GASTROINTESTINAL DRUGS ADVISORY COMMITTEE
PEDIATRIC ADVISORY COMMITTEE
FDA Introductory Remarks

NDA 209904
stannsoporfin

Stephanie O. Omokaro, MD

Lead Medical Officer

Division of Gastroenterology and Inborn Errors Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research, FDA

Overview

- Objectives and scope

- Background

- Agenda

- Topics for discussion

- Voting questions

Focus of AC Meeting

- FDA is seeking advisory committee input on:
  - Adequacy of single study submitted to establish substantial evidence of effectiveness
  - Clinical meaning of total serum bilirubin (TSB) reduction
  - Dose selection
  - Adequacy of short-term, and long-term safety database
  - Need for postmarketing activities, if approved

Severe Neonatal Hyperbilirubinemia

- Neonatal hyperbilirubinemia (elevated serum bilirubin concentration)
  - Occurs in up to 84% of newborns, frequently self-limited
  - Neonates have a higher rate of bilirubin production and limited ability to conjugate and excrete

- Severe or extreme hyperbilirubinemia **(TSB≥25-30 mg/dL)** affects 7 to 40 newborns per 100,000 live births
  - Predisposing risk factors include hemolytic disease, jaundice in the first 24 hours, premature birth, and elevated pre-discharge bilirubin levels
  - Can lead to bilirubin-induced neurologic dysfunction which can result in significant long-term neurologic morbidity (kernicterus) and mortality

- Primary goal of treatment is to prevent bilirubin neurotoxicity
  - Early recognition and phototherapy treatment are mainstays of clinical management

Challenges in Clinical Management

- Although rare with current clinical management, kernicterus can still occur
    - Thus, an unmet medical need exists for additional therapies in these infants at risk

- No specific single TSB threshold coincides with onset of acute bilirubin encephalopathy or the chronic form (kernicterus)

- Risk factors such as premature birth, postnatal age, and comorbidities (e.g., hemolysis, infection) contribute to the risk of developing complications from severe hyperbilirubinemia

Product Overview

Product:	New Molecular Entity stannsoporfin (tin mesoporphyrin)
Mechanism of Action	Heme-oxygenase inhibitor; inhibits bilirubin production
Applicant Proposed Indication:	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
Proposed Dose:	Single Intramuscular Injection: 4.5 mg/kg of body weight

Regulatory History

FDA

| 1986 - 2002 | 2003 - 2005 | 2005 - 2012 | 2012-2018 |

1986 - 2002
- IND 029462 (Non-GCP)
- IND 064185 (GCP)

2003 - 2005
- Phase 3 protocol submitted
- Clinical hold (2/2003)
- AC Meeting #1 (6/2003): Drug development recommended for treatment but not prevention
- Hold removed (10/2004)
- Rights acquired by InfaCare

2005 - 2012
- Phase 2 protocol 64,185-202
- Partial clinical hold (8/2011)
- AC Meeting #2 (3/2013): appropriate target population and need for long-term follow-up data prior to use; voted as adjunct to PT
- Submitted protocol - Study 64,185–204
- Partial hold removed 9/2012

2012-2018
- FTDR granted* (12/2016)
- Complete NDA submitted (12/2017)
- InfaCare acquired by Mallinckrodt Public Limited Company (9/2017)
- Granted Priority Review (2/2018)

FDA granted fast track designation for the indication of adjunct therapy to phototherapy (PT) in neonates of ≥35 weeks gestational age with laboratory evidence of hemolysis and hyperbilirubinemia meeting the American Academy of Pediatrics (AAP) criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia

Regulatory Considerations

- Generally, 2 or more adequate and well-controlled trials, each convincing on its own, are required to establish effectiveness

- A single highly persuasive positive trial combined with confirmatory evidence that substantiates efficacy can support approval if (each can contribute):
  - Data from a large multicenter study, internal consistency across study subsets, evidence of an effect on multiple endpoints evaluating different events, statistically very persuasive findings

- An adequate number and duration of patient exposures is needed to characterize the safety risks of a drug
  - Less safety data may be required at the time of approval of a drug if the drug provides an important clinical benefit to address an unmet need

Regulatory Considerations (2)

FDA

- A risk management plan that uses risk minimization strategies beyond the professional labeling may be needed for certain drug products to ensure the benefits outweigh the risks

- Post-approval studies or clinical trials may also be required to assess serious risks related to the drug

Clinical Pharmacology Overview

- The metabolism of stannsoporfin is not well characterized in humans

- Terminal half-life ($t_{1/2}$) ~ 10-11 hours for 3 and 4.5 mg/kg doses in neonates

- Shallow inverse relationship between increasing systemic exposure and dose-dependent attenuation of TSB rise

Efficacy Overview

- One pivotal study (Study 64,185-204) of 91 neonates submitted to establish the safety and efficacy of stannsoporfin

- Primary endpoint of percent change from baseline in total serum bilirubin (TSB) at 48 hours post-treatment was statistically significant for both 3 and 4.5 mg/kg doses compared to placebo

- One secondary endpoint, (time [in hours] at which TSB crossed at or below the phototherapy threshold) was achieved for 4.5 mg/kg dose

Expert Consensus Guidelines

FDA

- Clinicians treat hyperbilirubinemia in term and late-preterm neonates based on clinical practice guidelines

- AAP guideline, updated most recently in 2004, is considered standard practice for neonatal care providers in the U.S. for management of neonates of at least 35 weeks gestation at birth
  - Aims are to prevent severe neonatal hyperbilirubinemia and bilirubin encephalopathy, while minimizing unintended harm and unnecessary treatment

- Nomograms designating (1) risk for severe hyperbilirubinemia, (2) thresholds for phototherapy treatment, and (3) thresholds for exchange transfusion were developed, incorporating data from decades of clinical investigation
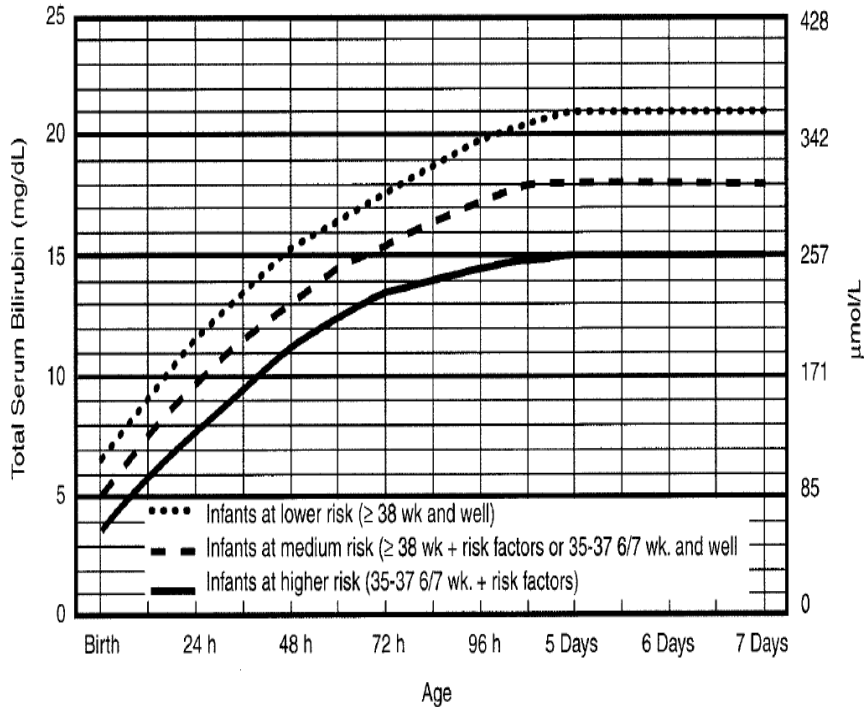
Designation of Risk – Assessing the Need for Early Outpatient Follow-Up
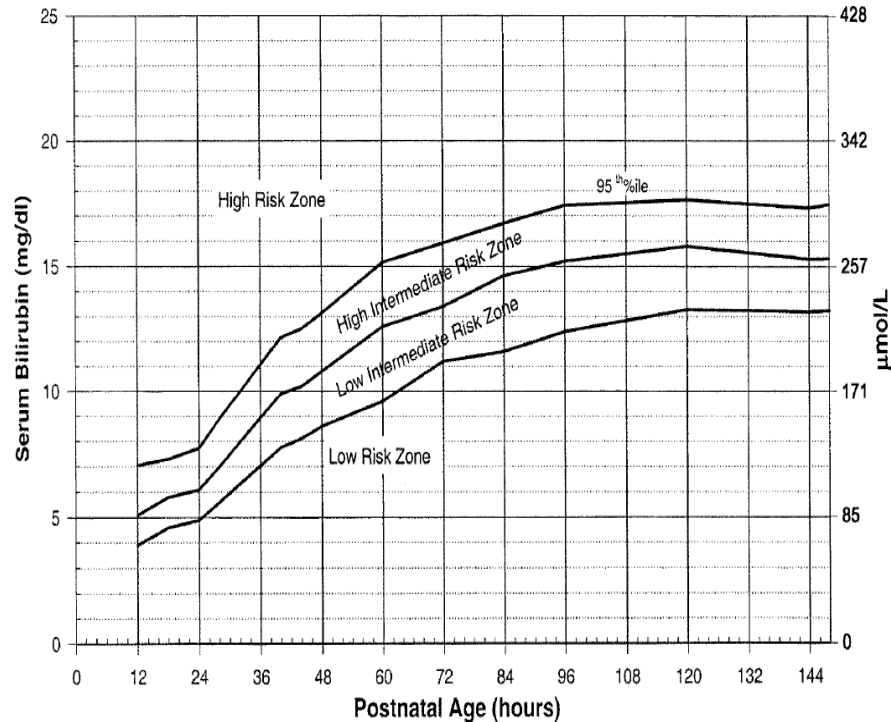
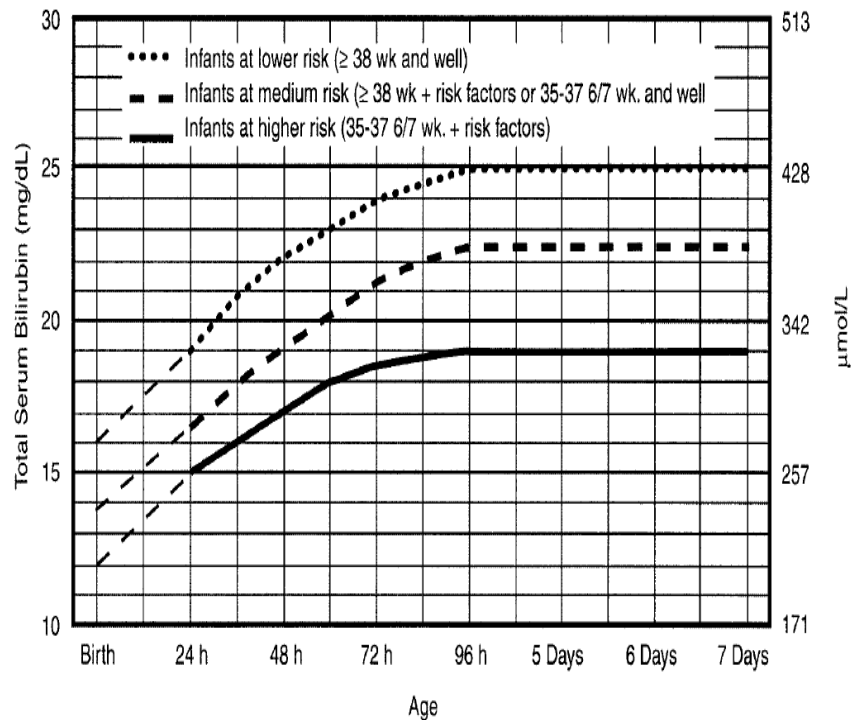## Risk Factors for Developing Severe Hyperbilirubinemia

- Jaundice noted before discharge

- Breastfeeding

- Gestation <38 weeks

- Significant jaundice in a sibling

- Bruising

- Blood group incompatibility

American Academy of Pediatrics Subcommittee on, H., *Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.* Pediatrics, 2004

13

Guidelines for Phototherapy for Infants ≥35 Weeks Gestation

Risk Factors for Complications

- Isoimmune hemolytic disease
- G6PD deficiency
- Asphyxia
- Significant lethargy
- Temperature instability
- Sepsis
- Acidosis
- Serum albumin <3 g/dL

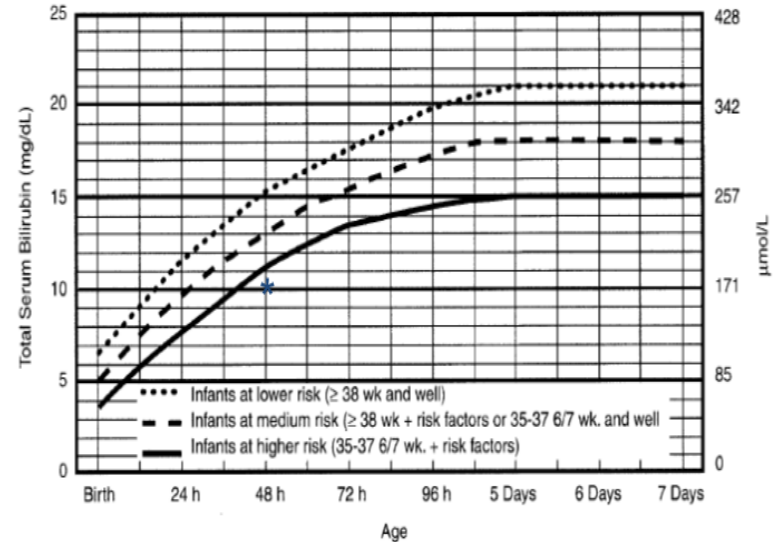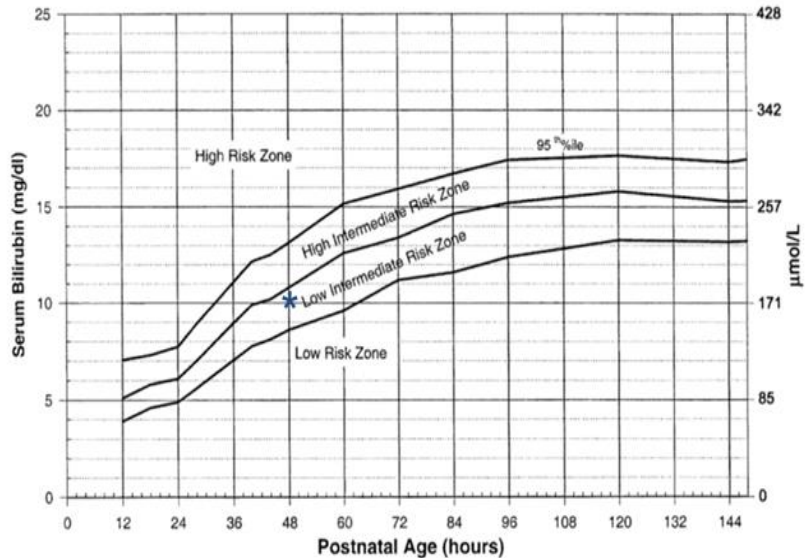American Academy of Pediatrics Subcommittee on, H., *Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.* Pediatrics, 2004

14

Guidelines for Exchange Transfusion for Infants ≥35 Weeks Gestation

Immediate Exchange Transfusion

- Acute bilirubin encephalopathy
  - Hypertonia
  - Arching
  - High-pitched cry
  - Opisthotonus
  - Fever

American Academy of Pediatrics Subcommittee on, H., *Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.* Pediatrics, 2004

Different Nomograms—Prevention and Treatment

FDA

Early Follow-Up	Phototherapy

American Academy of Pediatrics Subcommittee on, H., *Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.* Pediatrics, 2004

16

Clinical Meaning of a Reduction in TSB or Time to a Particular TSB Level is Unknown

Hemolysis

TSB ≥25

Asphyxia

TSB ≥30

Lack of follow-up

Infection

Prematurity

Risk of Kernicterus
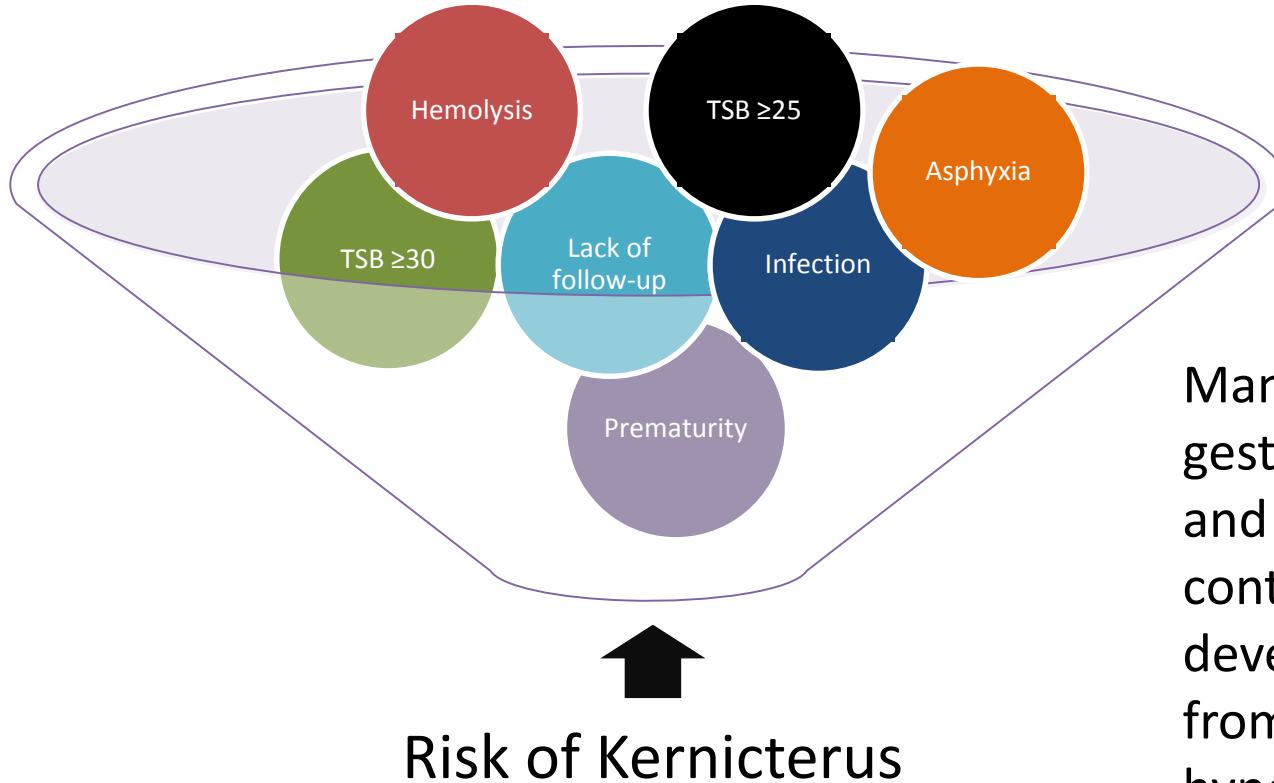
Many other factors such as gestational age, hour of life, and comorbidities contribute to the risk of developing complications from severe hyperbilirubinemia

Safety

- Major safety concerns of phototoxicity, thrombocytopenia and the potential for adverse neurodevelopmental outcomes

- The long-term neurodevelopmental database is small

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

Postmarketing Activities

- Benefit of treatment must be weighed carefully against the seriousness of the potential risks associated with use, including the risk of long-term neurodevelopmental toxicity

- FDA has the authority to require a REMS if additional measures beyond labeling are necessary to ensure the benefits of a drug outweigh the risks
  - Proposed REMS consists of restricted distribution, health care setting certification, safe use conditions and a registry

- If approved, postmarketing requirements may be needed to obtain additional long-term safety data
  - Implement an observational study
  - Complete ongoing long-term extension studies

AC Meeting Agenda

- Applicant presentation (1 hour and 15 minutes)
  - Clarifying Questions from the Committee

- FDA presentation (1 hour and 15 minutes)
  - Steven Li, PhD Clinical Pharmacologist
  - Feiran Jiao, PhD Mathematical Statistician
  - David Joseph, PhD Lead Pharmacologist
  - Y. Veronica Pei, MD Medical Officer
  - Charlotte Jones, MD, PhD, MSPH Medical Officer
  - Clarifying Questions from the Committee

- Open public hearing (1 hour)

- Committee discussion and voting

Discussion Question 1

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

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

Discussion Question 2

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

Voting Question 3

VOTE: Has the Applicant provided substantial and persuasive evidence of effectiveness for stannsoporfin as an adjunct to phototherapy in neonates greater than or equal to 35-weeks gestational age with laboratory evidence of hemolysis and hyperbilirubinemia meeting the American Academy of Pediatrics (AAP) criteria for phototherapy who are at risk for developing complications associated with severe hyperbilirubinemia?

Voting Question 4

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

Voting Question 5

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

Discussion Question 6

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

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

Voting Question 7

VOTE: Does the risk-benefit profile of stannsoporfin support approval?

    a.   Yes without a REMS

    b.   Yes with a REMS

    c.   No

Discussion Question 8

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

Clinical Pharmacology Findings of Stannsoporfin
NDA 209904

Shen (Steven) Li, PhD
Lian Ma, PhD
Insook Kim, PhD
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
May 3, 2018

Outline

- **Pharmacokinetics (PK) of stannsoporfin**

- **Dose/exposure-response for change in total serum bilirubin (TSB)**
  - **Supportive Study 64,185-202**
    - Subset of neonates received phototherapy (PT)
    - Timing of PT varied
  - **Pivotal Study 64,185-204**
    - All neonates received PT
    - PT within 30 min of stannsoporfin

Pharmacokinetics of Stannsoporfin

Absorption:

- Mean t_{max} 1.5 – 2.3 hours
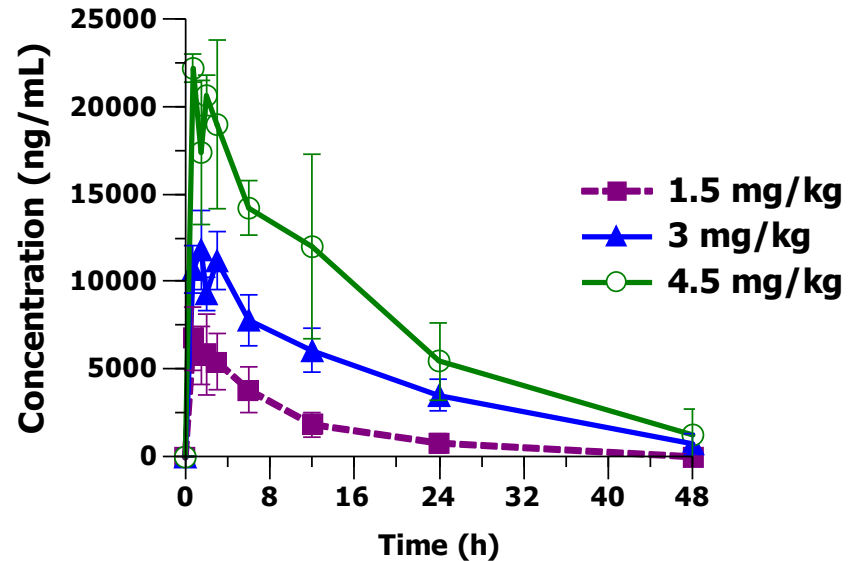
Distribution:

- V_d/F: 0.97 L for a neonate of 3.5 kg

Metabolism:

- Not well characterized
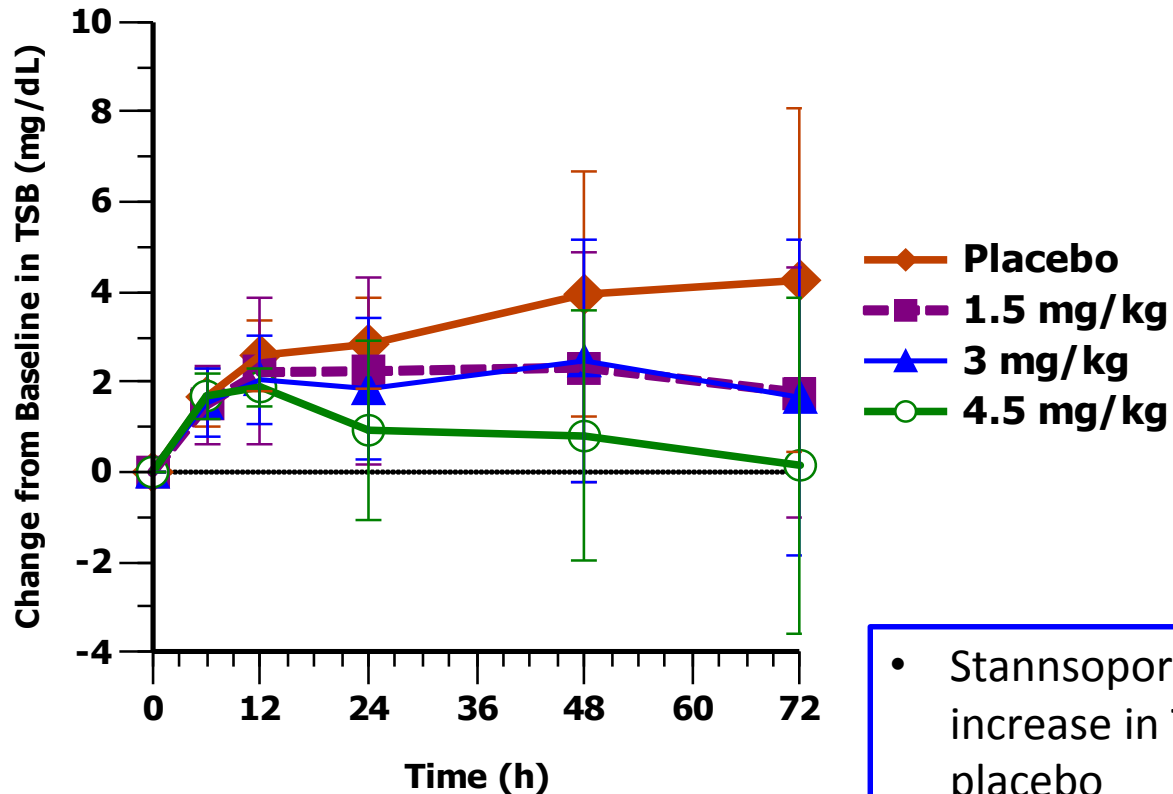- In vitro data: not CYP enzymes mediated

Elimination:

- Mean $t_{1/2}$ 10 - 11 hours following 3 and 4.5 mg/kg doses
- Major elimination pathway is unclear
- Urine recovery 0.2%-9.85% of the dose; feces 0%-13%, over 48 hours in adults

# Dose-Dependent Mean Change in TSB over Time
Study 64,185-202

Chart: Change from Baseline in TSB (mg/dL) vs Time (h), with curves for Placebo, 1.5 mg/kg, 3 mg/kg, and 4.5 mg/kg.

Dose (mg/kg)	Patients received phototherapy (n [%])
Placebo (N=15)	8 (53.3%)
1.5 (N=17)	3 (17.6%)
3 (N=18)	6 (33.3%)
4.5 (N=8)	2 (25.0%)

- Stannsoporfin appeared to attenuate the increase in TSB over time as compared to placebo
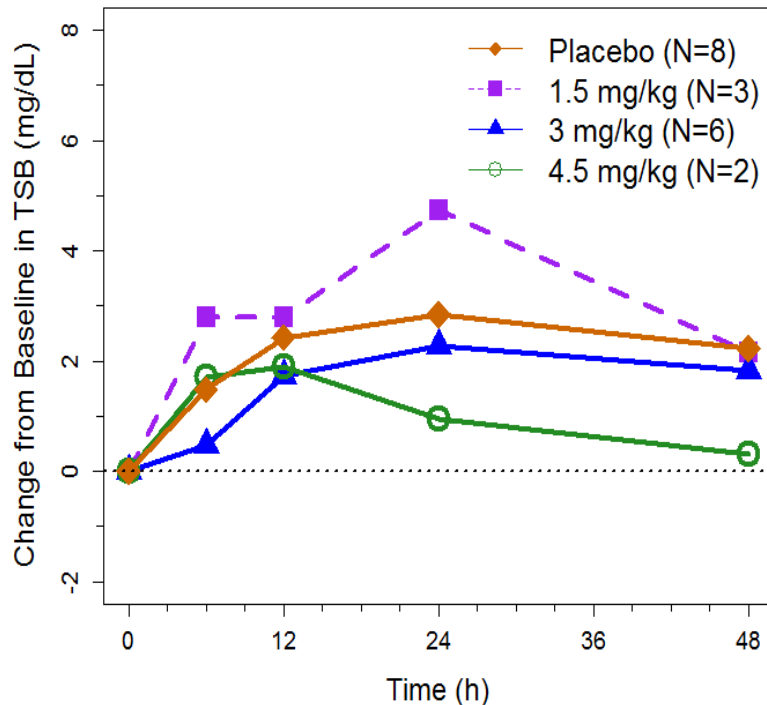
Mean Change in TSB over Time without or with PT
Study 64,185-202
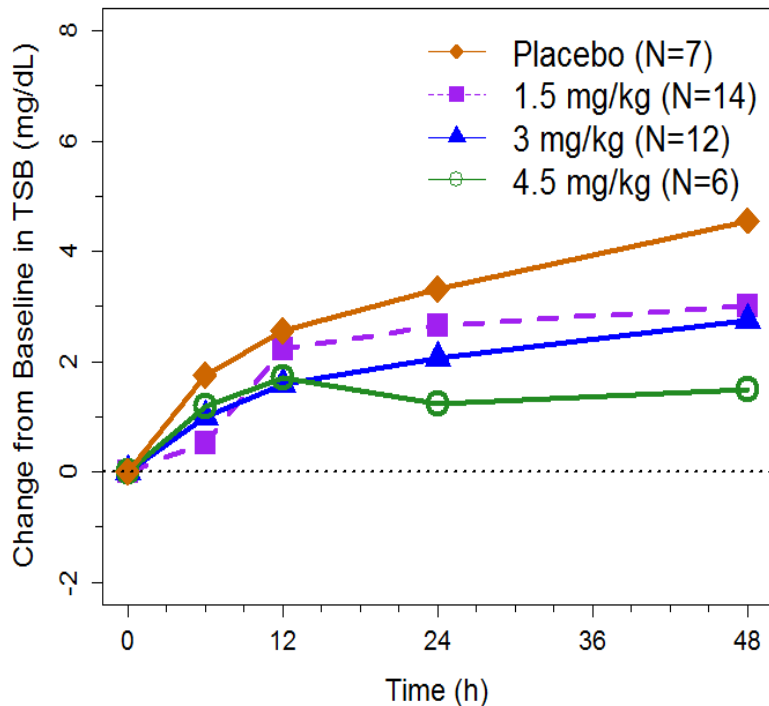
PT: phototherapy

Exposure-Response Relationships for Change in TSB
Study 64,185-202

- Exposure vs. change from baseline in TSB:
    - Individual stannsoporfin AUC values in neonatal patients
    - Change from baseline in TSB at 48 and 72 hours
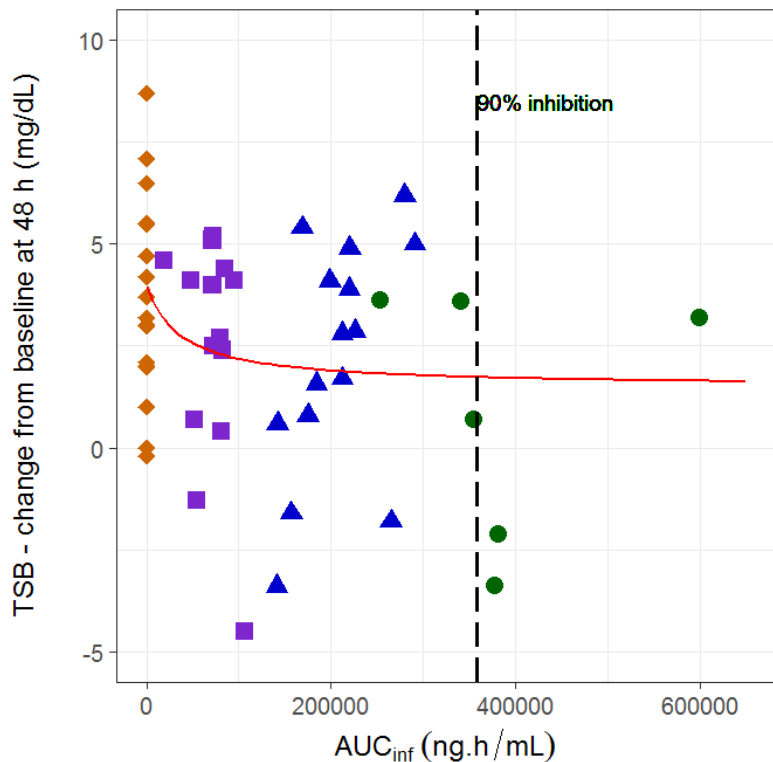

- Overall graphical assessment of exposure-response relationship indicates that there is an inverse relationship between increasing systemic exposure for stannsoporfin and change from baseline in TSB

Systemic Exposure-Change from Baseline in TSB
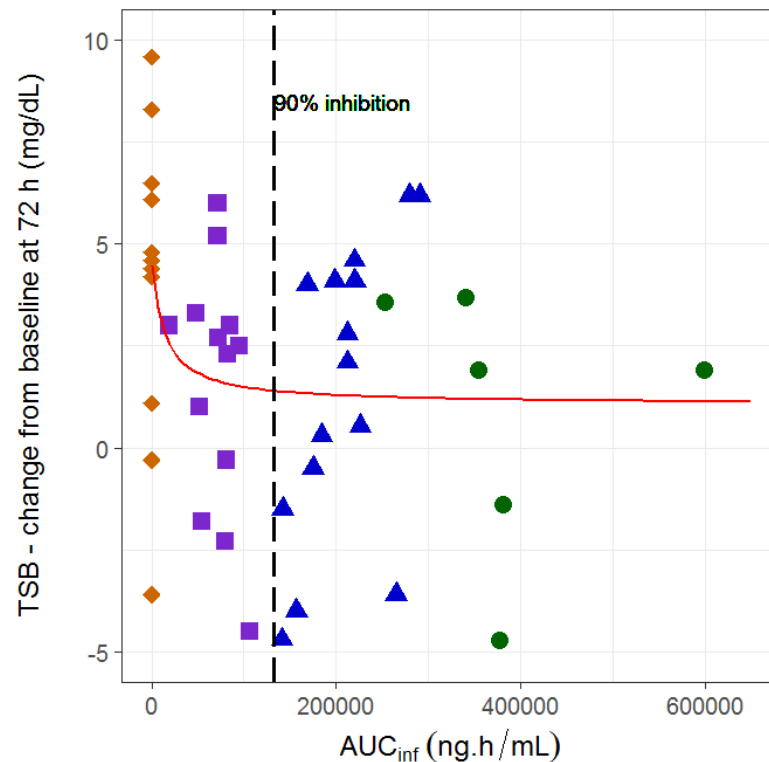## Study 64,185-202

Systemic Exposure-Change from Baseline in TSB
Without PT (upper panel) or with PT (lower panel)
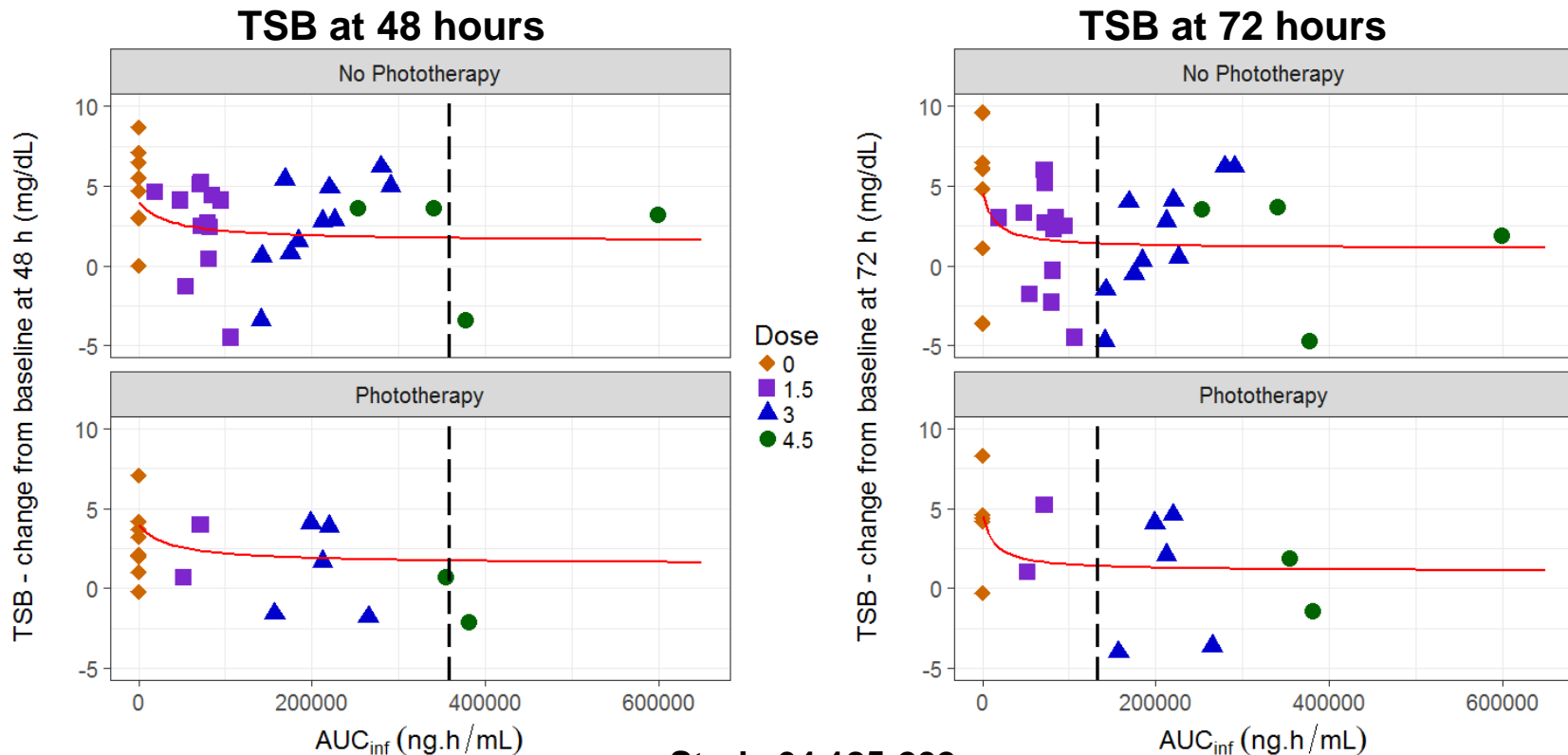
Study 64,185-202

Mean Change in TSB over Time in Neonates with PT
Study 64,185-204
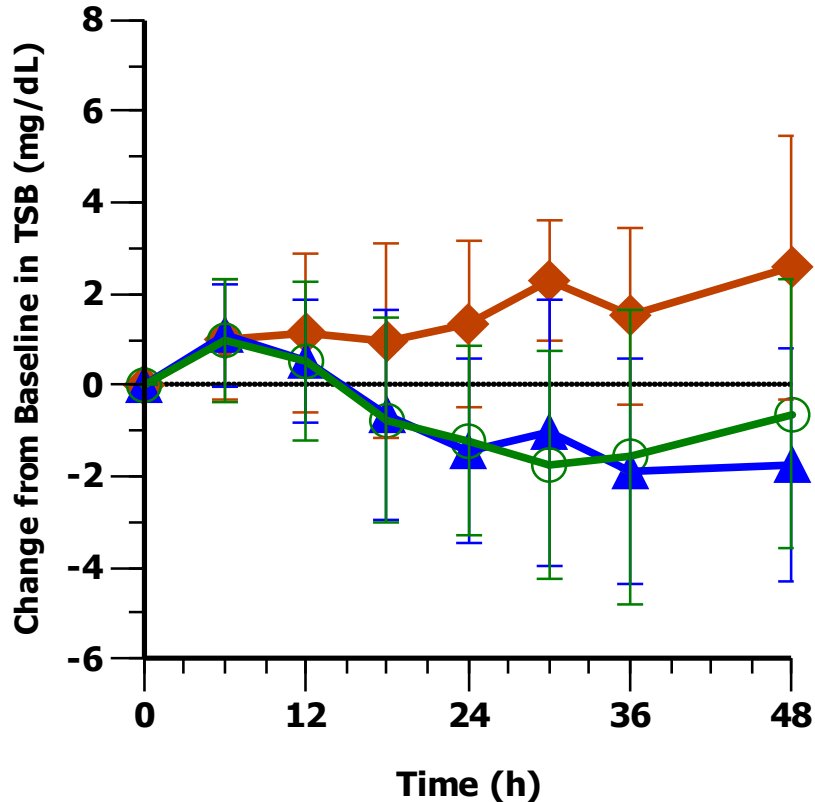
- Both 3 mg/kg and 4.5 mg/kg doses decreased TSB over time compared to placebo treatment

- No apparent difference between 3 mg/kg and 4.5 mg/kg for change from baseline in TSB

Summary

- Apparent dose-dependent attenuation of TSB rise (Study 64,185-202)

- Apparent inverse relationship between increasing systemic exposure and change from baseline in TSB regardless of phototherapy (Study 64,185-202)
  - Smaller sample size for 4.5 mg/kg compared to lower doses

- No difference in mean change from baseline in TSB over time between 3 mg/kg and 4.5 mg/kg (Study 64,185-204)

NDA 209904
stannsoporfin

Analyses of Efficacy Data

Feiran Jiao, PhD
Statistical Reviewer
Division of Biometrics III
Office of Biostatistics, CDER, FDA
May 3, 2018

Trial 64,185-204

- Multicenter, randomized, placebo-controlled, double-blind
- N = 91
- Phototherapy (PT)

Gestational age ≥ 35 weeks

Age 0-48 hr

Risk factors for severe hyperbilirubinemia

Required initiation of phototherapy based on AAP guideline

Birth weight ≥ 2500 g

Phototherapy
+
placebo (single dose)
(N = 30)

Phototherapy
+
stannsoporfin
(single 3 mg/kg dose)
(N = 30)

Phototherapy
+
stannsoporfin
(single 4.5 mg/kg dose)
(N = 31)

Primary Endpoint:

% change from baseline total serum bilirubin (TSB) at 48-hours post dose

Followed for 30 days

42

Demographic Characteristics of Study 204

	Placebo	Stannsoporfin	
	N=30 n (%)	4.5 mg/kg N=31 n (%)	3 mg/kg N=30 n (%)
SEX			
F	13 (43.3%)	15 (48.4%)	15 (50.0%)
M	17 (56.7%)	16 (51.6%)	15 (50.0%)
AAP RISK CATEGORIES			
≥ 38 weeks + risk factors (AAP medium risk)	25 (83.3%)	28 (90.3%)	25 (83.3%)
<38 weeks + risk factors (AAP high risk)	5 (16.7%)	3 (9.7%)	5 (16.7%)
DIRECT AGGLUTINATION TEST (DIRECT COOMBS TEST)			
Negative	3 (10.0%)	2 (6.5%)	1 (3.3%)
Positive	27 (90.0%)	29 (93.5%)	29 (96.7%)

Individual Trajectories of High-risk Neonates

Gestational Age < 38 weeks + Risk Factors
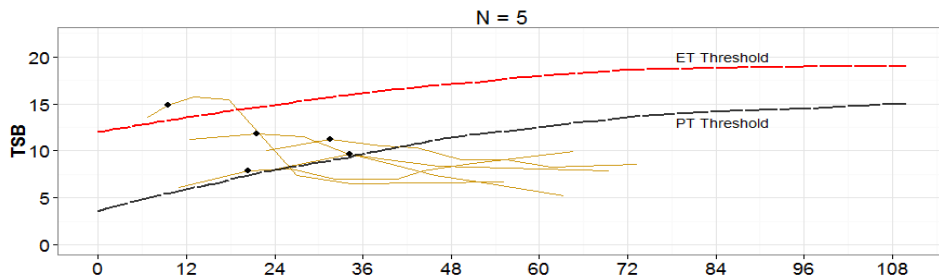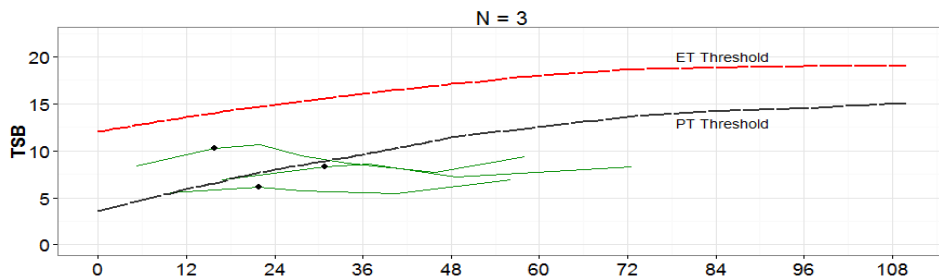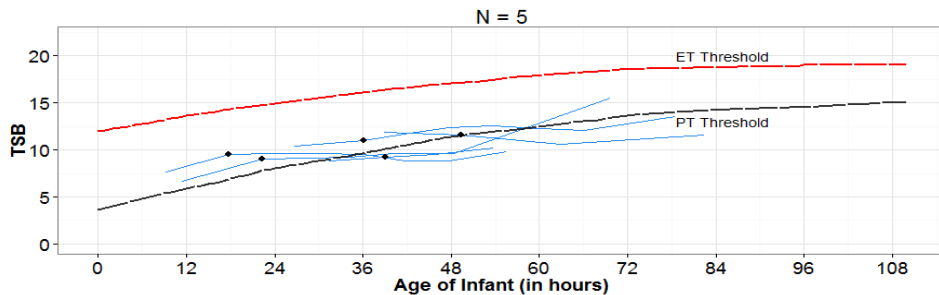
Individual Trajectories of Medium-risk Neonates

Gestational Age ≥ 38 weeks + Risk Factors
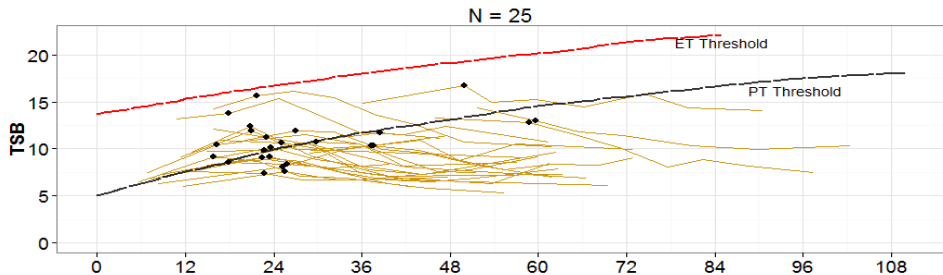
FDA Sensitivity Analysis Excludes 27 Neonates

FDA Sensitivity Analysis Excludes 27 Neonates

11 neonates had baseline TSB values below the age-specific PT threshold
(4 in 3 mg/kg, 2 in 4.5 mg/kg and 5 in placebo)

N=91

80 neonates

FDA Sensitivity Analysis Excludes 27 Neonates

FDA

11 neonates had baseline TSB values below the age-specific PT threshold
(4 in 3 mg/kg, 2 in 4.5 mg/kg and 5 in placebo)

N=91

N=80

65 neonates

15 neonates had negative interpolated time values
(3 in 3 mg/kg, 6 in 4.5 mg/kg and 6 in placebo)

48

FDA Sensitivity Analysis Excludes 27 Neonates

11 neonates had baseline TSB values below the age-specific PT threshold
(4 in 3 mg/kg, 2 in 4.5 mg/kg and 5 in placebo)

N=91

N=80

N=65

64 neonates

15 neonates had negative interpolated time values
(3 in 3 mg/kg, 6 in 4.5 mg/kg and 6 in placebo)

1 neonate had baseline TSB exceeding the exchange transfusion (ET) threshold and received ET
(in 3 mg/kg)
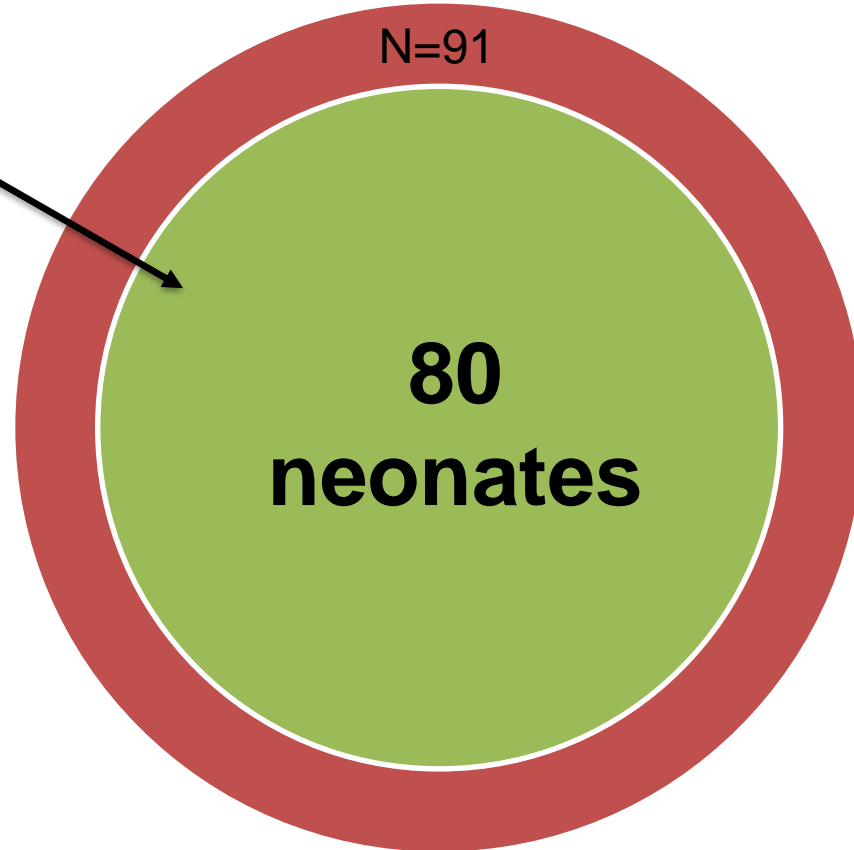
Primary Endpoint Analyses

		Placebo	Stannsoporfin	
			4.5 mg/kg	**3 mg/kg**
Applicant % change from baseline for TSB at 48H post-dose ITT, 91 neonates[1]	N	30	31	30
	Mean difference vs placebo (95% CI)*		-27 (-40, -15)	-32 (-44, -19)
FDA % change from baseline for TSB at 48H post-dose 64 neonates[2]	N	19	23	22
	Mean difference vs placebo (95% CI)*		-30 (-44, -16)	-42 (-56, -27)

[1] Results were extracted from Table 14.2.1.1 in the Applicant's Clinical Study Report
[2] 64 = 91-15-11-1 neonates
* p-values were all highly significant (<0.0001) and were based on the analysis of covariance model, which included treatment arms and baseline TSB as covariates.

Secondary Endpoints

- 3 secondary endpoints sequentially tested based on the following pre-specified hierarchical order

  1. Time at which TSB crosses at or below the age-specific PT threshold
  2. PT failure (restart PT, hospital readmission, IVIG used, or require ET)
  3. Incidence of rebound hyperbilirubinemia (an increase in TSB above the age-specific PT threshold following discontinuation of the initial PT)

- For each of the primary endpoint and 3 secondary endpoints, test starting from 4.5 mg/kg and then 3 mg/kg if 4.5 mg/kg is significant at alpha 0.05

Time (in hours) from Injection to TSB Crossing at or below Age-Specific PT Threshold (T_TSB)
(1st Secondary Endpoint)

		Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
Applicant Interpolated T_TSB* *76 (= 91-15) neonates[1]*	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
FDA Interpolated T_TSB* *64 (= 91-15-11-1) neonates[2]*	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

*Each event occurring at the various percentiles was estimated using the Kaplan-Meier method and analyzed using the log-rank test.
[1] 15 neonates who had negative time values were removed from the analysis. Results were extracted from Table 14.2.4.1 in the Applicant's CSR.
[2] 64 = 91-15-11-1 neonates

PT Failure Defined as Restart PT, Hospital Readmission, IVIG use, or Exchange Transfusion

(2nd Secondary Endpoint)

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

[1] Results were extracted from Table 14.2.5.5 in the Applicant's CSR.

[2] 64 = 91-15-11-1 neonates

Rebound Hyperbilirubinemia

(3rd Secondary Endpoint)

		Placebo	Stannsoporfin	
			4.5 mg/kg	**3 mg/kg**
Applicant Rebound hyperbilirubinemia *ITT, 91 neonates[1]*	N	30	31	30
	Occurred n (%)	3 (10%)	1 (3%)	0 (0%)
FDA Rebound hyperbilirubinemia *64 neonates[2]*	N	19	23	22
	Occurred n (%)	3 (16%)	1 (4%)	0 (0%)

[1] Results were extracted from Table 14.2.5.7 in the Applicant's CSR.
[2] 64 = 91-15-11-1 neonates

FDA Exploratory Analysis:
Duration of Hospitalization Results

		Placebo	Stannsoporfin	
			4.5 mg/kg	3 mg/kg
Duration of hospitalization* *91 neonates*	N	30	31	30
	50th percentile (hr) (95% CI)	46.3 (29.0, 56.0)	47.0 (37.3, 49.4)	46.8 (44.4, 49.2)
Duration of hospitalization* *64 (=91-15-11-1) neonates*	N	19	23	22
	50th percentile (hr) (95% CI)	55.3 (46.0, 72.7)	48.3 (43.1, 51.3)	47.1 (43.2, 62.1)

* Each event occurring at the various percentiles was estimated using the Kaplan-Meier method.

Efficacy Summary

- For the primary endpoint (percent change from baseline in TSB at 48 hours)
  - Both 3 mg/kg and 4.5 mg/kg stannsoporfin exhibited a greater reduction compared to placebo based on both the Applicant's and FDA's sensitivity analyses (p-values < 0.0001)

- For the 1st secondary endpoint (time from injection to when TSB below PT threshold)
  - 4.5 mg/kg stannsoporfin had shorter time to cross at or below the age-specific threshold for discontinuing PT than placebo in both the Applicant analysis (N=76 neonates; p-value = 0.003) and the FDA analysis (N=64 neonates; p-value = 0.014)

- Are the results from Study 204, the 1 completed efficacy study, statistically persuasive?

NDA 209904
stannsoporfin

Summary of Findings from Nonclinical Safety Studies in Neonatal Animals

David B. Joseph, PhD
Lead Pharmacologist
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
May 3, 2018

Outline

➢ Single-dose intramuscular phototoxicity study in neonatal guinea pigs (with operating room light exposure [ORL])

➢ Pivotal toxicology studies: 28-Day (daily dosing) intramuscular studies in neonatal rats and neonatal dogs

- Study design with 28-day treatment duration conforms with standard regulatory recommendations for single use drug products, to support a marketing application

➢ Distribution of ^{119m}Sn-stannsoporfin in neonatal rat brain (single dose)

Key Safety Findings in Nonclinical Studies

FDA

➢ Neonatal albino guinea pigs given a <u>single IM injection</u> of 20 mg/kg stannsoporfin (1.5 times dose in neonatal humans based on mg/m^2) followed by 6 hr exposure to ORL starting at 30 min post-dose:

- 11/12 animals died compared to 1/12 in control group (vehicle injection + ORL exposure)

- Dermal and epidermal necrosis noted

➢ 28-Day (<u>daily dosing</u>) intramuscular toxicity studies in neonatal rats and neonatal dogs

- Same doses tested in both studies (1, 4.5, and 20 mg/kg/day); plasma exposure (AUC) differed substantially between species

- In rats, cumulative plasma AUC for stannsoporfin was 1.7, 11, and 53 times the human AUC at the proposed dose of 4.5 mg/kg

- In dogs, AUC multiples of 0.3, 1.1, and 4.5

Key Safety Findings in Nonclinical Studies (2)

➤ Rats showed minimal growth impairment at 20 mg/kg/day only (weight ↓5-6%), whereas dogs showed moderate growth impairment at 4.5 and 20 mg/kg/day (weight ↓9-15%)

- Bodyweight reductions only seen after <u>repeated administration</u> in both species (18 days in rats, 6 days in dogs)

  - May not be relevant to single use in neonatal humans

➤ Effects in neurobehavioral tests occurred in male rats at a cumulative human AUC multiple of 6.7-fold, and in female rats at a multiple of 34-fold, after <u>repeated administration</u>. Inconclusive results for females

  - May not be relevant to single use in neonatal humans

➤ No evidence of neurotoxicity in dogs, but AUC was ~ 10% of rat AUC

Key Safety Findings in Nonclinical Studies (3)

- ➢ 2/32 dogs died in high dose group, with cumulative AUC at 3.3 times the human AUC, after repeated administration (at 21 and 23 days)

- ➢ Microscopic changes in liver in both species, but effects were different

  - Rats - hepatocyte (single cell) necrosis in high dose group (13/20 rats), reversible
  - Dogs - pigment accumulation (likely the drug) in all animals, irreversible

- ➢ Thyroid atrophy in dogs at high dose, reversed at 1-month recovery

Neurobehavioral Effects in Rats (28-Day IM Toxicity Study)

➢ **Male rats:** Decreased motor activity at 4.5 and 20 mg/kg/day (↓47% and 45%, respectively) on study day 18 (equivalent human age on day of test was ~ 2 years)

- Cumulative AUC at 6.7 and 32 times the human AUC for proposed dose

- No significant change on 14th day of recovery, but motor activity remained lower (↓28% at 20 mg/kg/day)

➢ **Female rats:** Decreased response (↓31%) in acoustic startle test at 20 mg/kg/day on study day 19; however, the test appeared inadequate based on control values that deviated from expected outcome, therefore results are inconclusive

- Effect observed at cumulative AUC of 34 times the human AUC for proposed dose; no effect in females at 4.5 mg/kg/day (AUC multiple of 7)

- Partially reversed (↓19%) on 15th day of recovery

^{119m}Sn-stannsoporfin
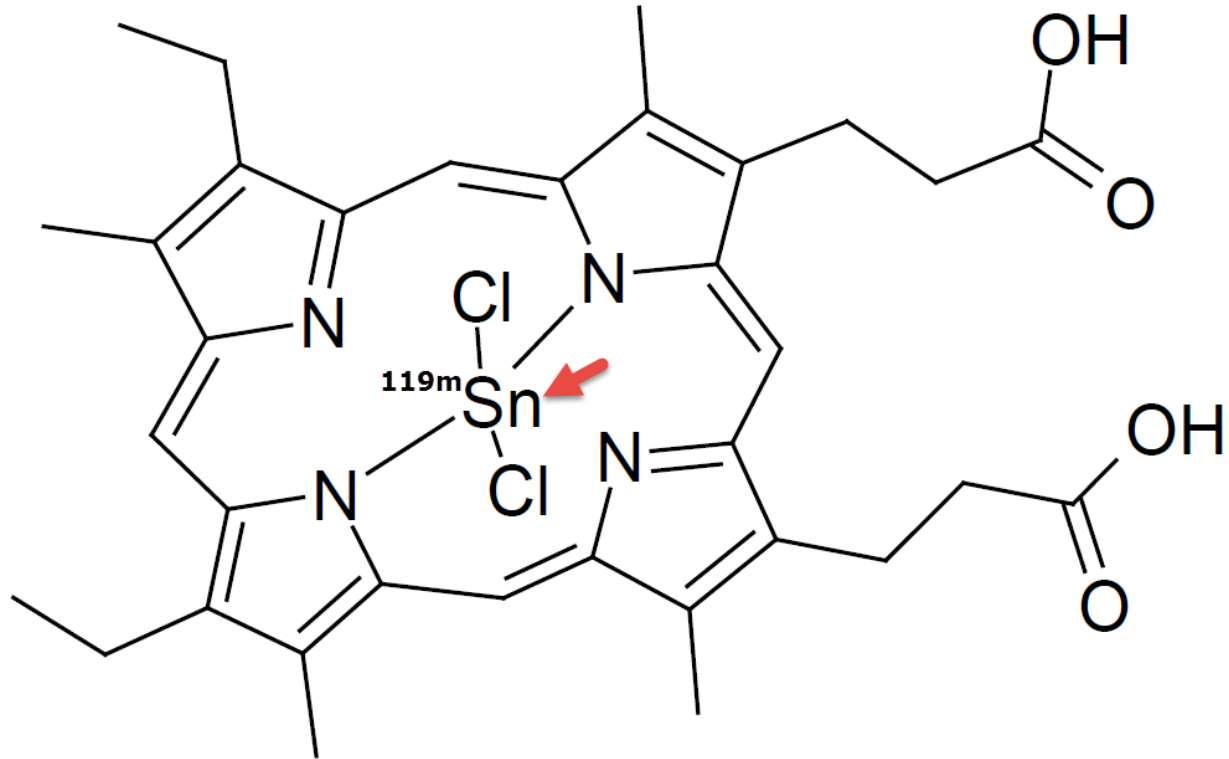
^{119m}Sn-stannsoporfin Distribution in Neonatal Rat Brain (6 mg/kg <u>single</u> IM dose containing radioactive tin)

	Nanogram Equivalents ^{119m}Sn-stannsoporfin/g Tissue						
	1 hr	12 hr	24 hr	72 hr	168 hr	336 hr	1920 hr
Cerebrum	319	216	221	141	BLQ	BLQ	BLQ
Cerebellum	730	486	444	259	BLQ	BLQ	BLQ
Olfactory lobe	381	356	253	239	BLQ	BLQ	BLQ
Medulla	330	269	135	169	BLQ	BLQ	BLQ
CSF (cerebrum ventricle)	3270	2390	2310	2570	944	919	NS
CSF (subarachnoid ventricle)	2710	2360	2360	3720	2200	1810	2520

Values are from females, study # 7611-102; BLQ: below limit of quantitation (<133 ng equivalents/g tissue); NS: not sampled (sample shape not discernable)

Summary: Potential Mechanisms for Neurobehavioral Effects based on Totality of Data

➢ Drug (radiolabeled) was detected in brain and CSF in neonatal rats after single IM injection of a clinically relevant dose; rat AUC was 0.85 times the human AUC at 4.5 mg/kg, and 1.6 times human AUC at 3 mg/kg

➢ Brain distribution data suggest that drug may accumulate with daily dosing (quantifiable levels remained for at least 72 hr after a single dose)

➢ Drug target (heme oxygenase) is expressed in brain, therefore target-related or off-target effects are possible

➢ Potential release of tin from metabolized or degraded stannsoporfin

➢ Available animal data provide minimal information about the potential for neurobehavioral effects from a single administration

Safety Concerns – Tin Exposure from Stannsoporfin

FDA

➢ ICH Q3D Guideline for Elemental Impurities - Permitted Daily Exposure (lifetime):

0.64 mg/day parenteral (inorganic tin)

➢ Single dose of stannsoporfin @ 4.5mg/kg delivers:

2.13 - 2.83 mg Tin (inorganic)

(assuming birth weight of 3 - 4 kg)

➢ Slight but significant reductions (<10%) in hemoglobin parameters (MCH, MCHC) in 28-day toxicity studies in rats and dogs are consistent with toxicity from inorganic tin, but not conclusive

FDA Gastrointestinal Drugs Advisory Committee (GIDAC)
Focused Safety Evaluation

NDA 209904

stannsoporfin

Y. Veronica Pei, MD, MEd, MPH

Medical Officer

Division of Gastroenterology and Inborn Errors Products

Center for Drug Evaluation and Research

May 3, 2018

Outline

- Overview of safety datasets

- Evaluation of integrated (pooled) safety population from short-term studies (64,185-013w, 64,185-202, 64,185-204)

- Evaluation of potential long-term neurodevelopmental outcomes

- Risk/Benefit considerations

Potential Safety Concerns

1. Short-term:
   – Phototoxicity
   – Thrombocytopenia

2. Long-term:
   – Neurological adverse events (AEs)
   – Neurodevelopment assessments

3. Target organs of toxicity based on nonclinical studies:
   – Liver
   – Brain

Integrated (Pooled) Datasets Supporting Safety

FDA

Short-term Safety **(IND 64,185)**	**Long-term Safety** **(IND 64,185)**	**Long-term Neurodevelopment** **(INDs 64,185 and 29,462)**
•**64,185-204** – Risk factors for severe HB needing PT, ≥ 35 weeks GA •**64,185-202** – TSB within 2 mg/dL below criteria for PT, ≥ 35 weeks GA •**64,185-013W** – No risk factors for severe HB, ≥ 35 weeks GA	• **64,185-205 (On-going)** – LT extension of 64,185-204 • **64,185-203** – LT extension of 64,185-202 • **64,185-01C3W** – LT extension of 64,185-013W	•**Integrated GCP dataset** – 64,185-205 (On-going) – 64,185-203 – 64,185-01C3W •**Integrated Non-GCP dataset** – 6 studies

GA = Gestational age; GCP = Good Clinical Practice; HB = hyperbilirubinemia; PT = Phototherapy; TSB = Total serum bilirubin

Safety Population for Stannsoporfin

		Stannsoporfin N=887[a]					Control[b] N=543
Study No.		**0.75 mg/kg**	**1.5 mg/kg**	**2.25 mg/kg**	**3 mg/kg**	**4.5 mg/kg**	
GCP	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**
Non-GCP	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
All Studies Total = 1430		69	94	32	107	585	543

Table title: **Neonates Participated in Stannsoporfin Development Program N= 1430 (N is the sum of all available numbers from the columns below)**

GCP = Good Clinical Practice
[a] 18 neonates enrolled via compassionate use are not included; [b] Control population includes neonates receiving placebo $\pm$ phototherapy or phototherapy alone.

Evaluation of Integrated (Pooled) Safety Population from Short-term Studies (64,185-013W, 64,185-202, 64,185-204)

Demographic Characteristics of Integrated Short-term Studies

	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 (%)
AAP RISK CATEGORIES				
<38 weeks + risk factors (AAP high-risk)	24 (17.9%)	22 (17.5%)	5 (10.4%)	2 (11.8%)
≥38 weeks + risk factors (AAP medium-risk)	110 (82.1%)	104 (82.5%)	43 (89.6%)	15 (88.2%)
COOMBS TEST (only for Studies 64,185-204 and 64,185-202)				
Negative	4 (8.9%)	5 (12.8%)	1 (2.1%)	1 (5.9%)
Positive	41 (91.1%)	34 (87.2%)	47 (97.9%)	16 (94.1%)

Deaths in Stannsoporfin Development Program

FDA

- ## 12 deaths
  - 9 received stannsoporfin; 2 received placebo; 1 screened but not enrolled

IND 64,185 (GCP)	IND 29,462 (non-GCP)	Compassionate Use & Emergency INDs

• No deaths in subjects enrolled in short-term studies
 	
• 1 neonate screened but not enrolled
 	
• 1 neonate died from SIDS* in LT follow-up (Day 126)
	• Study 29,462-04 (N=465, GA 30 to < 36 weeks)
	  – 8 deaths (age 3 days to 36 weeks old)
	  – Respiratory distress syndrome most common cause
		• Total N = 18 (follow-up available for 16 subjects)
		• 2 deaths:
		  – SIDS at 5 month*
		  – GA 25 weeks, complications due to perforated and necrotic bowel (Day 48 in surgery)

GA = Gestational age; GCP = Good Clinical Practice; SIDS = Sudden Infant Death
* SIDS confirmed on autopsy. SIDS rates 39.4 deaths per 100,000 live births in 2015 in the U.S. (Source: https://www.cdc.gov/sids/data.htm)

Serious Adverse Events (SAEs) in Integrated Short-Term Studies

- Reported for 27 neonates
- 1 neonate (3 mg/kg) with baseline TSB > exchange transfusion (ET) threshold and required ET
- Most SAEs occurred in single occurrences

Common Serious Adverse Events (SAEs) (≥2 Neonates in Any Treatment Arm) in Integrated Short-Term Studies

	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 Neonate 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%)

Selected Common Treatment Emergent Adverse Events (TEAEs) in Integrated Short-Term Studies

	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 (%)
Rash neonatal[1]	12 (9%)	7 (5.6%)	11 (22.9%)	3 (17.6%)
Erythema[2]	1 (0.7%)	11 (8.7%)	7 (14.6%)	0 (0%)
Thrombocytopenia[3]	0 (0%)	4 (3.2%)	3 (6.3%)	0 (0%)

[1] Includes rash neonatal, erythema toxicum neonatorum, milia, acne infantile, transient neonatal pustular melanosis, candida nappy rash, dermatitis diaper
[2] Includes erythema, photosensitivity reaction (red rash when exposed to light), rash erythematous, generalized erythema
[3] Includes thrombocytopenia, platelet count decrease

Adverse Events of Special Interest (AESI): Dermatologic Adverse Events

- No serious adverse events

- Most common treatment-emergent adverse event

- More commonly reported in neonates treated with stannsoporfin compared to control

- Risk of photosensitivity reaction from operating room lights immediately after drug exposure is unknown:

  - 16 pediatric patients required surgical procedures
    - All occurred 140-1136 days from receiving study drug
    - None reported photosensitivity related AE

AESI: Thrombocytopenia in Studies 64,185-202 and 64,185-204
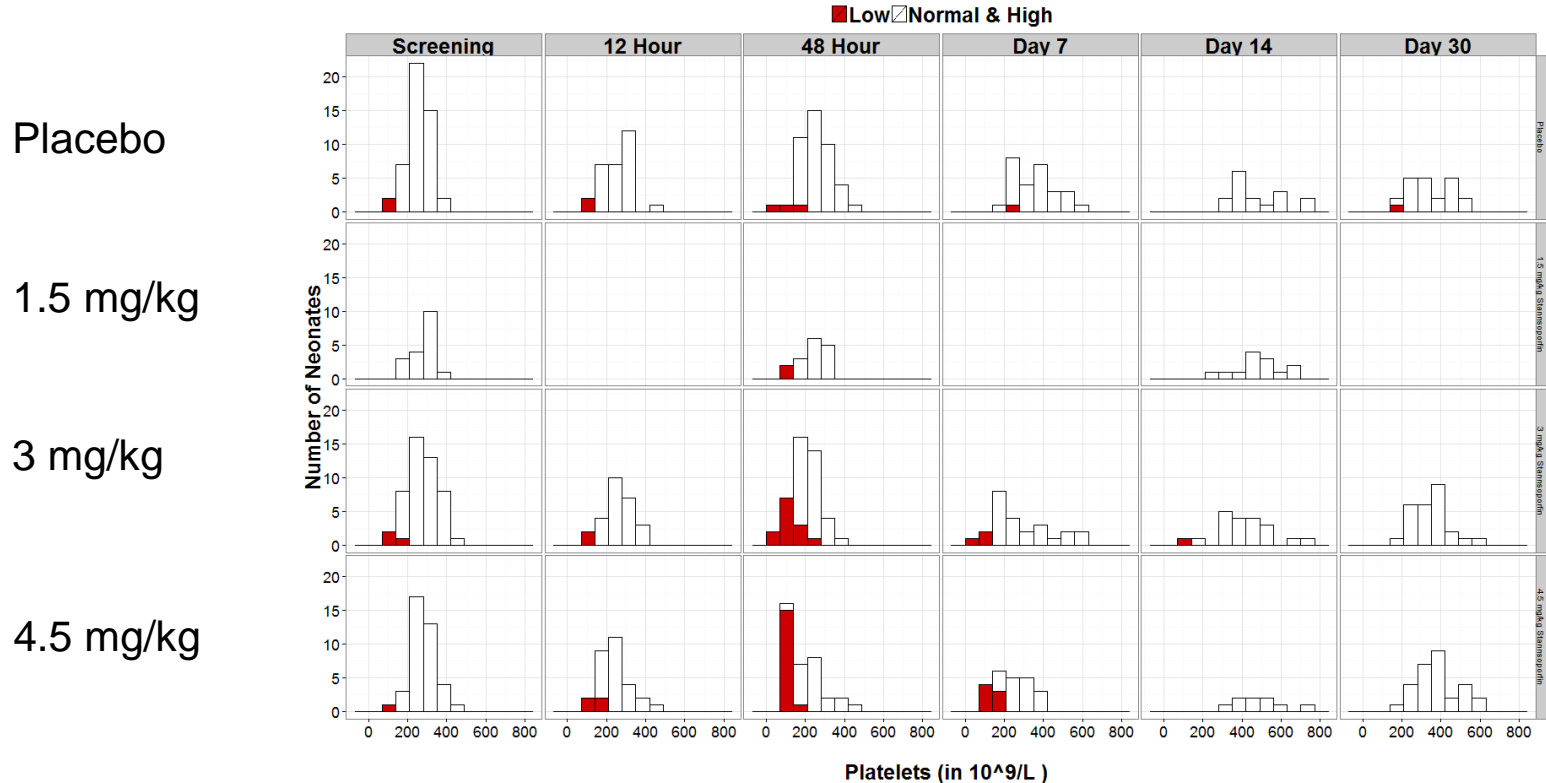
AESI Thrombocytopenia

Platelet Levels in Neonates for Study 64,185-202 and 64,185-204 by Treatment Arm (Neonates with baseline thrombocytopenia excluded)

Platelets (x 10^9/L)	Placebo N=43 n (%)	Stannsoporfin		
		4.5 mg/kg N=38 n (%)	3 mg/kg N=45 n (%)	1.5 mg/kg N=17 n (%)
≥150	41 (95.3%)	20 (52.6%)	37 (82.2%)	15 (88.2%)
< 150	2 (4.7%)	18 (47.4%)	8 (17.8%)	2 (11.8%)
100 to <150	2 (8.9%)	14 (36.8%)	7 (15.6%)	2 (11.8%)
50 to <100	0 (0%)	3 (7.9%)	1 (2.2%)	0 (0%)
< 50	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)

- More subjects in stannsoporfin arms experienced thrombocytopenia compared to placebo
- No bleeding events
- Unclear mechanism

81

Evaluation of Potential Long-term Neurodevelopmental Outcomes

Potential Long-Term Neurodevelopmental Effects

- Potential effect of tin (heavy metal) exposure to the developing brain

- Effects on brain of inhibiting heme oxygenase is unknown

- **March 13, 2012 AC Recommendations:**
  - 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

Summary of Long-Term Follow-Up Studies Assessing Neurological Adverse Events

Short-term Study	Long-term Extension Study		Comments
	Enrolled	**Completed**	
64,154-204 (N= 91)	64,185-205 (N= 68)	Ongoing	Year 1 = 35 pediatric patients Year 2 = 9 pediatric patients
64,185-202 (N= 58)	64,185-203 (N= 42)	N=23	stannsoporfin =15 pediatric patients control = 8 pediatric patients
64,185-01-3W (N= 176)	64,185-01C-3W (N= 87)	N=63 (3 years) N=59 (6 years)	Lower risk population

Summary of AEs related to Neurological, Psychological, Auditory, or Motor Conditions

	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 (%)
Speech disorder	4 (5.3%)	10 (13.7%)	0 (0.0%)	1 (9.1%)
Deafness	0 (0.0%)	5 (6.8%)	1 (2.7%)	0 (0.0%)

Overview of Neurodevelopmental Assessments Performed Across Studies

*Study 64,185-01C3W enrolled a healthy population without risk factors for severe hyperbilirubinemia

	Months				Years			
	3	6	12	18	2	3	4	6
Indices of General Cognitive Development								
Wechsler						Study 01C3W (N=63) Study 203 (N = 12)	Study 203 (N = 17) **Study 205 (Pending)**	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)**			
Bayley				Study 01C3W (N = 55)				
Indices of General Behavior Problems								
Conners					Study 203 (N = 20) **Study 205 (N = 5)**	Study 203 (N = 16) **Study 205 (Pending)**	Study 203 (N = 22) **Study 205 (Pending)**	
Child behavior checklist				Study 01C3W (N = 58)		Study 01C3W (N = 63)		Study 01C3W (N = 59)

86

Summary of Long-Term Assessments Performed Across Studies

- Within individual assessments, similar results across treatment arms

- Some differences noted
  - Mullen Scales of Early Learning (3 months to Year 2) Percentile Rank: Drug group scored lower at Month 3 (Visual reception, Receptive language, Expressive language, early learning composite) and Year 2 (Visual reception)

Limitations of Available Long-Term Neurodevelopmental Data

- Study 64,185-205 is ongoing with limited available data
- Longest follow-up in Study 64,185-01C3W: lower risk neonates compared to pivotal trial population
- Lack of standardization across studies in:
  - Enrollment population, administration of neurological exams and neurodevelopmental assessments
- Various instruments used at different ages
  - Data not poolable across studies
  - Limited power to detect an overall safety signal or a signal within individual age groups

Benefit/Risk Assessment

FDA

Benefit	**Risks**	**Uncertainties**
• Additional therapies needed for neonates at risk for bilirubin-induced neurological dysfunction • Additive effect as adjunctive therapy to phototherapy • Potential to reduce the need for exchange transfusion	• Photosensitivity related AEs most common • Thrombocytopenia • Sparse long-term neurodevelopment data • Higher rates of abnormal speech and hearing	• Single pivotal trial • Clinical meaningfulness of % change in TSB alone is unclear • Low dose (3 mg/kg) also effective in pivotal study (trend not statistically significant in supportive study) • Limited long-term clinical outcome data

Potential Safety Postmarketing Requirements

- Completion of ongoing long-term extension Study 64,185-205

- Observational neurodevelopmental outcome study for 7 years:
  - Patients treated with PT alone vs. PT + stannsoporfin
  - Compare standard neurodevelopment scales
    - Global measure of development
    - Global measure of intellect

Proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 209904 Stannsoporfin

May 3, 2018

Charlotte Jones, MD, PhD, MSPH

Medical Officer -Risk Management Analyst

Center for Drug Evaluation and Research

Division of Risk Management

Overview

- REMS Background

- Safety Considerations

- Risk Management
  - Applicant proposal
  - FDA proposal

Risk Evaluation and Mitigation Strategy (REMS)*

- A risk management plan that uses strategies **beyond FDA-approved professional labeling** to ensure that the benefits of a drug outweigh the risks

- Designed to achieve specific goals to mitigate risks associated with the drug

- FDA may require a REMS if determined necessary to ensure the benefits outweigh the risks
  - REMS can be required at the time of initial approval, or post approval if a new safety concern arises
  - Applies to NDAs, BLAs, and ANDAs
  - REMS are enforceable

Section 505-1 of the Federal Food, Drug, and Cosmetic Act 18 (FD&C Act) (21 U.S.C. 355-1)

REMS Factors to Consider

- Estimated size of the population likely to use the drug
- Seriousness of the disease/condition to be treated
- Expected benefit of the drug with respect to such disease/condition
- Expected/actual duration of treatment
- Seriousness of any known/potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- Whether a drug is a new molecular entity

Components of a REMS

A REMS can include
- Medication Guide or Patient Package Insert
- Communication plan for healthcare providers (HCPs)
- Elements to assure safe use (ETASU)
- Implementation System

A REMS must include
- a timetable for submission of assessments

Elements to Assure Safe Use (ETASU)

A. Certification and/or specialized training of HCPs who prescribe the drug

B. Certification of pharmacies or other dispensers of the drug

C. Dispensing/administration of drug in limited settings e.g., hospitals

D. Drug is dispensed/administered only with evidence of safe-use conditions

E. Each patient using the drug is subject to certain monitoring

F. Enrollment of treated patients in a registry

Considerations for ETASU

- A product can be approved only if an ETASU is put in place to mitigate the risk

- ETASU must be commensurate with specific serious risk(s) listed in the labeling

- ETASU cannot be unduly burdensome on patient access to drug, considering in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care

Considerations for ETASU

- To minimize the burden on the healthcare delivery system, ETASU must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

Safety Considerations

- Potential long-term neurodevelopmental toxicity
  - Tin (heavy nonessential metal) exposure
  - Inhibitor of heme oxygenase (neuroprotective role in brain)
- Preliminary safety data concerns for speech and hearing disorders
- Incomplete long-term follow up in pivotal study population

What to Accomplish with Risk Mitigation

- Restriction to the hospital setting

- Use in the indicated population as identified in the label

- Parent/legal guardian counseling

- Enforceability

APPLICANT RISK MANAGEMENT PROPOSAL (NON-REMS)

Risk minimization will be implemented through

- the product label, which will state that only single dose administration is approved, use is not approved in premature infants, and chronic use is not approved
- commercial distribution will be to hospital pharmacies only
- commercial representatives will be trained in emphasizing the limits of the intended target population
- close monitoring of neonates by healthcare professionals

Agency REMS Proposal Overview

REMS with Elements to Assure Safe Use

B & C	Dispensing/administration of drug in limited settings e.g., certified hospitals
D	Drug is dispensed/administered only with evidence of safe-use conditions
F	Enrollment of treated patients in a registry

Agency REMS Goal Proposal

To mitigate the potential risk of neurodevelopmental toxicity in neonates following 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 toxicity associated with its use

Agency REMS Goal Proposal

To mitigate the potential risk of neurodevelopmental toxicity in neonates following the use of stannsoporfin by:

3. Ensuring that the legal guardians are informed about the potential long-term neurodevelopmental risk of stannsoporfin and the need for obtaining neurodevelopmental screening

4. Enrolling all patients in a registry to ensure the safe use of stannsoporfin and further support long-term safety

Agency REMS Proposal

FDA

Drug dispensing and administration restricted to certain settings

- Stannsoporfin is restricted to hospitals that provide care for neonates, with expertise in the treatment of hyperbilirubinemia in infants who may require an exchange transfusion

- Certified hospitals must implement policies and procedures to ensure prescriber training, parent/legal guardian education, and patient enrollment

Agency REMS Proposal

FDA

| Safe Use Conditions | • Patient's legal guardian is counseled regarding the potential long- term neurodevelopmental risk of stannsoporfin, and the need for obtaining neurodevelopmental screenings, as documented on a patient enrollment form |

Agency REMS Proposal

Registry

- Supports long-term safety of stannsoporfin by providing information to determine if the REMS is functioning as intended

- Provides a source of contact information for patients who may elect to participate in a PMR

Proposed REMS Potential Impact on Healthcare System and Stakeholders

- **Hospitals**
  - Must put processes and procedures in place to train staff on REMS requirements including proper patient selection, counseling, and patient enrollment

- **Parents/Legal Guardians**
  - Must receive counseling
  - Must enroll child in registry by providing demographic information