonatal unconjugated hyperbilirubinaemia.* Cochrane Database Syst Rev, 2017. **8**: p. Cd011891.
38. Lamola, A.A., et al., *Neonatal bilirubin binding capacity discerns risk of neurological dysfunction.* Pediatr Res, 2015. **77**(2): p. 334-9.
39. Oh, W., et al., *Influence of clinical status on the association between plasma total and unbound bilirubin and death or adverse neurodevelopmental outcomes in extremely low birth weight infants.* Acta Paediatrica, 2010. **99**(5): p. 673-678.
40. American Academy of Pediatrics Subcommittee on, H., *Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.* Pediatrics, 2004. **114**(1): p. 297-316.
41. Dash, N., et al., *Pre exchange Albumin Administration in Neonates with Hyperbilirubinemia: A Randomized Controlled Trial.* Indian Pediatr, 2015. **52**(9): p. 763-7.
42. Hosono, S., et al., *Effects of albumin infusion therapy on total and unbound bilirubin values in term infants with intensive phototherapy.* Pediatr Int, 2001. **43**(1): p. 8-11.

43. Hosono, S., et al., *Follow-up study of auditory brainstem responses in infants with high unbound bilirubin levels treated with albumin infusion therapy.* Pediatr Int, 2002. **44**(5): p. 488-92.
44. Mitra, S., et al., *Pre-exchange 5% albumin infusion in low birth weight neonates with intensive phototherapy failure--a randomized controlled trial.* J Trop Pediatr, 2011. **57**(3): p. 217-21.
45. Shahian, M. and M.A. Moslehi, *Effect of albumin administration prior to exchange transfusion in term neonates with hyperbilirubinemia--a randomized controlled trial.* Indian Pediatr, 2010. **47**(3): p. 241-4.
46. Vodret, S., et al., *Albumin administration prevents neurological damage and death in a mouse model of severe neonatal hyperbilirubinemia.* Sci Rep, 2015. **5**: p. 16203.
47. Koch, M. and H.U. Schnitzler, *The acoustic startle response in rats--circuits mediating evocation, inhibition and potentiation.* Behav Brain Res, 1997. **89**(1-2): p. 35-49.
48. Hyperbilirubinemia, A.A.o.P.S.-c.o., *Management of hyperbilirubinemia in the new-born infant 35 or more weeks of gestation.* Pediatrics, 2004. **114**: p. 297-316.
49. Wennberg, R.P., et al., *Toward understanding kernicterus: a challenge to improve the management of jaundiced newborns.* Pediatrics, 2006. **117**(2): p. 474-85.
50. Ahlfors, C.E., *Predicting bilirubin neurotoxicity in jaundiced newborns.* Curr Opin Pediatr, 2010. **22**(2): p. 129-33.
51. Ahlfors, C.E., *Bilirubin-albumin binding and free bilirubin.* J Perinatol, 2001. **21 Suppl 1**: p. S40-2; discussion S59-62.
52. Lindsey, I., A. Vahratian, and H. Hoffman, *Communication Disorders and Use of Intervention Services Among Children Aged 3-17 Year: United States, 2012*, in *NCHS Data Brief*. 2015, CDC National Center for Health Statistics.
53. *Identifying infants with hearing loss - United States, 1999-2007.* MMWR Morb Mortal Wkly Rep, 2010. **59**(8): p. 220-3.
54. Oh, W., et al., *Association Between Peak Serum Bilirubin and Neurodevelopmental Outcomes in Extremely Low Birth Weight Infants.* Pediatrics, 2003. **112**(4): p. 773-779.
55. Wickremasinghe, A.C., et al., *Risk of Sensorineural Hearing Loss and Bilirubin Exchange Transfusion Thresholds.* Pediatrics, 2015. **136**(3): p. 505-512.
56. Saluja, S., et al., *Auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice.* Int J Pediatr Otorhinolaryngol, 2010. **74**(11): p. 1292-7.
57. O'Hare, A. and L. Bremner, *Management of developmental speech and language disorders: Part 1.* Archives of Disease in Childhood, 2016. **101**(3): p. 272-277.
58. Mulrine, C. and B. Kollia, *Speech, language, hearing delays: time for early intervention?* J Fam Pract, 2015. **64**(3): p. E1-9.
59. Mackrides, P.S. and S.J. Ryherd, *Screening for developmental delay.* Am Fam Physician, 2011. **84**(5): p. 544-9.

10.APPENDIX

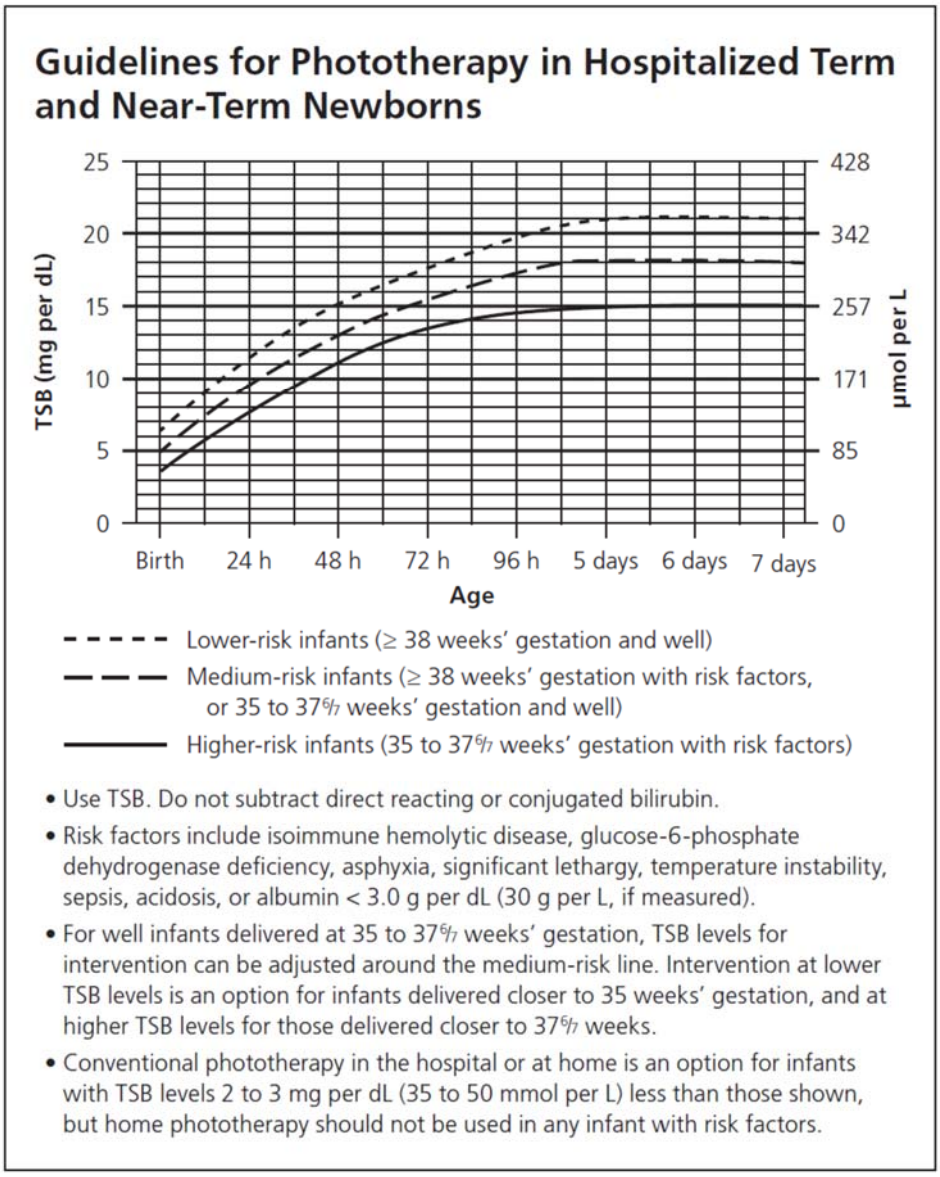
10.1. Appendix 1: Nomogram for Risk of Hyperbilirubinemia Based on Hour-Specific Serum or Plasma Total Bilirubin (TSB) Concentration in Infants ⩾35 Weeks' Gestation[1]



The red, blue, and green lines denote the 95th, 75th, and 40th percentiles, respectively. Risk zones are designated according to percentile: high (TSB ≥95th), high intermediate (95th >TSB ≥75th), low intermediate (75th >TSB ≥40th), and low (TSB <40th). Infants with values in the high risk zone are at increased risk for the development of clinically significant hyperbilirubinemia requiring intervention.

[1] Adapted from the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004;114(4):1138]. Pediatrics. 2004;114(1):297-316.

10.2. Appendix 2. Guidelines for Phototherapy in Hospitalized Infants Delivered at ⩾35 Weeks' Gestation (TSB = Total Serum Bilirubin)[1]



[1] American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004;114(4):1138]. Pediatrics. 2004;114(1):297-316.

10.3. Appendix 3: Literature Review of Phototherapy Treatment Exposure on Neurodevelopmental Complications: 11 Publications that Met the Search Criteria

A summary of study findings and the corresponding barriers to interpretation are discussed below. The term 'healthy' refers to neonates that did not have any evidence of jaundice or hyperbilirubinemia and therefore did not receive phototherapy treatment.

Four studies investigated auditory related outcomes. Salehi et al. (2016)[1] conducted a cross-sectional study that aimed to evaluate the Auditory Brainstem Response (ABR) in hyperbilirubinemia neonates treated with phototherapy compared to the ABR in a group of healthy neonates. ABR is a reliable and objective electrophysiological method for evaluating ascending auditory systems and change in latency values can be indicative of disturbance in the auditory brainstem function. Significantly prolonged mean ABR absolute latency values were observed across the neonates with hyperbilirubinemia treated with phototherapy (n=42) compared to the healthy group (n=40). However, since the aim of the study was not to assess phototherapy as an independent risk factor for changes in ABR latency values and the control group included neonates with no evidence of hyperbilirubinemia, confounding by hyperbilirubinemia cannot be ruled out. Of the three additional studies (Coenraad (2011),[2] Duman (2004),[3] Polat (2014)[4]) that investigated auditory outcomes, none identified phototherapy treatment exposure as a potential independent risk factor for these outcomes. Two (Coenraad 2011, Duman 2004) of these studies evaluated transient evoked otoacoustic emissions (TEOAE) or brainstem auditory evoked potentials (BAEP) measurements at unspecified timepoints relative to the time of phototherapy treatment exposure. Also, the study by Coenraad et al. included some children with a gestational age <35 weeks. In the third study by Polat et al., 57 newborns, undergoing phototherapy for hyperbilirubinemia without any other known risk factors, were administered the TEOAE test prior to and following phototherapy treatment. No differences were observed in pre- and post-phototherapy TEOAE amplitudes or reproducibility ratios within the phototherapy treatment group or compared to the same measurements in a healthy group (n=53). Further studies with larger sample sizes are needed to validate these findings.

Only one study investigated ocular findings. Kara et al. (2017)[5] aimed to evaluate if phototherapy received in the neonatal period was associated with phototherapy-related permanent ocular damage in children at 3 to 5 years of age; the study group (n=57) underwent phototherapy for at least 24 hours; the comparison group (n=43) did not receive phototherapy. All children were orthophoric (normal balance of bilateral ocular muscles), had normal eye

[1] Salehi, N., Bagheri, F., & Ramezani Farkhani, H. (2016). Effects of Hyperbilirubinemia on Auditory Brainstem Response of Neonates Treated with Phototherapy. Iran J Otorhinolaryngol, 28(84), 23-29.

[2] Coenraad, S., Goedegebure, A., van Goudoever, J. B., & Hoeve, L. J. (2011). Risk factors for auditory neuropathy spectrum disorder in NICU infants compared to normal-hearing NICU controls. Laryngoscope, 121(4), 852-855. doi:10.1002/lary.21430

[3] Duman, N., Ozkan, H., Serbetcioglu, B., Ogun, B., Kumral, A., & Avci, M. (2004). Long-term follow-up of otherwise healthy term infants with marked hyperbilirubinaemia: should the limits of exchange transfusion be changed in Turkey? Acta Paediatr, 93(3), 361-367.

[4] Polat, C., Aydin, M., Sakallioglu, O., Akyigit, A., Unsal, S., Soylu, E., & Keles, E. (2014). Evaluation of the effects of phototherapy on cochlear function in newborns. Int J Pediatr Otorhinolaryngol, 78(12), 2068-2071. doi:10.1016/j.ijporl.2014.09.006

[5] Kara, S., Yalniz-Akkaya, Z., Yeniaras, A., Ornek, F., & Bilge, Y. D. (2017). Ocular findings on follow-up in children who received phototherapy for neonatal jaundice. J Chin Med Assoc, 80(11), 729-732. doi:10.1016/j.jcma.2017.08.003

movement, and normal prism tests. Significant differences were observed between the phototherapy treated and the non-phototherapy treated groups for convergence near point and right and left eye cycloplegic spherical equivalents; these findings did not differentially relate to a need for eyeglasses and therefore, were not clinical significant in terms of vision impairment.

A retrospective cohort study by Wu et al. (2016)[6] aimed to quantify the risk of autism spectrum disorder (ASD) associated with elevated total serum bilirubin levels (TSB) and with phototherapy. After adjustment for autism related risk factors, including TSB, phototherapy was not associated with ASD (HR=1.10, 95% CI=0.98-1.24). The study included a large sample size; 34,452 (8% of 457,855) neonates received phototherapy treatment. Despite the large sample size, several limitations may have impacted the null finding. First, the study used physician diagnoses of ASD, in place of standardized diagnostic assessment which may have led to misclassification of ASD status. Second, the adoption of universal bilirubin screening led to a decrease in hyperbilirubinemia frequency and an increase in phototherapy treatment as the study progressed. Third, the presence of missing data was not accounted for. Although the proportion of missing data is relatively minimal, it is not clear whether data was missing differentially across important categories, including TSB and receipt of phototherapy treatment, and if so, how it may have impacted the observed results. Further, it is unclear how these issues combined would impact the observed HR.

Chen et al. (2014)[7] conducted a prospective cohort study of 2,016 newborns with neonatal jaundice (of which 987 (49%) received phototherapy treatment), and 8,064 healthy newborns to examine the association between neonatal phototherapy and an array of neurocognitive complications. After adjustment for sex, level of urbanization (level 1 to level 4; level 1: most urbanized region; level 4: least urbanized region) and comorbid perinatal conditions, phototherapy was not statistically significantly associated with the risk of developing ASD, ADHD, any developmental delay, speech, language, or coordination disorder, and intelligence disability. However, the authors reported statistically significant increased risks between neonatal jaundice and ASD, and any developmental delay, speech, or language disorder. As no information was provided on TSB levels or criteria to receive phototherapy treatment, it is difficult to assess the underlying risk profiles between the entire population and the sub-population. Therefore, it is difficult to reconcile the inconsistent findings.

In the (Arbol 1998,[8] Lozada 2015[9]) remaining two studies investigating behavioral related outcomes, neonates with jaundice or hyperbilirubinemia were included in the comparison group that did not receive phototherapy. These studies reported positive associations with the

[6] Wu, Y. W., Kuzniewicz, M. W., Croen, L., Walsh, E. M., McCulloch, C. E., & Newman, T. B. (2016). Risk of Autism Associated With Hyperbilirubinemia and Phototherapy. Pediatrics, 138(4). doi:10.1542/peds.2016-1813

[7] Chen, M.-H., Su, T.-P., Chen, Y.-S., Hsu, J.-W., Huang, K.-L., Chang, W.-H., . . . Bai, Y.-M. (2014). Is neonatal jaundice associated with autism spectrum disorder, attention deficit hyperactivity disorder, and other psychological development? A nationwide prospective study. Research in Autism Spectrum Disorders, 8(6), 625-632. doi:https://doi.org/10.1016/j rasd.2014.03.006

[8] Abrol, P., & Sankarasubramanian, R. (1998). Effect of phototherapy on behaviour of jaundiced neonates. Indian J Pediatr, 65(4), 603-607.

[9] Lozada, L. E., Nylund, C. M., Gorman, G. H., Hisle-Gorman, E., Erdie-Lalena, C. R., & Kuehn, D. (2015). Association of Autism Spectrum Disorders With Neonatal Hyperbilirubinemia. Glob Pediatr Health, 2, 2333794x15596518. doi:10.1177/2333794x15596518

phototherapy treated group and the outcomes, but neither adjusted for TSB levels to assess an independent effect of phototherapy.

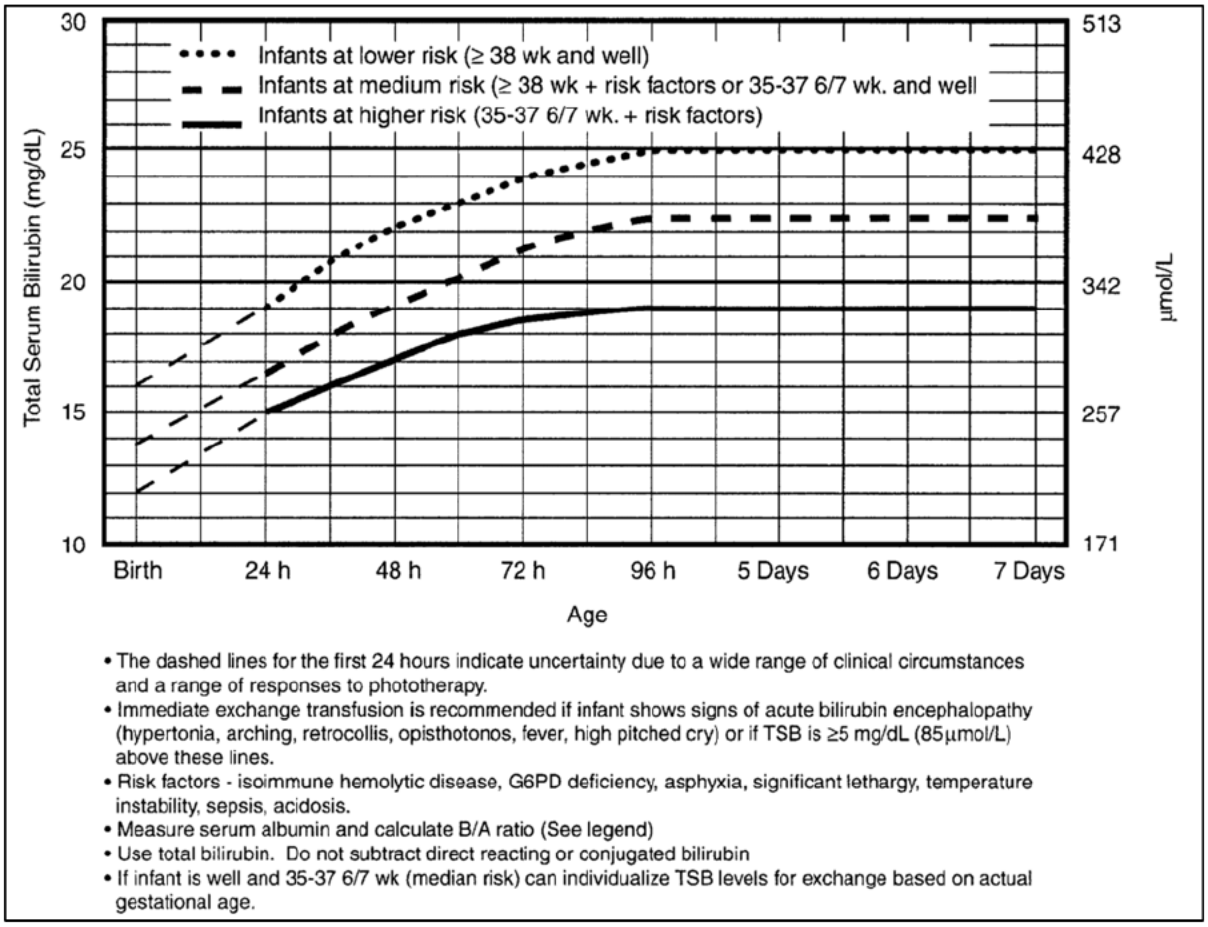
A study by Maimburg et al. (2016)[10] evaluated newborn exposure to phototherapy treatment and the subsequent development of epilepsy. Specifically, the study reported that neonates treated with phototherapy for hyperbilirubinemia (n=3,162) had a higher risk of developing epilepsy in early childhood (adjusted HR=1.66, 95% CI=1.23-2.24) compared to the neonates not exposed to phototherapy (n=67,068). However, the comparison group was healthy controls without a similar risk profile for epilepsy. Therefore, it's difficult to disentangle whether the observed effects were due to exposure to phototherapy treatment or the underlying risk posed by the disease.

A case-control by Fallah et al. (2013)[11] was conducted to study developmental status of 18-month old children with neonatal indirect non-hemolytic hyperbilirubinemia treated with phototherapy (n=56) compared to healthy controls (n=56). Neurodevelopmental status was evaluated using the Persian version of the Ages and Stages Questionnaires (ASQ). The developmental domains assessed included: gross motor, fine motor, problem solving, personal and social skills, and communication. While 14.3% of children with moderate neonatal hyperbilirubinemia had delay in developmental domains compared to 7.1% in the control group, the mean scores in all developmental domains did not differ significantly between the case and control groups. Several limitations should be noted. The authors state that some cases of hyperbilirubinemia may have gone unrecognized and did not lead to investigation or admission into the study. The ASQ is one of the developmental screening tests and not a diagnostic test and is unable to detect milder delay. Further, some disorders, such as ADD, ASD and mild mental retardation, are typically diagnosed after 2 years of age; thus, longer follow-up observation is required.

[10] Maimburg, R. D., Olsen, J., & Sun, Y. (2016). Neonatal hyperbilirubinemia and the risk of febrile seizures and childhood epilepsy. Epilepsy Res, 124, 67-72. doi:10.1016/j.eplepsyres.2016.05.004

[11] Fallah, R., Karimi, M., & Bafrooee, H. B. (2013). Does moderate unconjugated hyperbilirubinemia in healthy term neonates play a role on their neurodevelopmental status at the age of 18 months? J Med Liban, 61(3), 170-174.

10.4. Appendix 4. Guidelines for Exchange in Hospitalized Infants Delivered at ⩾ 35 Weeks' Gestation (TSB = Total Serum Bilirubin)[1]



[1] American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004;114(4):1138]. Pediatrics. 2004;114(1):297-316.

10.5. Appendix 5: Summary of Advisory Committee Meeting in 2003 and 2012

	Questions to the Advisory Committee	Committee Recommendations
Pediatric Subcommittee of Anti-Infective Drugs Advisory Committee Meeting – Open Session[a] June 11, 2003	1. Discuss the current controversies in the diagnosis and management of hyperbilirubinemia. 2. In the context of current medical practice, including phototherapy, should drugs be developed for an earlier intervention to prevent hyperbilirubinemia in newborn infants? 3. Assuming that hyperbilirubinemia only requires therapeutic intervention with phototherapy approximately 3 to 5 percent of the time, what safety information would you require from a sponsor for a new molecular entity before it could be introduced into the newborn population? 4. In today's healthcare setting, does the benefit of drug therapy to prevent hyperbilirubinemia in the newborn population as a whole outweigh the risk to individual newborns, the majority of whom require no intervention?	• Committee supported conducting studies to provide an alternative therapy to prevent kernicterus. • Committee expressed support for development of stannsoporfin in a specific target population. • Concern was raised regarding short-term toxicity (phototoxicity, potential for cardiac arrhythmia) and the absence of long-term safety data. • Phototherapy should remain the treatment of choice for neonates with low risk of developing severe hyperbilirubinemia. • Committee members did not favor prevention of hyperbilirubinemia as the initial focus of clinical development.
Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting – Open Session[b] March 13, 2012	1. What is the appropriate target neonatal population for new drug products that inhibit bilirubin production? What clinical and diagnostic criteria can be used to identify this target population? 2. Assuming high risk neonates are identified using currently accepted clinical criteria (e.g., ABO blood group incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, total serum bilirubin (TSB) in high-risk zone) and are evaluated using currently defined American Academy of Pediatrics (AAP) hyperbilirubinemia treatment guidelines (based on age-specific TSB level), is there currently enough information to support development of new drug products that inhibit bilirubin production for the following indications (vote yes or no for each indication): • As adjunctive treatment of significant hyperbilirubinemia (i.e., TSB > 95th percentile for age in hours) with phototherapy • As treatment of significant hyperbilirubinemia instead of phototherapy. • For the prevention of significant hyperbilirubinemia (i.e., used prior to the need for phototherapy). 3. What specific trial designs should be used to evaluate the effectiveness of new drug products that inhibit bilirubin production in neonates with significant hyperbilirubinemia? 4. What specific trial designs should be used to evaluate the short- and long-term safety of new drug products that inhibit bilirubin production (e.g., effects on neurocognitive development)?	• Drug development should evaluate stannsoporfin as an adjunct to phototherapy in a high-risk population. • Recommended long-term safety of stannsoporfin should be assessed prior to its acceptability as a treatment to prevent the need for phototherapy. • Long-term neurocognitive outcomes including neurocognitive testing at preschool age (e.g., at 3 years of age) and again during primary school (e.g., at 7 years of age) should be assessed prior to use of stannsoporfin in a prevention trial.

[a] CDER 2003 Meeting Documents. Available at: https://www fda.gov/ohrms/dockets/ac/cder03 html#Anti-Infective

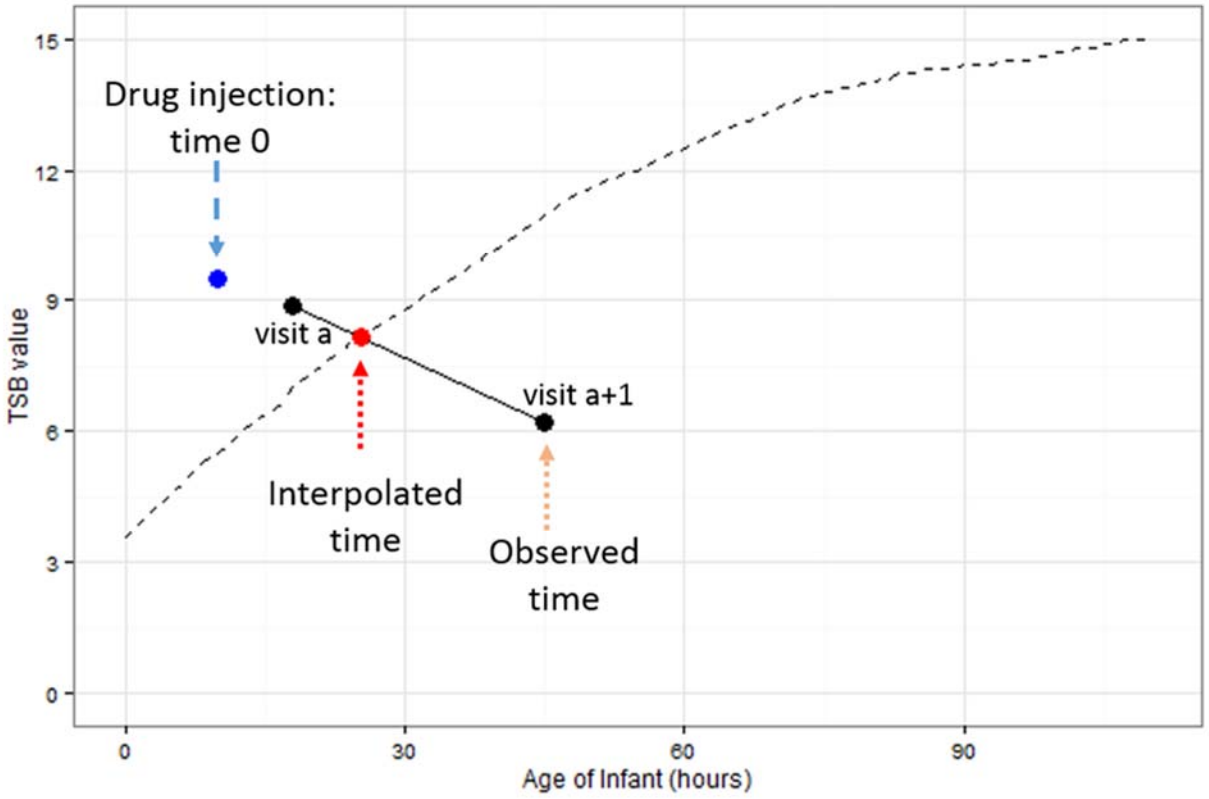
[b] 2012 Meeting Materials, Gastrointestinal Drugs Advisory Committee https://wayback.archive-it.org/7993/20170403223936/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm291609 htm

10.6. Appendix 6: Overview of the Clinical Development Program for Stannsoporfin

Study No.		Study Population	Adults/Children Exposed N	Neonates Exposed N
Study 29,462	01	Healthy volunteers	23	
	02	Porphyria	3	
	03	Crigler-Najjar	6 (2 adults; 4 children)	
	04	Phase 1: GA <37 weeks Phases 2-6: GA ≥30 to <36 weeks		261
	05	Phase 1: Healthy male, GA ≥37 weeks Phase 2: Healthy, GA ≥35 to <38 weeks		48
	06	G6PD, GA >30 weeks		205
	07	Part A: Direct Coombs Test (DCT) + Part B: elevated TSB regardless of DCT		35
	08	GA ≥30 to ≤36 weeks		30
	09	Healthy, GA ≥38 to ≤41 weeks		80
Study 64,185	01-3W[a]	Healthy, GA ≥35 to ≤38 weeks		87
	01C3W			
	02-1W	Healthy volunteers	12	
	06-2ISNHP	GA ≥35 GA at risk of ET		37
	06LT			
	202[b]	GA ≥35 to ≤43 weeks with TSB within 1-2 mg/dL of AAP age-specific threshold for PT		43
	203			
	204	GA ≥35 to ≤43 weeks with indicators of hemolysis meeting AAP age-specific cutoff for PT		61
	205[c]			
	99A	Compassionate Use		18
Total			44 (40 adults and 4 children)	905

[a] Early termination due to Clinical Hold for inappropriate study population.
[b] Early termination due to Division's concern of study design.
[c] Study on-going.

10.7. Appendix 7: Example of Linear Interpolation Method



Note: This example was not based on real data.