Stannsoporfin for Neonatal Hyperbilirubinemia

InfaCare, A Mallinckrodt Pharmaceuticals Company

Gastrointestinal Drugs Advisory Committee and

Pediatric Drugs Advisory Committee

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Introduction

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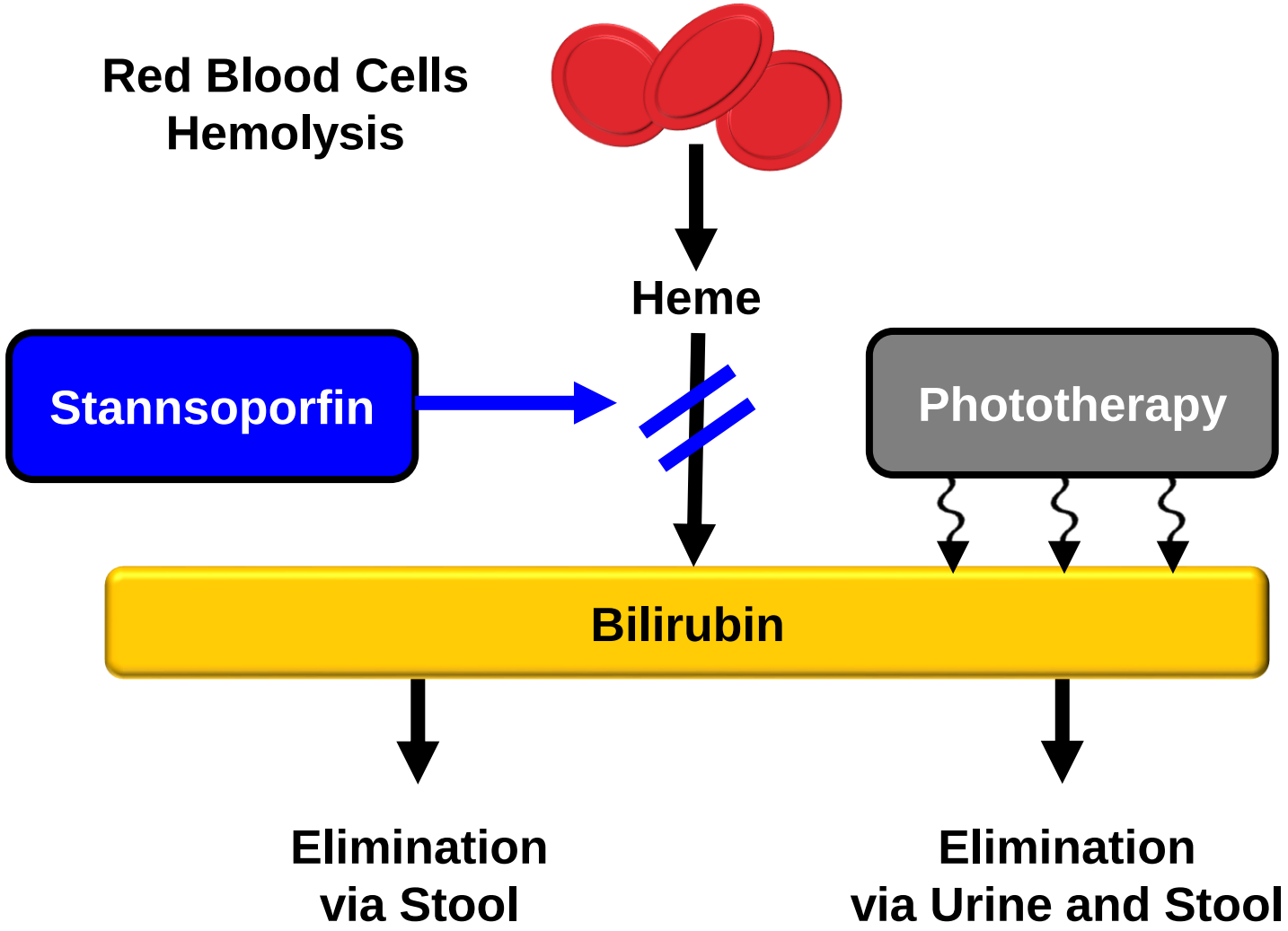
Neonatal Hyperbilirubinemia: Clinical Condition of Excess Bilirubin

- Imbalance between production and clearance of bilirubin
- Unconjugated bilirubin production results from red blood cell breakdown, or hemolysis
- Currently treated with blue light phototherapy
- Goal of treating hyperbilirubinemia is to prevent
  - Invasive interventions, like exchange transfusion
  - Serious neurodevelopmental complications

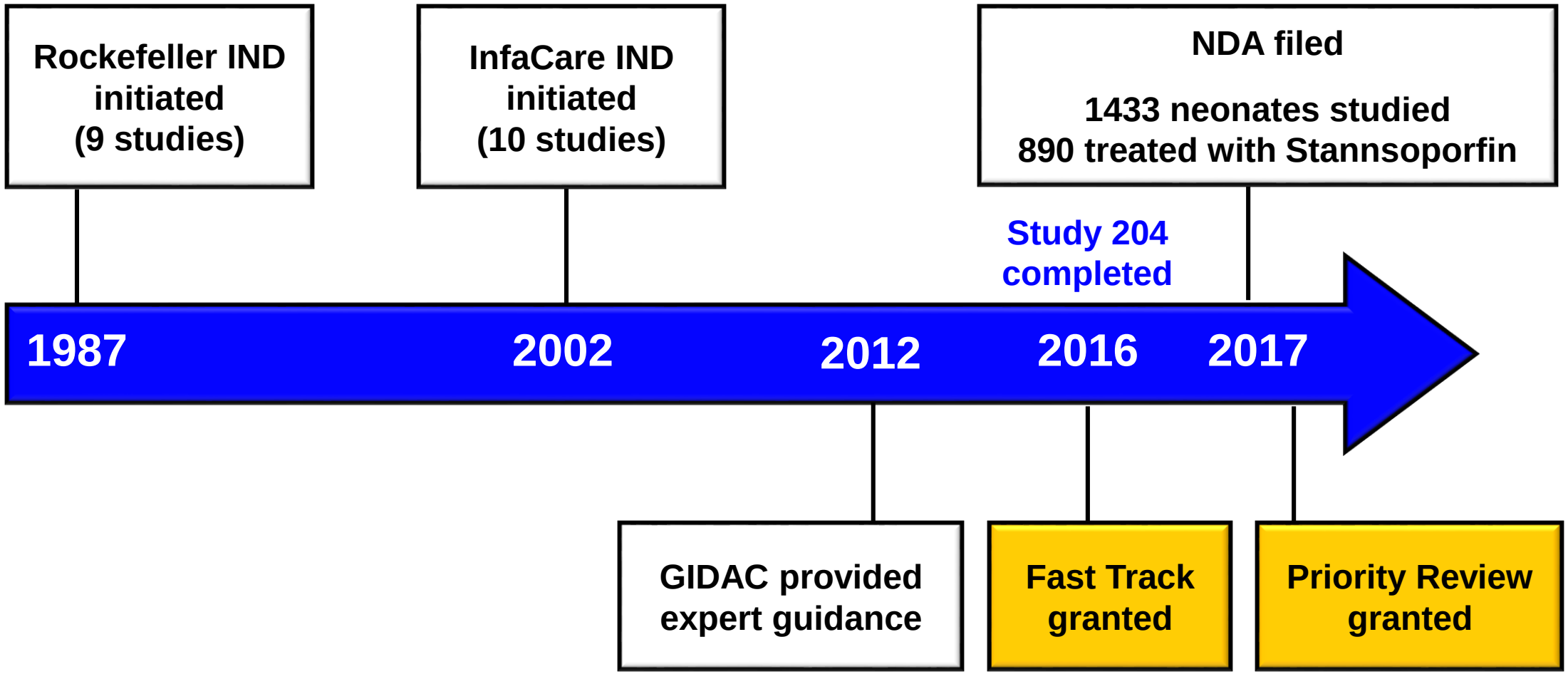
Stannsoporfin: First Pharmacotherapy to Effectively Treat Neonatal Hyperbilirubinemia

- Stannsoporfin studied with and without phototherapy
- Mechanism of action does not require phototherapy
- Inhibits bilirubin production at its source
- Rapid, sustained reduction in total serum bilirubin (TSB)

Stannsoporfin Novel Mechanism of Action Targets Bilirubin Production



Two Investigational New Drug Applications Support Efficacy and Safety of Stannsoporfin



Stannsoporfin Preclinical Program

6 Radiolabeled ADME Studies

- After IV/IM Administration
  - Neonatal rats
  - Neonatal dogs

12 Safety Pharmacology Studies

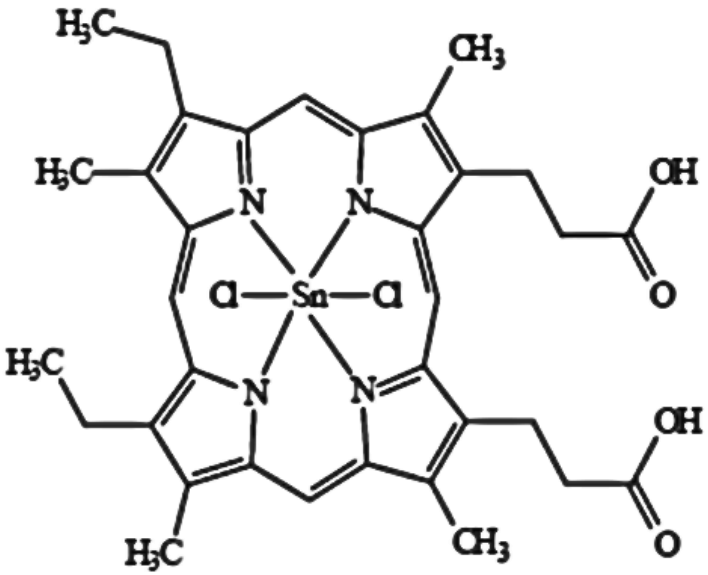
- Cardiac, renal and CNS

27 Toxicology Studies

- Acute and repeat dose
- Genotoxicity/mutagenicity
- Juvenile animals and local tolerance
- Phototoxicity reproductive

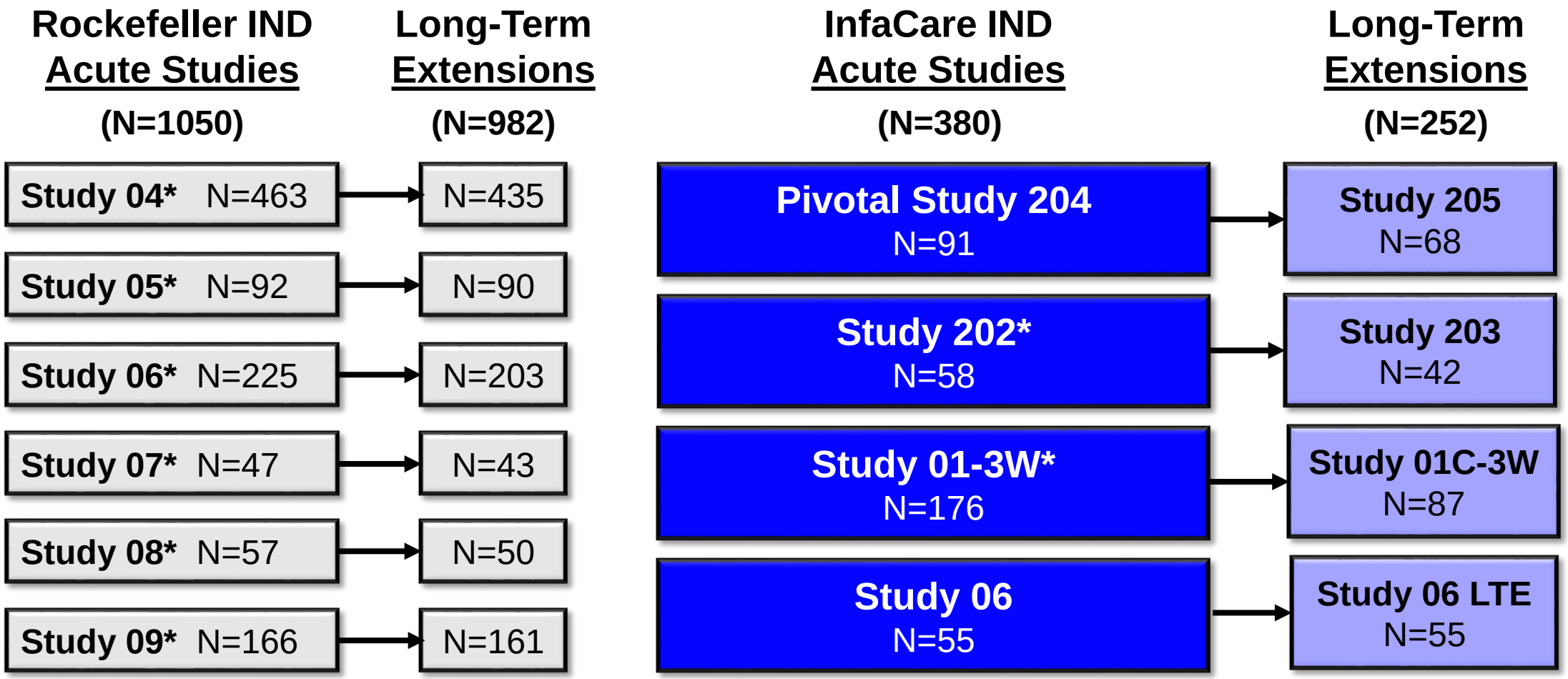
Stannsoporfin Preclinical Program Supports Favorable Safety Profile With Clinically Relevant Doses

- Stannsoporfin is 754-Dalton tin mesoporphyrin
  - Does not readily cross blood brain barrier
  - > 96% protein bound
  - No major metabolites identified
  - Intact excretion in urine and bile



- No neuropathology in any toxicology study
- No effects seen in rat development study
- No mechanistic basis for theoretical long-term risk

Stannsoporfin Clinical Development Program



* Studied stannsoporfin without phototherapy

Single Stannsoporfin 4.5 mg/kg Intramuscular (IM) Injection Demonstrated Efficacy and Safety

- Results in statistically significant and clinically meaningful reduction in TSB
  - In hemolyzing neonates for whom phototherapy is indicated
  - Guidelines for TSB intervention broadly used by hospitals
- Favorable short- and long-term safety profile
- Rockefeller studies provide evidence of consistent stannsoporfin benefit and replicate TSB effect

Stannsoporfin Proposed Indication

- Stannsoporfin inhibits bilirubin production and is indicated for the treatment of neonates ≥ 35 weeks of gestational age, with indicators of hemolysis, at risk of developing severe hyperbilirubinemia

Sponsor Commitment to Collect Additional Safety Data Through Future Studies

- Robust Risk Management Plan to collect long-term data
  1. Facilitating access to appropriate patient population
  2. Educating prescribers and parents
  3. Collecting and reporting long-term safety data

Agenda

Unmet Need	**Jeffrey Maisels, MD, DSc** Chair Emeritus and Professor Department of Pediatrics Oakland University William Beaumont School of Medicine
Clinical Pharmacology, Efficacy and Safety	**Nancy Ruiz, MD** Senior Medical and Clinical Advisor InfaCare, A Mallinckrodt Pharmaceuticals Company
Long-Term Neurodevelopmental Safety	**Dawn Phillips, PhD, PT, MS** Research Scientist Evidera
Risk Management Plan	**Lawrence A. Hill, PharmD, MBA**
Benefit-Risk / Clinical Perspective	**Jeffrey Maisels, MD, DSc**

Additional External Experts

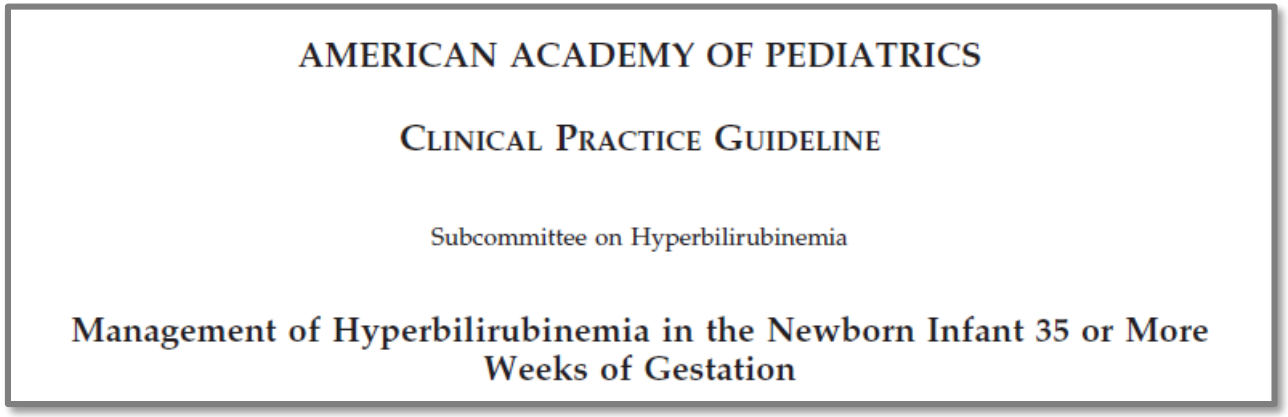
Vinod Bhutani, MD	**Neonatology** Professor of Pediatrics Division of Neonatal and Developmental Medicine Stanford University School of Medicine Lucile Packard Children's Hospital
Martin Roessner, MS	**Statistics** Corporate Vice President, Global Biostatistics PAREXEL
Simon Tulloch, BM, Bch	**Rockefeller IND Studies** Consultant Previous Chief Medical Officer InfaCare, A Mallinckrodt Pharmaceuticals Company

Unmet Need

Jeffrey Maisels, MD, DSc

Chair Emeritus and Professor
Department of Pediatrics
Oakland University William Beaumont School of Medicine

American Academy of Pediatric Guidelines


AMERICAN ACADEMY OF PEDIATRICS

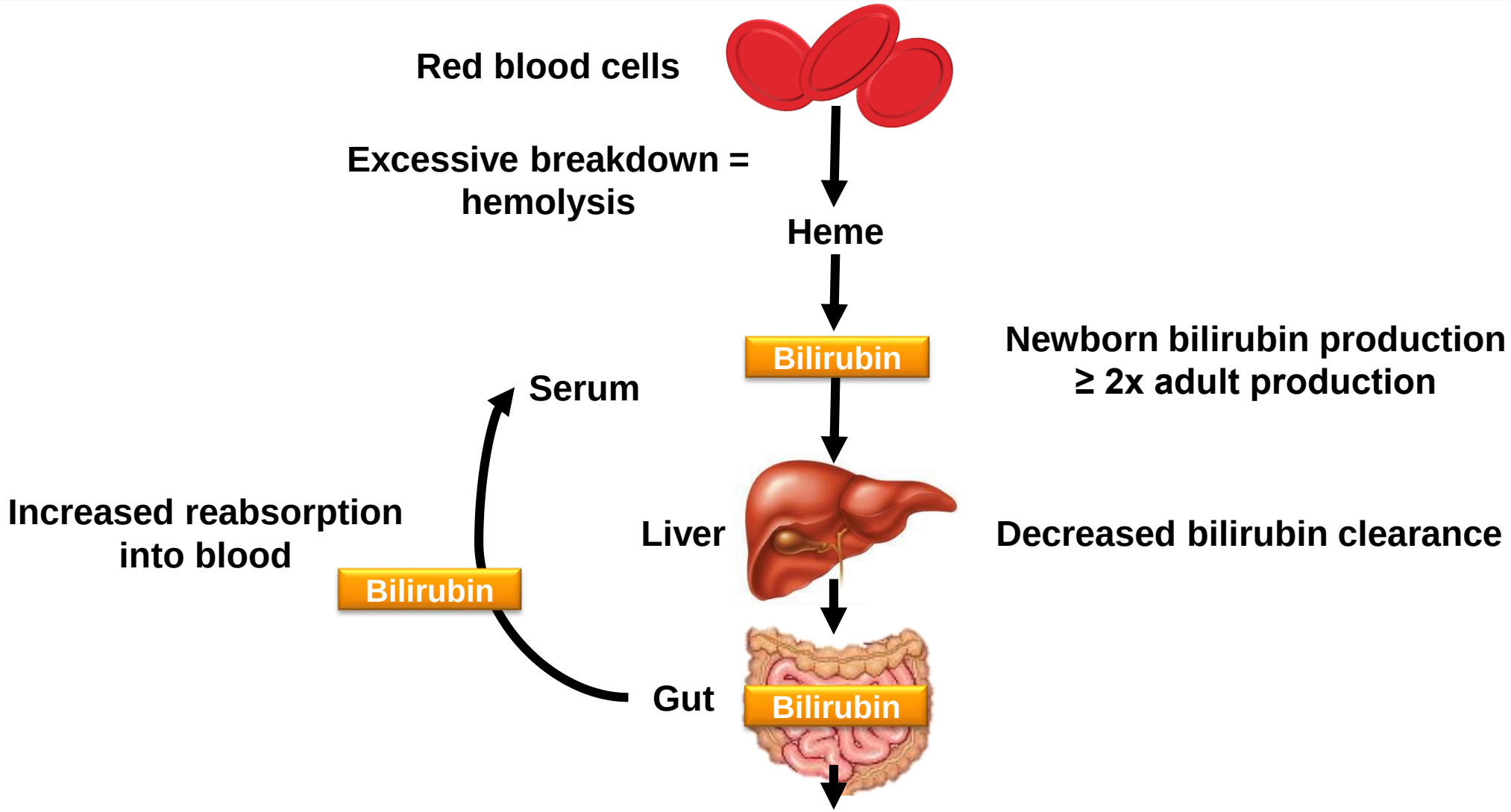
CLINICAL PRACTICE GUIDELINE

Subcommittee on Hyperbilirubinemia

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

- Primary author
  - 2004 AAP guidelines
  - 2009 update of guidelines

Newborn Bilirubin Metabolism – Normal Breakdown of Aging Red Blood Cells



8 out of 10 Newborns Jaundiced in First Week

- Newborns
  - Produce more bilirubin
  - Have decreased ability to clear bilirubin
  - Reabsorb bilirubin from gut
- Excessive levels of bilirubin in blood can cross blood brain barrier and cause brain damage

Infant's Serum Bilirubin Reflects Rate of Bilirubin Production and Elimination

- When rate of production exceeds ability to clear, serum bilirubin level rises
- Almost every newborn is jaundiced in first week of life
  - Primarily due to babies producing too much bilirubin
- For majority, bilirubin level only a concern if increases to point requiring intervention

Neonatal Hyperbilirubinemia Treated With Phototherapy for > 60 years

- Each year in US, ~7% of babies ≥ 35 weeks gestation (~260,000) receive phototherapy[1,2]
  - About two-thirds receive phototherapy before discharge
    - Most are hemolyzing
  - One-third readmitted for phototherapy
- Jaundice is a leading causes of hospital readmissions[3]

1. Maisels, J Perinatol, 2015. 2. Chang et al., Pediatrics, 2017. 3. Young et al., Pediatrics, 2013.

Therapeutic Limitations of Phototherapy

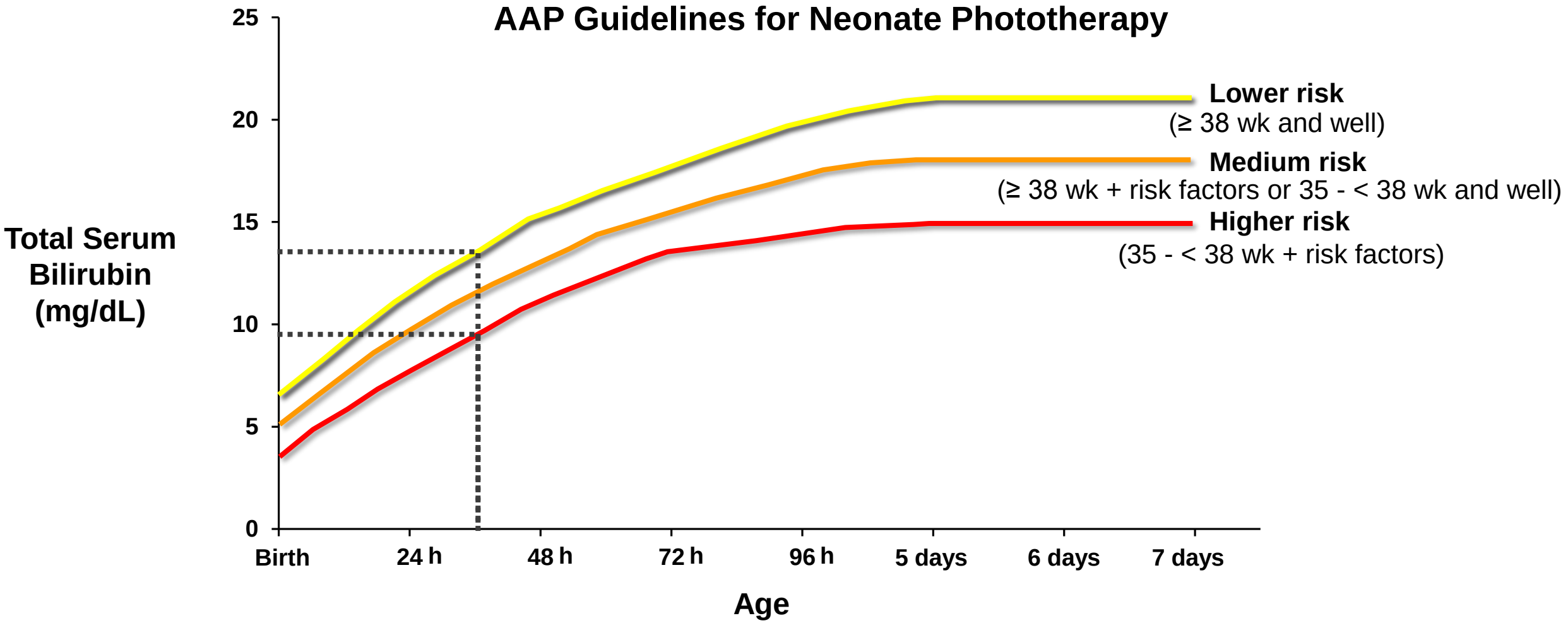
- Removes excess bilirubin, does not inhibit production
- Does not always lower or prevent bilirubin from rising
  - Requires prolonged light exposure or need for exchange transfusion
- Rebound TSB requires repeat phototherapy in ~ 5% of infants[1]
  - Rebound occurs in as many as 28% of infants with hemolytic disease[2]

1. Chang Pediatrics 2017.
2. Barak, Acta Pediatrica 2008.

Total Serum Bilirubin (TSB) is Key Parameter in Management of Hyperbilirubinemia

- TSB tells us when to
  - Start, stop, restart phototherapy
  - Use off-label blood products (IVIg)
  - Perform exchange transfusion
  - Discharge baby from hospital
  - Readmit for phototherapy

AAP Guidelines for Initiating Phototherapy Use TSB, Gestational Age and Various Risk Factors



Adapted from AAP, 2004.

Phototherapy Does Not Directly Address Root Cause of Hyperbilirubinemia

- Inability to quickly lower bilirubin level can lead to
  - More severe hyperbilirubinemia
  - Extended need for phototherapy and time for mother and newborn in hospital
  - Need for exchange transfusion

Phototherapy Separates Baby From Mother

- Babies placed in bassinet or incubator
  - Intensive blue light
  - Diaper and eye protection
- Under lights continuously
- Removed for short periods for feeding

Separation Disrupts Breastfeeding and Mother-Infant Bonding[1]

- Breastfeeding benefits well-established
- The longer the need for PT, the longer the separation
- Mothers report feeling “robbed” of bonding time and worried about ability to bond, touch, breastfeed[2,3]
  - Particularly if moms discharged before infants
- Eye covering prevents face to face contact, mutual recognition

Sooner bilirubin level decreases,
the sooner infant and mother can reunite

1. Szucs and Rosenman, Pediatrics, 2013.
2. Brethauer and Carey, Am J Maternal/Child Nursing, 2010.
3. Hannon et al., Arch Pediatr Adolesc Med, 2001.

Need to Advance Treatment Options for Neonates with Hyperbilirubinemia

- No pharmacologic options inhibit bilirubin production
- Need safe therapy to directly address bilirubin production that
  - Reduces the duration of intensive PT
  - Reduces restarts of PT and rehospitalization
  - Decreases rate of PT failures
  - Supports mother-infant bonding and breastfeeding
- Meaningful addition to available therapies in US

Clinical Pharmacology, Stannsoporfin Efficacy and Safety

Nancy M. Ruiz, MD

Senior Medical and Clinical Advisor

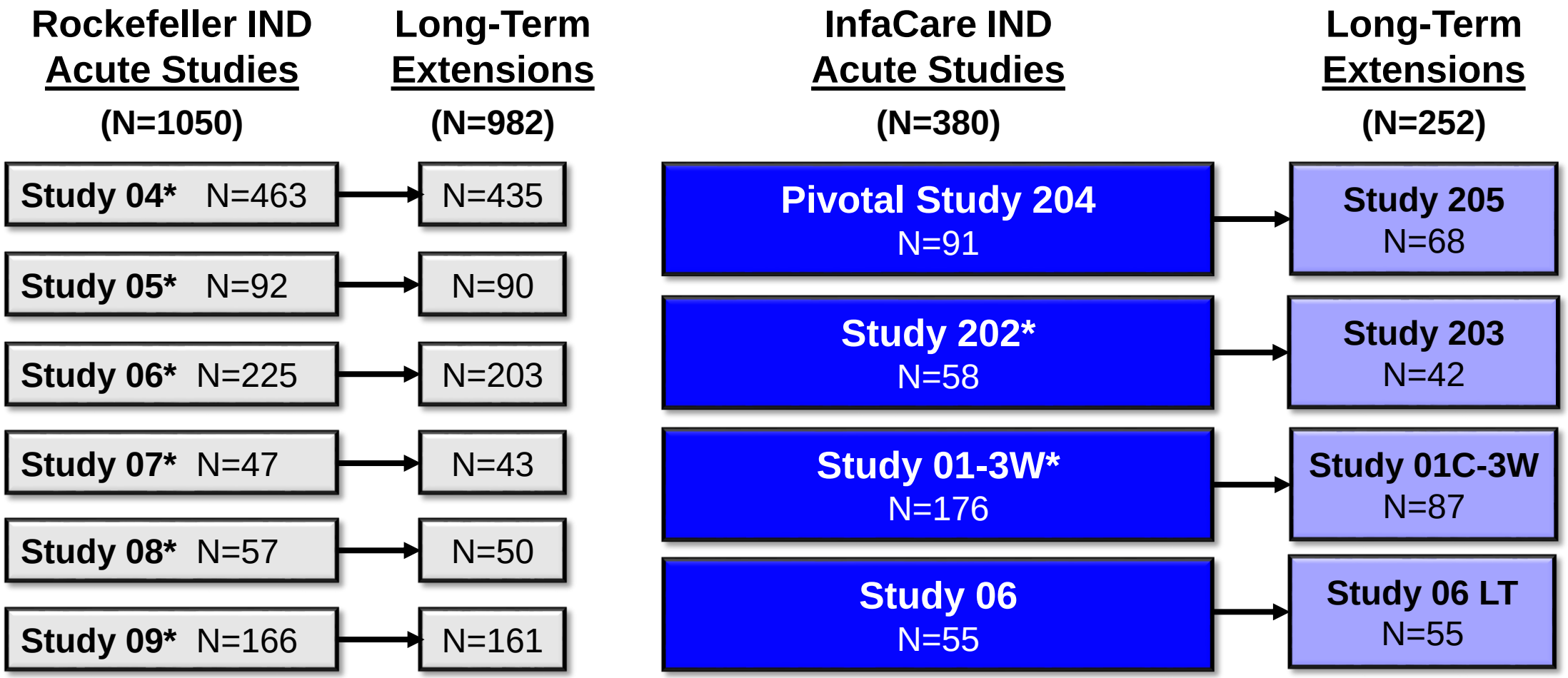
InfaCare

A Mallinckrodt Pharmaceuticals Company

Pharmacokinetic Parameter Estimates of Stannsoporfin

- All doses rapidly and well absorbed
- Peak concentrations observed in 1-2 hours
- Terminal elimination half-life: ~10 hours
- Dose-proportional increase in C_{max} (1.5 to 4.5 mg/kg)
  - Slightly more than dose-proportional increase in AUC of ~20-25% (3.0 to 4.5 mg/kg dose)

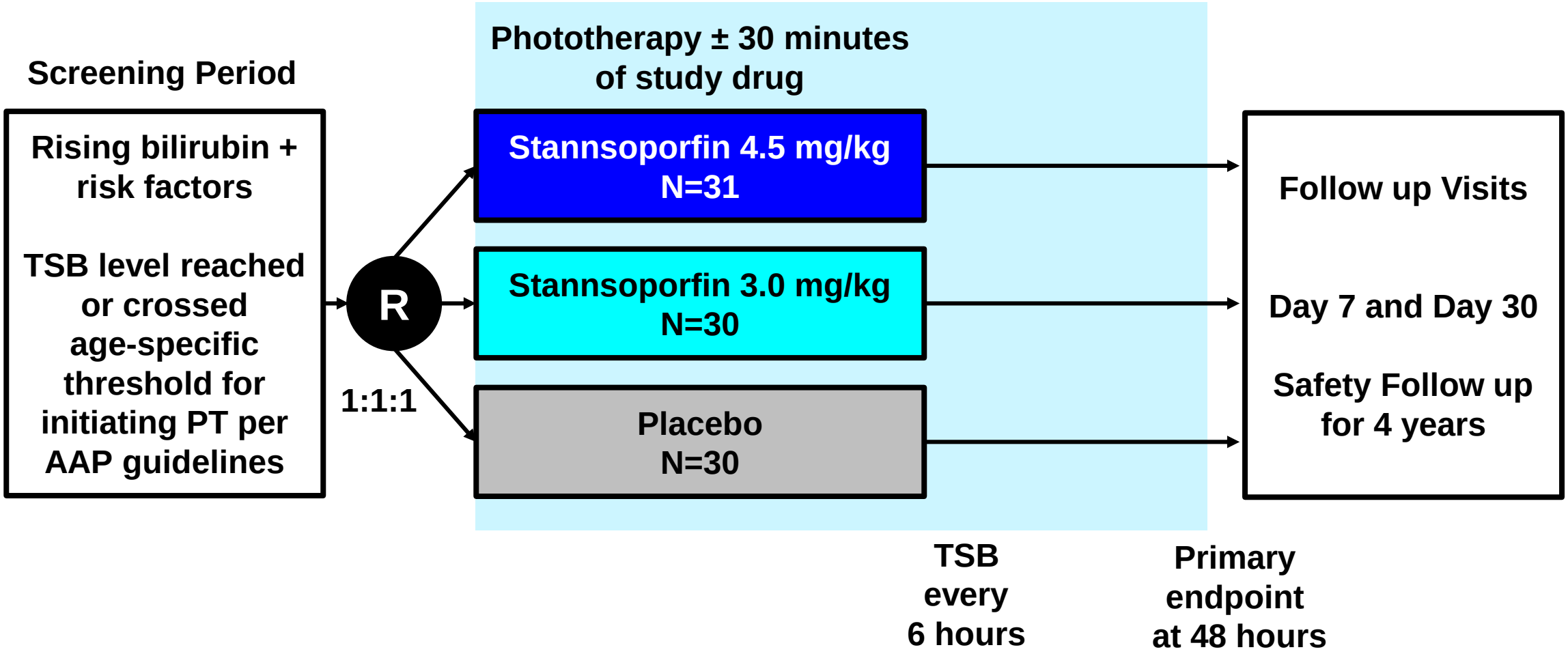
Stannsoporfin Efficacy Studies



* Studied stannsoporfin without phototherapy

Study 204 (Pivotal)

Study 204: Randomized, Controlled Study Design



Study 204: Inclusion Criteria

- Gestational age (GA) ≥ 35 and < 43 weeks
- At or above the threshold for PT (rapidly rising bilirubin)
- ABO / Rh incompatibility
- Coombs positive OR
- Coombs negative with reticulocyte > 6%

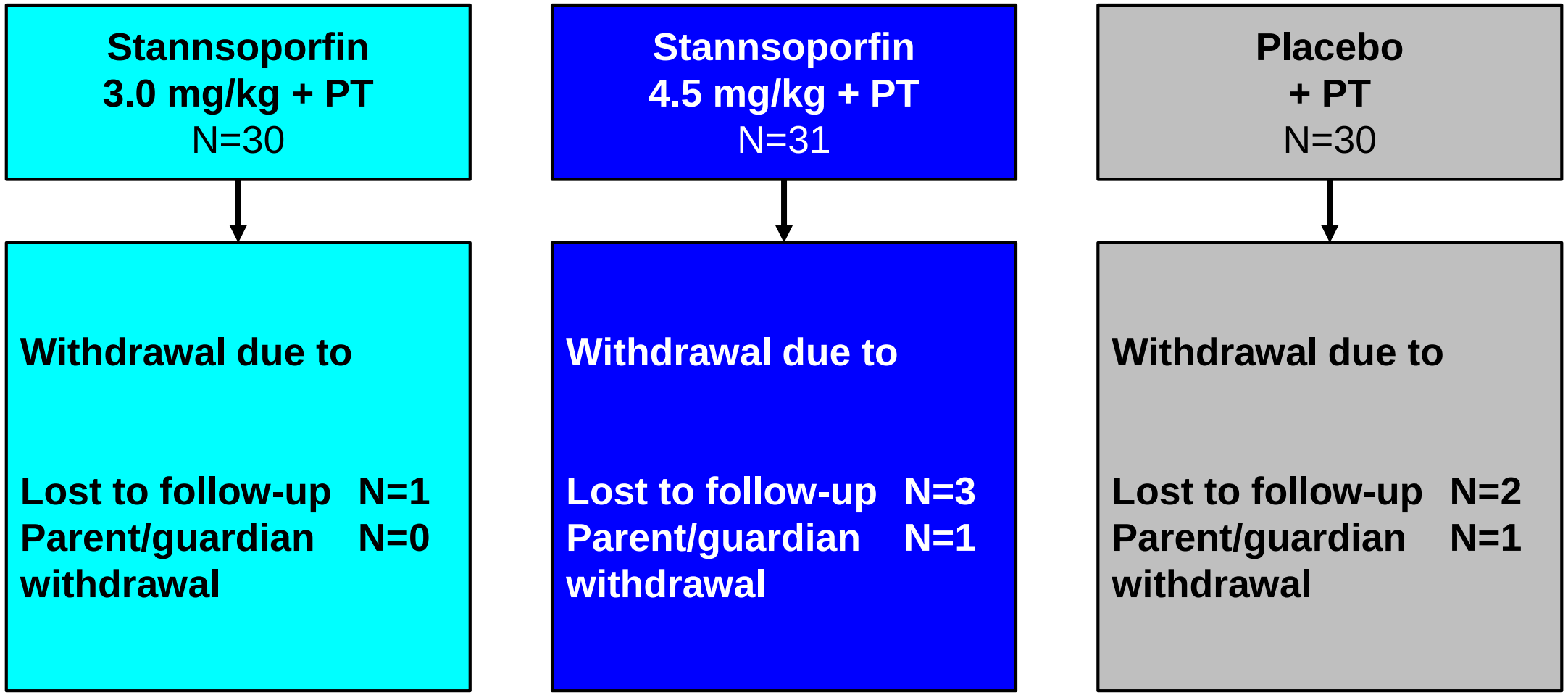
Study 204 Primary Endpoint

- Percent change from baseline in TSB at 48 hours post-dose
- Change in TSB
  - Addresses primary concern in neonatal hyperbilirubinemia
  - Provides clinical meaningfulness
  - Enables other clinically meaningful benefits

Study 204 Key Prespecified Secondary Endpoints

- Time at which TSB crosses at or below defined threshold for discontinuation of phototherapy
- Phototherapy failure defined as
  - Restart of phototherapy > 6 hours after stopping
  - Rehospitalization for hyperbilirubinemia
  - Use of intravenous immunoglobulin (IVIg)
  - Need for exchange transfusion
- Rebound hyperbilirubinemia
  - Increased TSB crossing phototherapy threshold ≤ 54 hours after discontinuation

Study 204 Disposition Similar Across Treatment Groups



ITT Analysis Set

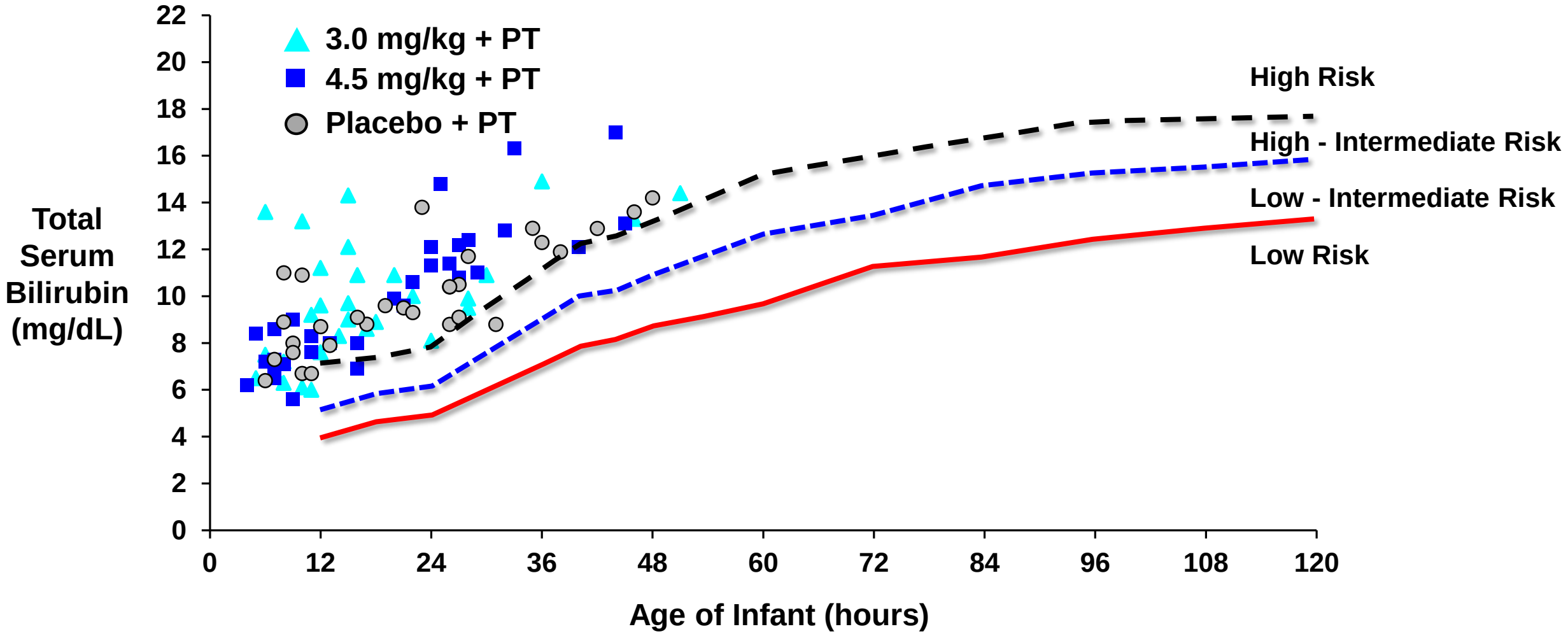
Study 204: Baseline Characteristics Balanced Across Treatment Groups

	Stannsoporfin 3.0 mg/kg + PT N=30	Stannsoporfin 4.5 mg/kg + PT N=31	Placebo + PT N=30
Gestational age, wk, mean (SD)	38.9 (1.23)	39.0 (1.21)	38.9 (1.09)
Direct Coombs test positive	96.7%	93.5%	90.0%
Age at time of dosing, h, mean (SD)	21.2 (11.45)	23.6 (11.04)	25.5 (12.31)
Birth weight, g, mean (SD)	3290.0 (478.10)	3347.4 (460.65)	3295.2 (404.05)
Bilirubin, mg/dL, mean (SD)	9.82 (2.64)	9.97 (2.97)	9.92 (2.21)

- All patients entered study within first 48 hours
  - 65% before the first 24 hours of life for 4.5 mg/kg

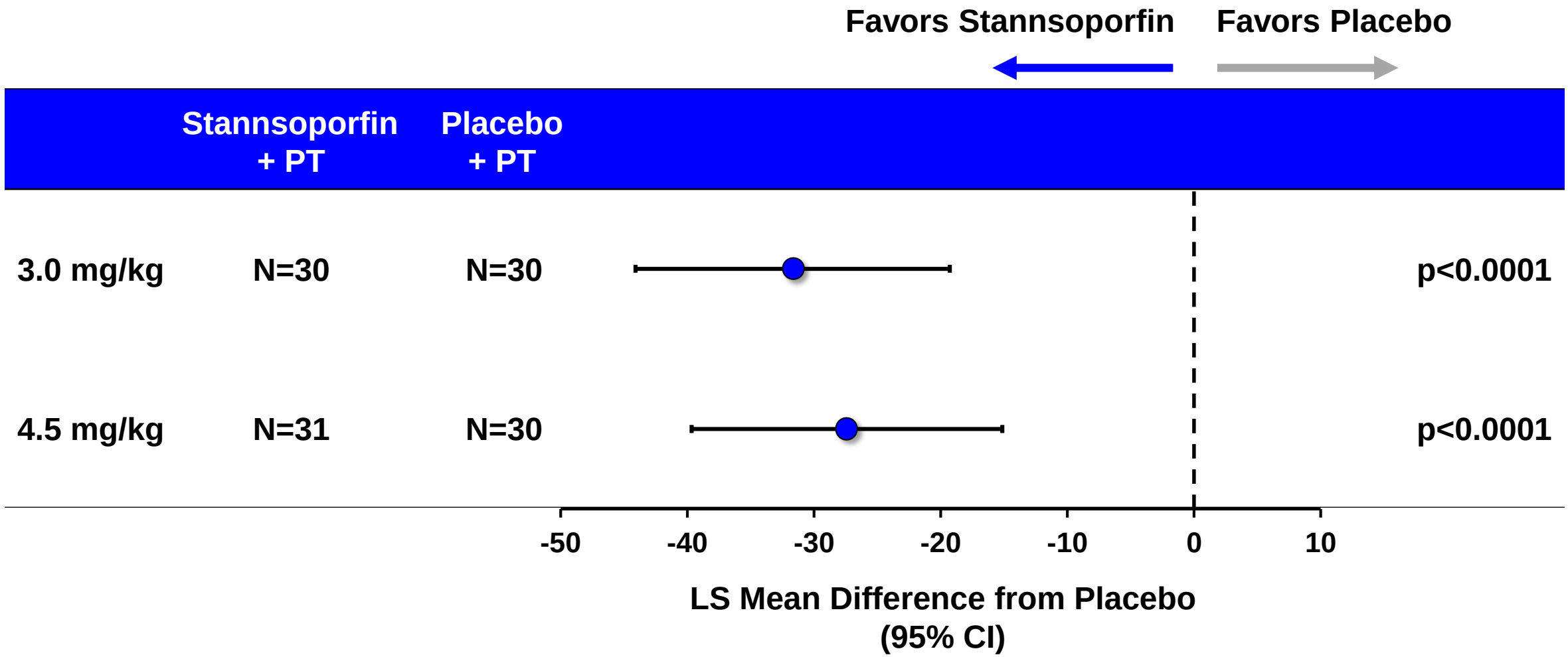
ITT Analysis Set

Study 204: Baseline TSB Levels on Bhutani Nomogram



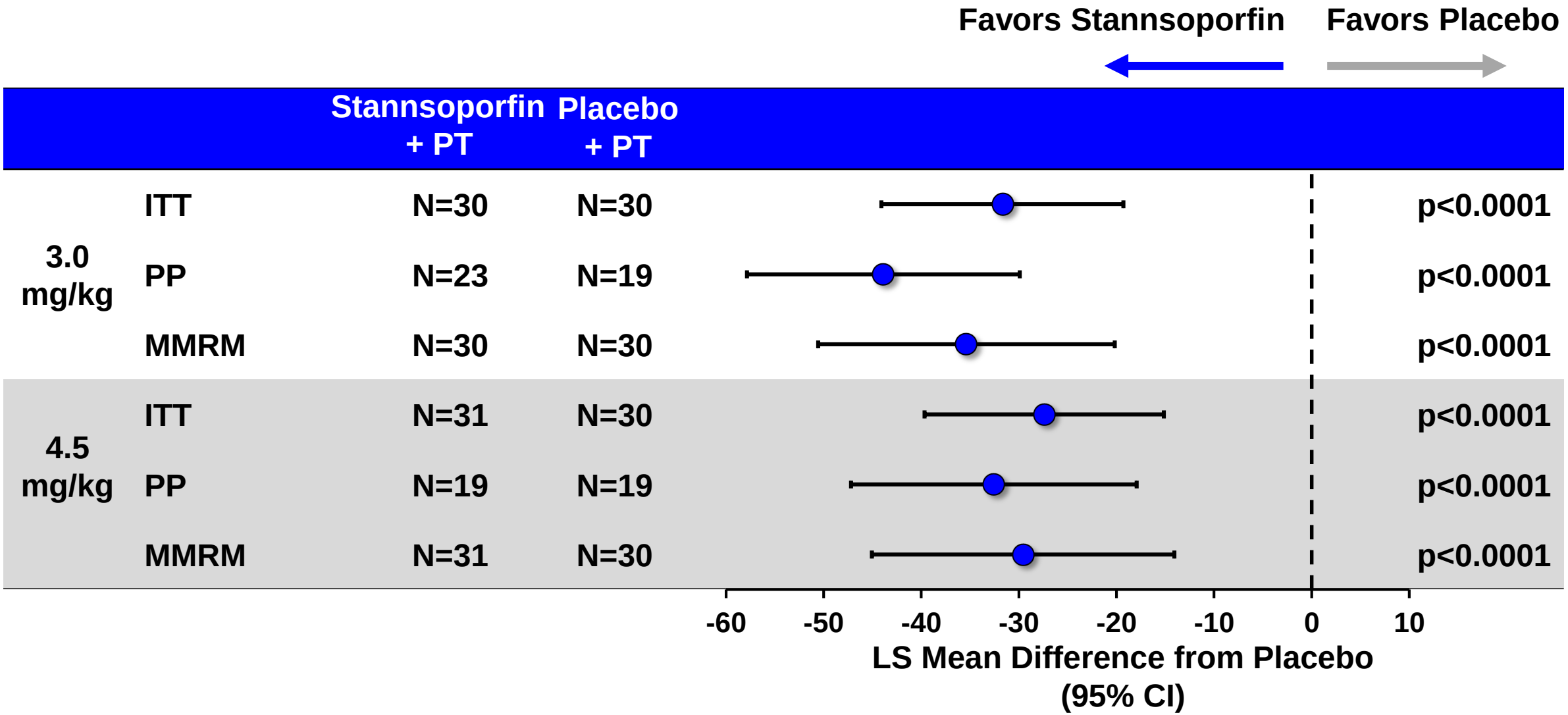
Adapted from Bhutani nomogram

Study 204: Stannsoporfin Superior to Placebo in Decreasing TSB Percent Change from Baseline at 48 Hours

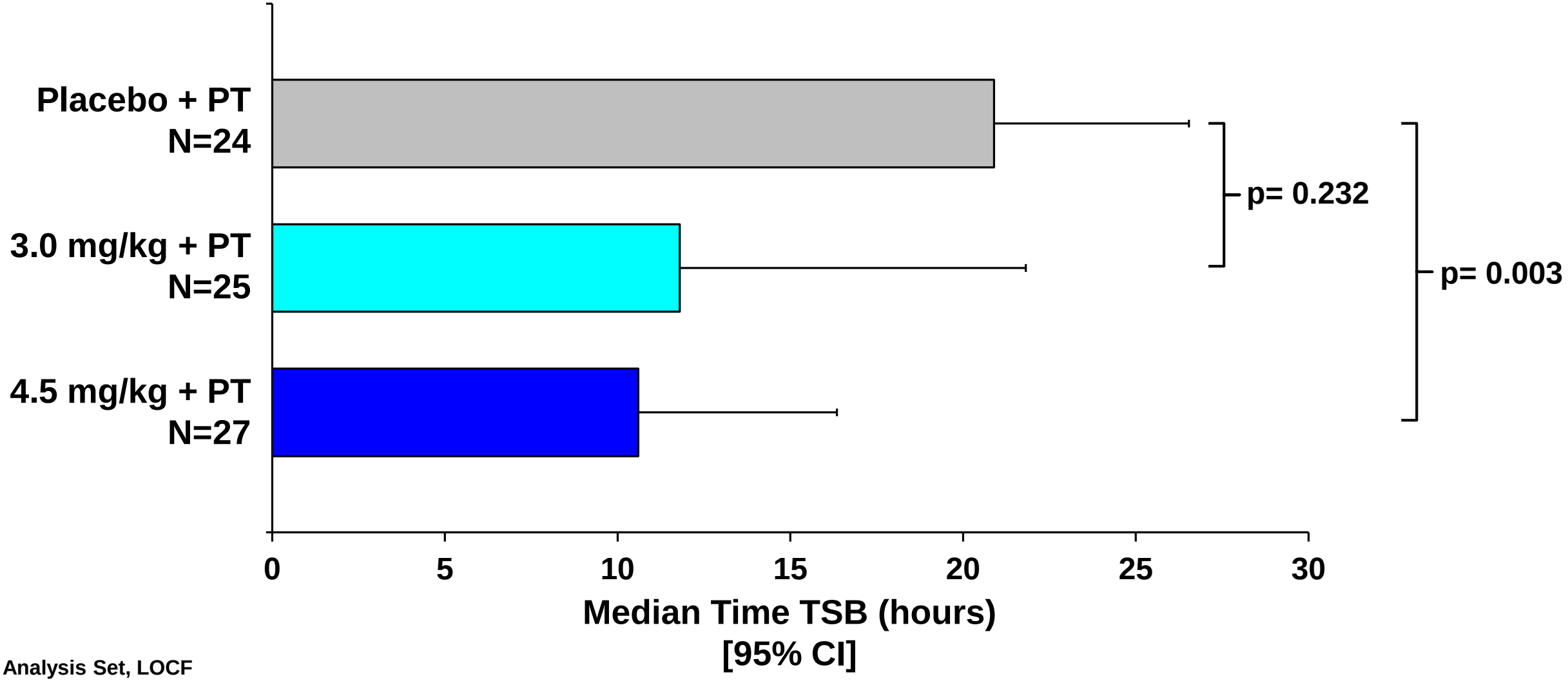


ITT Analysis Set, LOCF

Study 204: Sensitivity Analyses Verified Primary Endpoint Results

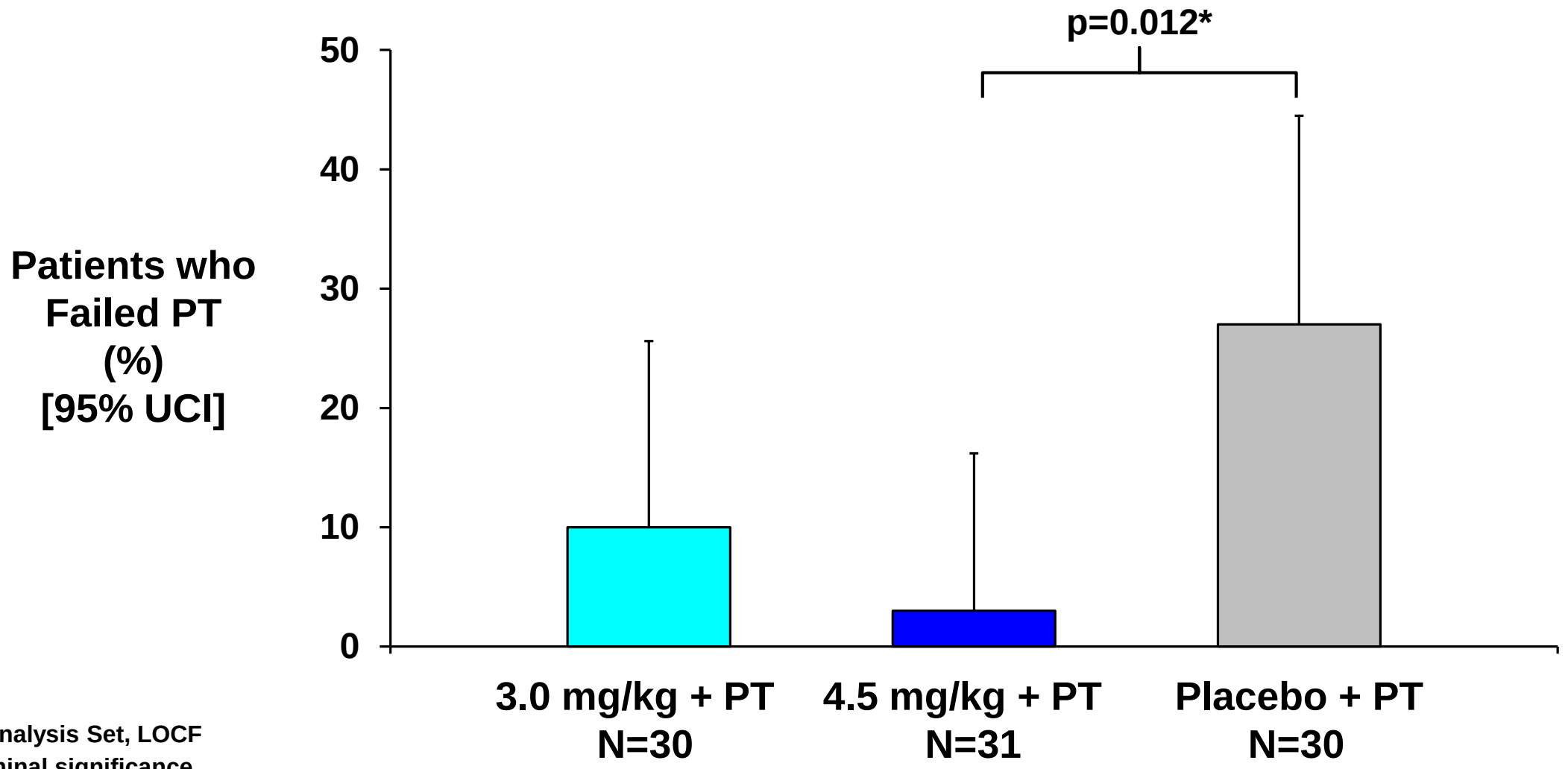


Study 204: Median Time to Crossing Threshold for PT Discontinuation Sooner for Stannsoporfin 4.5 mg/kg



ITT Analysis Set, LOCF

Study 204: Stannsoporfin Reduced Frequency of Phototherapy Failure



ITT Analysis Set, LOCF
* nominal significance

Study 204: Fewer Phototherapy Failures in Patients Receiving Stannsoporfin 4.5 mg/kg

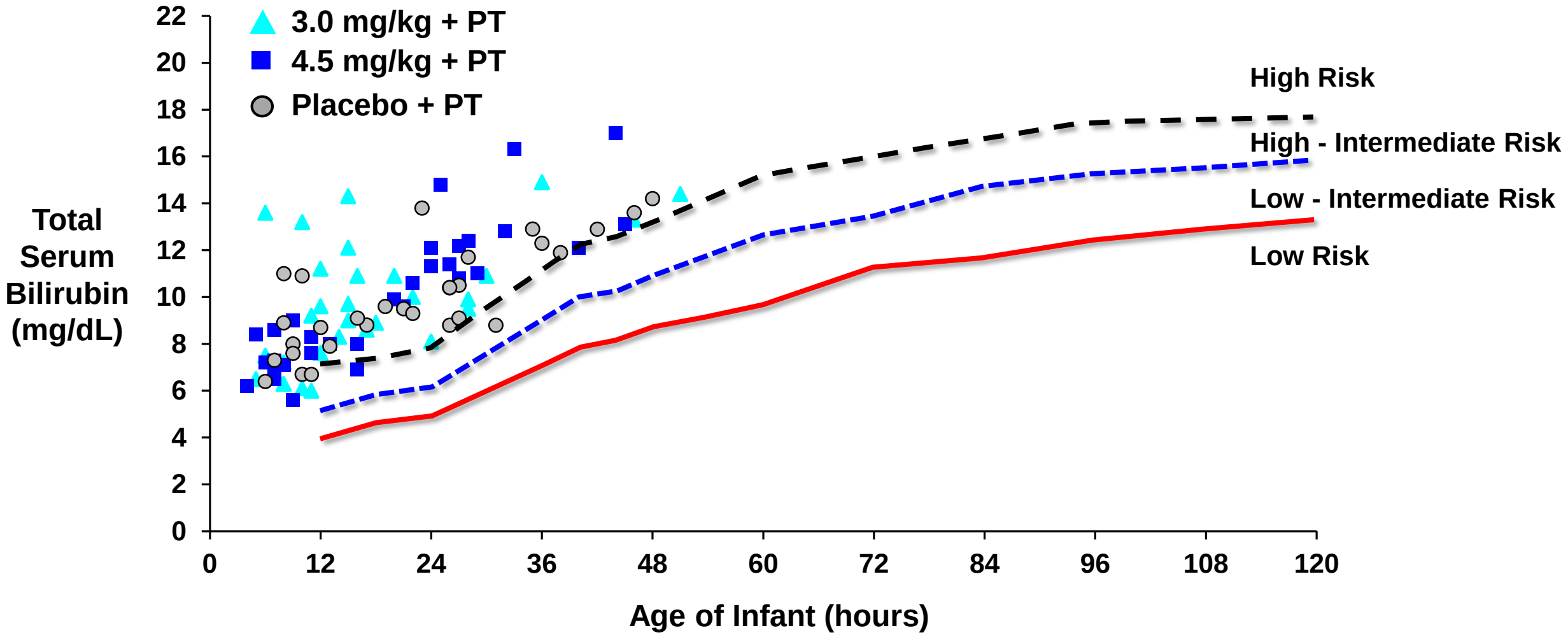
Patients Reasons	Stannsoporfin 3.0 mg/kg + PT N=30 n	Stannsoporfin 4.5 mg/kg + PT N=31 n	Placebo + PT N=30 n
Patients with failure (could have ≥ 1 reason)	3	1	8
Required exchange transfusion	1	0	0
Hospital readmission for hyperbilirubinemia	0	1	3*
Restarted phototherapy	1	1	8†
IVIg used	1	0	1
p-value		p=0.012**	

* 4 events in 3 patients
† 9 events in 8 patients
** nominal p-value is for overall patients with failure for stannsoporfin 4.5 mg/kg (n=1) vs placebo (n=8)

Study 204 Demonstrated Stannsoporfin 4.5 mg/kg Statistically Superior to Placebo

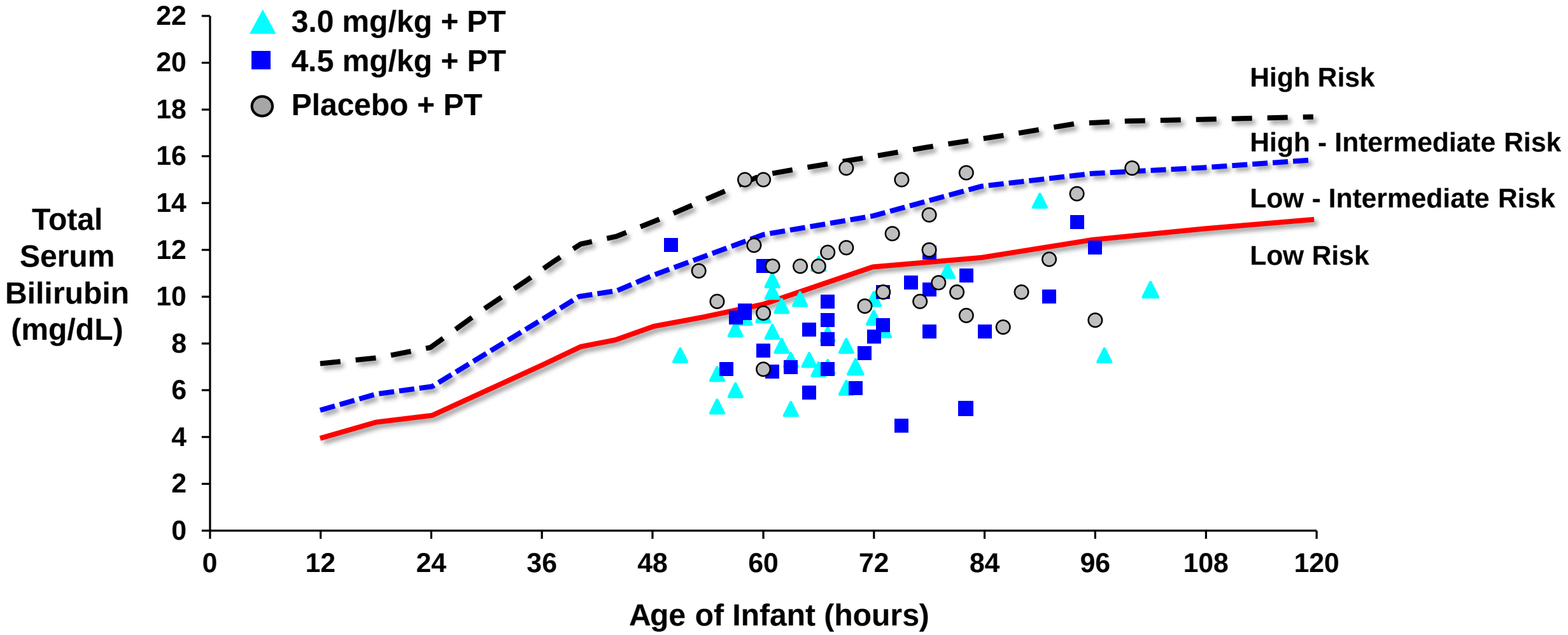
- Statistically significant and clinically meaningful reduction from baseline TSB at 48 hours
- Reduced time for TSB levels to cross AAP threshold for discontinuing phototherapy
- Decrease in phototherapy failures including
  - Rehospitalization
  - Restart of phototherapy

Study 204: Baseline TSB Levels on Bhutani Nomogram



Adapted from Bhutani nomogram

Study 204: 87% of Patients on Stannsoporfin 4.5 mg/kg Shifted from High to Low Risk vs 40% of Placebo Group



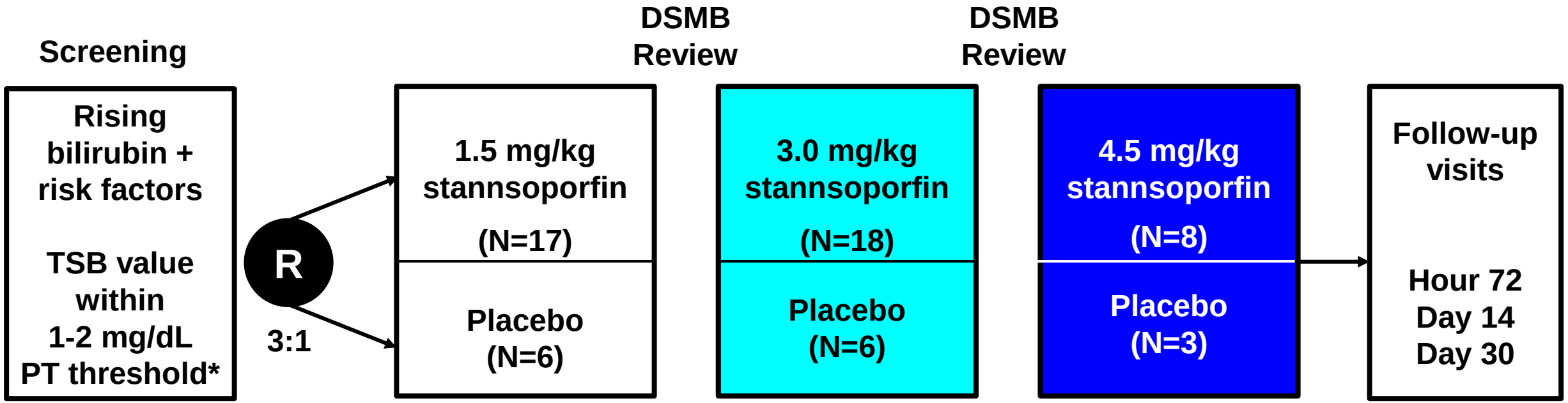
Adapted from Bhutani nomogram

Study 204 Meets Regulatory Characteristics of Highly Persuasive Single Pivotal Trial

- Data from a multicenter study
- Highly statistically persuasive evidence
- Internal consistency across study subgroups
- Evidence of effect on multiple endpoints
- Consistency across various sensitivity analyses
- Consistency among supportive studies

Study 202

Study 202 Design: Study Entry 1-2 mg/dL Below Phototherapy Threshold



- TSB every 6 hours
- PT started if TSB crossed PT threshold*

Safety follow-up for 4 years

*** according to 2004 AAP guidelines**

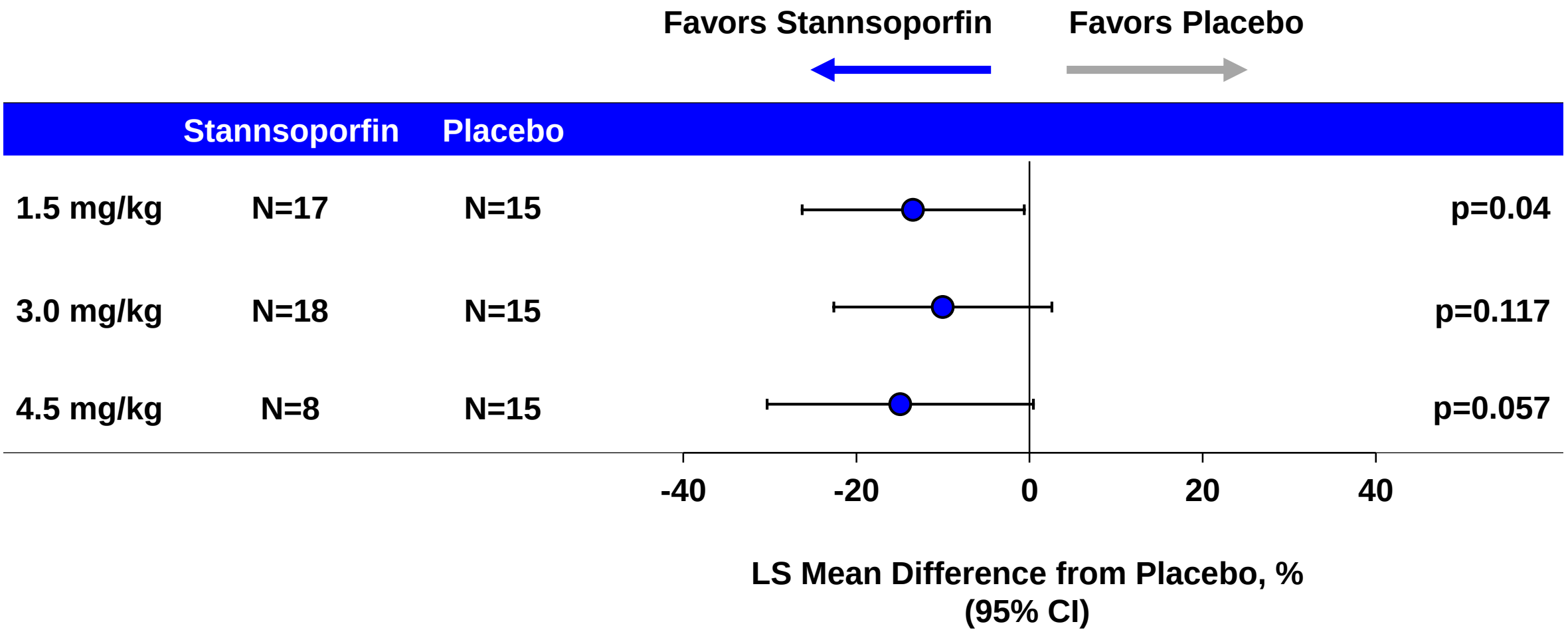
Study 202: Primary Endpoint

- Change in adjusted TSB from baseline to 48 hours after treatment
  - TSB adjusted for age-specific phototherapy threshold TSB value

Study 202: Key Secondary Endpoints

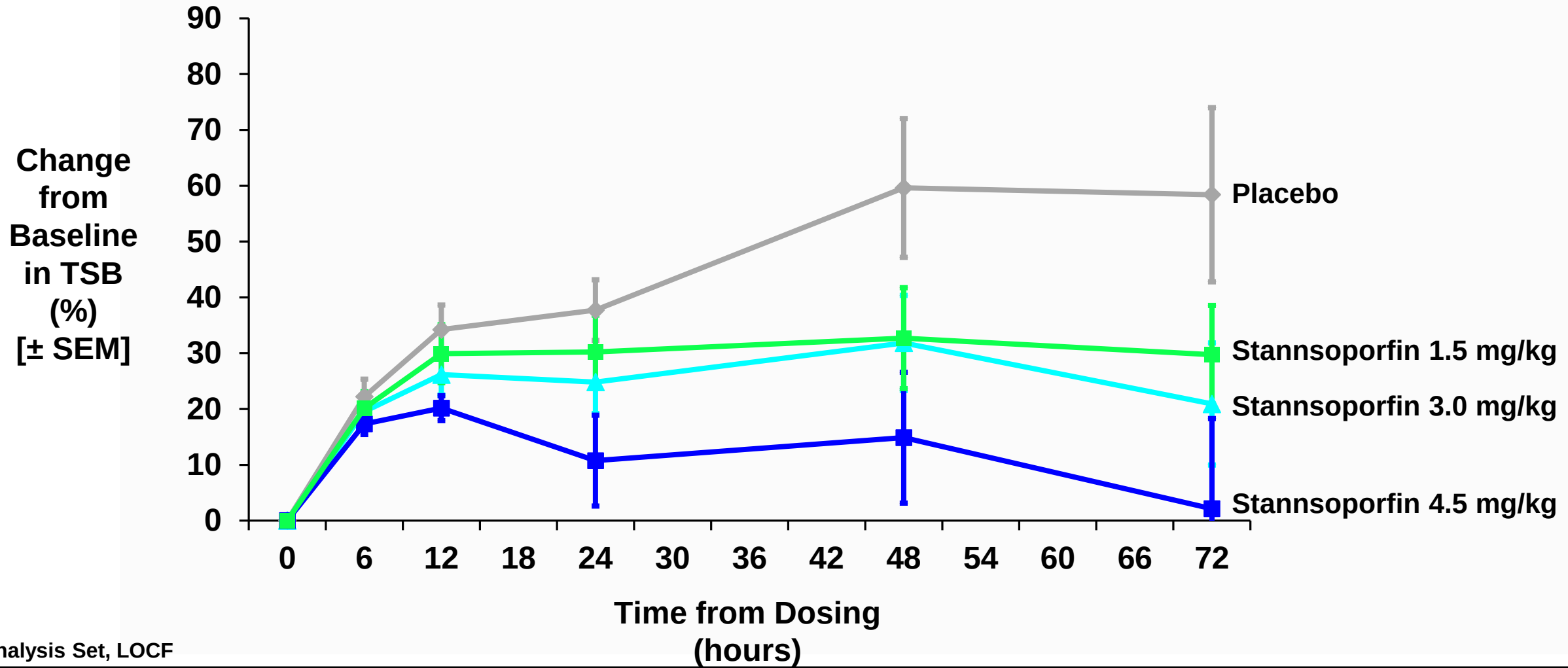
- Change from baseline in TSB at 48 hours after treatment
- Patients requiring phototherapy or exchange transfusion

Study 202: Change in Adjusted TSB Favored Stannsoporfin 4.5 mg/kg at 48 Hours vs Placebo



ITT Analysis Set, LOCF
Placebo patients pooled

Study 202: Stannsoporfin 4.5 mg/kg Demonstrated Earlier Onset of Effect Compared to Placebo



ITT Analysis Set, LOCF

Study 202: Stannsoporfin 4.5 mg/kg Reduced Need for Phototherapy by 50%

	Stannsoporfin 1.5 mg/kg N=17		Stannsoporfin 3.0 mg/kg N=18		Stannsoporfin 4.5 mg/kg N=8		Placebo N=15	
Phototherapy required	3	(17.6%)	6	(33.3%)	2	(25.0%)	8	(53.3%)
Exchange transfusion required	0	–	0	–	0	–	0	–
Hospital readmission	0	–	0	–	0	–	2	(13.3%)

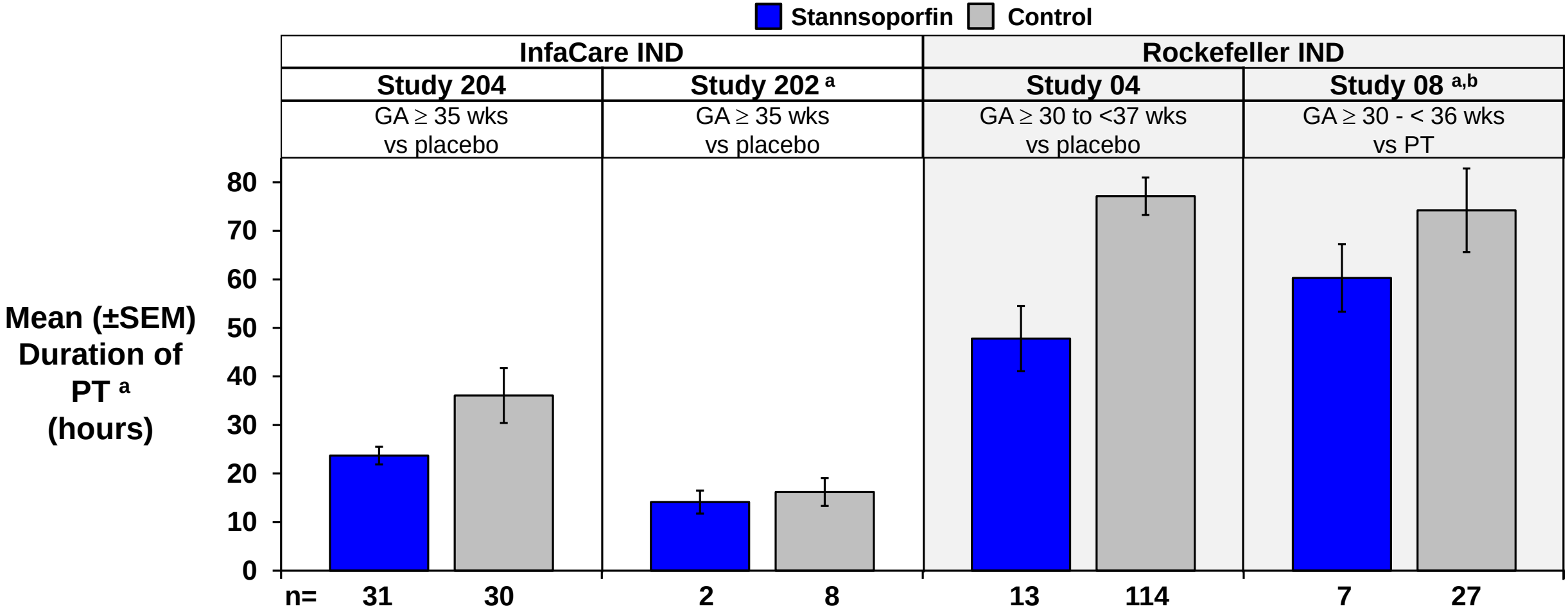
Study 202 Provides Supportive Data Demonstrating Reduction in TSB

- More favorable change from baseline in TSB at 48 hours post-dose vs placebo
- Confirmed dose selection of 4.5 mg/kg from Rockefeller studies
- Supportive evidence for Study 204 secondary endpoints

Rockefeller IND

Studies 04, 05, 06, 07, 08, 09

Stannsoporfin 4.5 mg/kg Consistently Reduced Duration of PT Across INDs



a. Values based on total number of patients who required PT
b. Studies 202 and 08 were discontinued prior to fully enrolling patients
No patients in 05 and 09 required PT

Stannsoporfin 4.5 mg/kg Effectively Treats Neonatal Hyperbilirubinemia

- Pivotal study 204
  - Highly statistically persuasive evidence
  - Internal consistency across subgroups and endpoints
- Study 202 and Rockefeller IND
  - Consistently supportive results
- Consistency of data across both INDs supports proposed indication

Stannsoporfin Clinical Safety

Stannsoporfin Development Program Included >1400 Neonates (890 Stannsoporfin Exposures)

	Stannsoporfin Dose (mg/kg)						All Doses + Control
	0.75	1.5	2.25	3.0	4.5	All Doses	
	Neonates Treated (N)						
InfaCare IND	19	35	0	48	129	231	383
Rockefeller IND	50	59	32	59	459	659	1050
Total	69	94	32	107	588	890	1433

Safety Methodology and Data Pooling

Rockefeller IND Pooled Acute Studies
(N=1050)

- **Study 04*** N=463
- **Study 05*** N=92
- **Study 06*** N=249
- **Study 07*** N=47
- **Study 08*** N=101
- **Study 09*** N=166

Pivotal Study 204
(N=91)

- **Pivotal Study 204**

InfaCare IND Acute Pooled Studies
(N=325)

- **Pivotal Study 204** → **Study 205**
- **Study 202*** → **Study 203**
- **Study 01-3W*** → **Study 01C-3W**

Pooled Long-Term Extensions
(N=197)

*Studied stannsoporfin without phototherapy

Study 204: Overall Safety Profile

	Stannsoporfin 3.0 mg/kg + PT N=30	Stannsoporfin 4.5 mg/kg + PT N=31	Placebo + PT N=30
TEAEs	93%	68%	73%
SAEs	17%	13%	20%
AE leading to discontinuation	0	0	0
Deaths	0	0	0

Study 204: Most Common TEAEs (> 2 Neonates in Any Treatment Group)

Preferred terms in > 2 of patients	Stannsoporfin 3.0 mg/kg + PT N=30	Stannsoporfin 4.5 mg/kg + PT N=31	Placebo + PT N=30
Any TEAE	93%	68%	73%
Erythema	20%	20%	3%
Rash	33%	16%	20%
Rash neonatal	20%	13%	27%
Cardiac murmur	17%	13%	13%
Dry skin	7%	10%	10%
Reticulocyte increase	7%	10%	3%
Anemia	13%	6%	10%
Umbilical hernia	13%	3%	0%
Hyperbilirubinemia	10%	10%	10%

Study 204: Serious TEAEs Similar Between Treatment Groups (> 1 Neonate in Any Group)

Preferred Term	Stannsoporfin 3.0 mg/kg = PT N=30	Stannsoporfin 4.5 mg/kg + PT N=31	Placebo + PT N=30
Any serious TEAE	17%	13%	20%
Sepsis	0	6%	0
Hyperbilirubinemia	3%	3%	10%
Medical observation*	7%	0	0

- No Serious TEAE led to study discontinuation

* Sepsis (N=1), Supraventricular tachycardia with congenital heart defect (N=1)

Pooled Acute, Double Blind, Placebo Controlled Studies

Study 204 (3.0 mg/kg, 4.5 mg/kg)

Study 202 (1.5 mg/kg, 3.0 mg/kg, 4.5 mg/kg)

Study 01-3W (4.5 mg/kg)

Pooled Acute Studies: Safety Profile

	Stannsoporfin 3.0 mg/kg N=48	Stannsoporfin 4.5 mg/kg N=126	Placebo N=134
TEAEs	79%	42%	37%
SAEs	13%	8%	7%
AE leading to discontinuation	0	0	0
Deaths	0	0	0

Studies 204, 202 and 01-3W

Pooled Acute Studies: Most Common TEAEs (> 5% Neonates in Any Treatment Group)

Preferred Term	Stannsoporfin 3.0 mg/kg N=48	Stannsoporfin 4.5 mg/kg N=126	Placebo N=134
Any TEAE	79%	42%	37%
Erythema	15%	9%	1%
Rash	23%	6%	7%
Rash neonatal	23%	6%	9%
Oral candidiasis	2%	4%	5%
Cardiac murmur	10%	4%	3%
Hyperbilirubinemia	8%	3%	5%
Anemia	10%	3%	2%
Umbilical hernia	10%	1%	0%
Thrombocytopenia	4%	2%	0

Studies 204, 202 and 01-3W

Pooled Acute Studies: Dermatologic TEAEs (≥ 2 Neonates in 4.5 mg/kg Treatment Group)

Preferred Term in ≥ 2 Patients	Stannsoporfin 3.0 mg/kg N=48	Stannsoporfin 4.5 mg/kg N=126	Placebo N=134
Any dermatologic AESI	58%	18%	16%
Erythema	15%	9%	1%
Rash	23%	6%	7%
Rash neonatal	23%	6%	9%
Dry skin	4%	2%	2%

- Guidance in label and educational materials
  - Protection from sunlight for 10 days
  - Use of special filters during surgery

Studies 204, 202 and 01-3W

Platelet Counts <100,000/mm^3 in All Groups

Study	GA (wks)	Dose (mg/kg)	Nadir (x 10^3)	Comment
202	38	4.5	41	Cefotaxime prophylaxis for possible sepsis
202	40	4.5	70	Meningitis (SAE) 4 days after birth
204	41	4.5	87	Low Platelet count noted in medical history
204	37	4.5	95	No other relevant history
204	37	3.0	36	Anemia at birth, double ET w/packed RBC; received platelets
204	38	3.0	30	Maternal history of Group B strep. Possible sepsis; received platelets
204	41	3.0	94	Reticulocytosis, macrosomia, occipital caput, bilateral hydrocele. Maternal history of previous infants with jaundice who received PT.
204	39	Placebo	63	No other relevant history

Pooled Acute Studies: Serious TEAEs Infrequent and Similar Between Groups (> 1 Neonate)

Preferred term	Stannsoporfin 3.0 mg/kg N=48	Stannsoporfin 4.5 mg/kg N=126	Placebo N=134
Any serious TEAE	13%	8%	7%
Meningitis	0	2%	0
Sepsis	0	2%	0
Hyperbilirubinemia	2%	1%	5%
Medical observation*	4%	0	0

*Rule out of sepsis (N=1), Supraventricular tachycardia with congenital heart defect (N=1)

Studies 204, 202 and 01-3W

Pooled 4-6 Year Long-Term (LT) Extension Studies

Study 205

Study 203

Study 01C-3W

Pooled 4-6 Year Long-Term Extension Studies: Overall Safety Profile

	Stannsoporfin 3.0 mg/kg N=37	Stannsoporfin 4.5 mg/kg N=73	Placebo N=76
AEs	54%	75%	76%
SAEs	11%	14%	9%
Deaths	0	0*	0

Studies 205, 203 and 01C-3W

Study 205 is ongoing. Table includes safety update; cutoff May 31, 2017

*1 death from Sudden Infant Death Syndrome from unconsented infant in Study 01C-3W at 4 months of age

Pooled 4-6 Year LT Extension Studies: Certain Neurocognitive and Neurodevelopmental AESI

System Organ Class Preferred terms in ≥ 10% of patients	Stannsoporfin 3.0 mg/kg N=37	Stannsoporfin 4.5 mg/kg N=74	Placebo N=76
Any AE	11%	27%	17%
Ear and labyrinth disorders	5%	7%	0
Deafness*	5%	7%	0
Nervous system disorders	5%	14%	9%
Dyspraxia	0	1%	0
Language disorder	0	1%	1%
Psychomotor hyperactivity	3%	0	0
Seizure	0	0	1%
Speech disorder*	3%	14%	5%
Tremor	0	0	1%

*Deafness and speech disorder (same patients) (includes 120 safety date update with 1 patients added to 3.0 mg/kg

Table includes safety update; cutoff May 31, 2017

Rockefeller IND

Studies 04, 09, 05, 06, 07, 08

Rockefeller IND Safety Profile Consistent with InfaCare IND Short and Long-Term Safety

- Rockefeller IND: 1050 neonates studied across arms
- Types of AEs comparable in both INDs
- Similar rates of AEs compared with control

Stannsoporfin 4.5 mg/kg Well-Tolerated with Favorable Safety Profile

- Transient erythema more common in treatment groups
  - Mild to moderate
  - Resolved without major intervention
  - Potential risk is manageable

Independent Assessment of Long-Term Neurodevelopmental Safety

Dawn Phillips, PhD, PT, MS

Research Scientist, Evidera

Adjunct Associate Professor

University of North Carolina Chapel Hill, School of Medicine

Independent Review to Identify Potential Neurologic and Neurodevelopmental Signals

- Data reviewed
  - Clinical judgments of site investigators
  - Neurodevelopmental test scores (assessments)

Factors to Consider in Drawing Conclusions About Long-Term Safety

Factors
1. Consistency in adverse events across studies
2. Severity of adverse events
3. Plausibility of alternative explanation for adverse events
4. Persistence of adverse events
5. Evidence that standardized neurodevelopmental outcomes are comparable to typically developing children and consistent across studies
6. Hierarchy of evidence

Stannsoporfin Follow-Up Studies Thoroughly Assessed Children's Neurodevelopment

- Blinded assessors used well-known, validated age-appropriate instruments
- Comprehensive assessments of general development
  - Cognitive development (e.g., IQ)
  - Language development and motor skills
  - General behavior and psychological status (e.g., attention, anxiety)
- Follow-up to preschool age (as old as 6 years)

InfaCare Controlled Long-Term Extension Studies

Long-Term Studies		Follow-up Visit Schedule							
		3 mo (n)	6 mo (n)	1 yr (n)	18 mo (n)	2 yr (n)	3 yr (n)	4 yr (n)	6 yr (n)
Study 01C-3W (01-3W Extension)	Stanns (N=44):	--	--	--	32	--	31	--	30
	Control (N=43):				28		32		29
Study 203 (202 Extension)	Stanns (N=29):	26	22	22	--	21	13	15	--
	Control (N=13):	13	11	10		10	5	8	
Study 205* (204 Extension)	Stanns (N=48):	--	43	30	--	10	1	0	--
	Control (N=20):		18	14		7	1	0	
Total	Stanns (N=121):	26	65	52	32	31	45	15	30
	Control (N=76):	13	29	24	28	17	38	8	29

* Study 205 is ongoing. May 31, 2017 cutoff.

Speech and Language AEs Identified in Pooled Long-Term Studies

Long-Term Extension Study 01C-3W: Speech and Language AEs (Stann: N=44, Placebo: N=43)

Sex	AE Preferred Term	Severity	Onset Age	AE Status	Mother's Age	Confounding Factors
4.5 mg/kg Dose						
M	Speech Disorder	Mod	23m	LTFU	17	Otitis media
M	Speech Disorder	Mod	18m	LTFU	18	Atopic dermatitis
M	Speech Disorder Language Disorder Dyspraxia	Mild Mild Mild	2y,4m 2y,6m 2y,6m	Resolved LTFU LTFU	32	Deafness
M	Speech Disorder	Mild	3y	Resolved	39	Contusion head, Bilateral ear infection; Bilateral otitis media (5x); Ear disorder; Otitis media (2X); Head injury (3X)
M	Speech Disorder	Mild	3y,1m	LTFU	19	None reported
M	Speech Disorder	Mild	3y,2m	LTFU	21	Otitis media
F	Speech Disorder Speech Disorder	Mild Mod	3y 3y,11m	Resolved Ongoing	17	Otitis media (2X), Bilateral otitis media, Hand/foot/mouth disease (10d before speech disorder), Abnormal WPPSI
M	Speech Disorder Speech Disorder	Mod Mod	4y,7m	Ongoing	20	Otitis media, Bilateral otitis media, Left head bump, Iron deficiency anemia, Eczema
M	Speech Disorder	Mod	4y	Ongoing	18	Child neglect, Otitis media (2X), Bilateral otitis media, Febrile seizure, Eczema
Placebo						
M	Language Disorder	Mild	22m	LTFU	24	Eczema
F	Speech Disorder	Mild	5y,6m	Ongoing	40	None reported
M	Speech Disorder Learning Disability	Mild Mild	5y,9m 6y	Resolved Ongoing	24	Eczema, Otitis media

Unique patients; LTFU = Lost To Follow Up

Long-Term Extension Study 203: Speech and Language AEs (Stann: N=29; Placebo: N=13)

Sex	Preferred Term	Severity	Onset	Status	Mother's Age	Confounding Factors
1.5 mg/kg						
M	Speech Disorder	Mild	2y,1m	Resolved	27	Eczema, Ear infection
4.5 mg/kg						
F	Speech Disorder	Mild	2y	Resolved	38	Trauma of the soft tissue of head
Placebo						
F	Speech Disorder	Mild	16m	Resolved	30	Dermatitis atopic, Ear infection
M	Speech Disorder	Mild	16m	Resolved	28	Otitis media, Hand/foot/mouth disease

Unique patients

Long-Term Extension Study 205: Speech and Language AEs (Stann: N=48; Placebo: N=20)

Sex	Preferred Term	Severity	Onset	Status	Mother's Age	Confounding Factors
3.0 mg/kg						
M	Speech Disorder	Mild	23m	Ongoing*	23	Hand/foot/mouth disease, Otitis media

* Patient continues in long-term follow-up study. Resolution not yet determined

Transient Conductive Hearing Loss Appeared ≥ 8 Months After Treatment

Study Group	Preferred Term	Verbatim	Severity	Onset	Status	Confounding Factors
Study 01C-3W						
4.5 mg/kg	Deafness	Hearing Deficit	Mild	6 yrs	Ongoing	Viral upper respiratory infection, right ear infection, pharyngitis
4.5 mg/kg	Deafness	Hearing Loss	Mod	8.5 mos	Resolved	Bronchiolitis, otitis, ear wax
4.5 mg/kg	Deafness	Bilateral hearing loss	Mod	4 yrs	Resolved	Bilateral serous otitis media, upper respiratory infection, chronic bilateral serous otitis media
4.5 mg/kg	Deafness	Hearing loss	Mild	2 yrs	Resolved	Rotavirus
Study 203						
3.0 mg/kg	Deafness	Bilateral mild conductive hearing loss	Mild	4 yrs	Resolved	Viral infection
4.5 mg/kg	Deafness	Bilateral conductive hearing loss	Mild	3 yrs	Resolved	Acute respiratory viral infection, trauma of the soft tissue of head, acute bronchitis
Study 205						
3.0 mg/kg	Deafness	Bilateral conductive hearing loss	Mod	2 yrs	Resolved	Left otitis media, eustachian tube salpingitis bilateral, recurrent otitis media, left acute suppurative otitis media, viral upper respiratory infection

All passed their hearing screenings

6 Rockefeller Studies Provide Considerable Long-Term Neurodevelopmental Safety Data

	Stannsoporfin 1.5 mg/kg N=59	Stannsoporfin 2.25 mg/kg N=32	Stannsoporfin 3.0 mg/kg N=59	Stannsoporfin 4.5 mg/kg N=459	Control, Placebo, or PT Only N=391
Any patient with Neurodevelopmental AE	**3%**	**9%**	**5%**	**4%**	**4%**

- No dose-response relationship
- 4% neurodevelopmental AEs in both 4.5 mg/kg and control groups
- 2.6% speech-language related AEs in stannsoporfin and control

Neurodevelopmental Test Scores (Pooled Extension Studies)

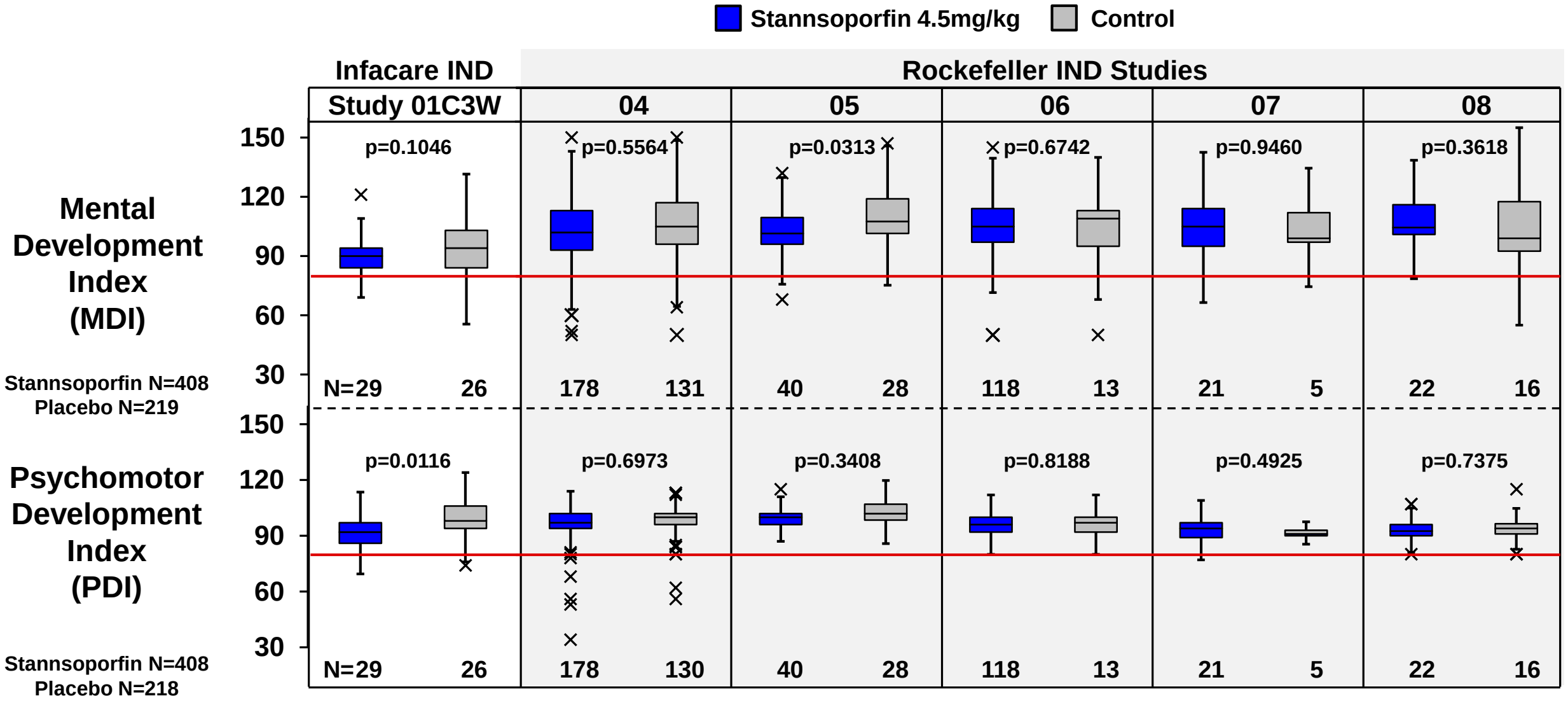
Use of Different Assessment Tools Across Longitudinal Studies

- Development varies greatly by age
- No single instrument available to capture global development from birth to age 6
- Multiple age-specific instruments typically used in clinical practice and clinical research
- Longitudinal studies often require transition between instruments

Variety of Standardized Neurodevelopmental Assessments Used in Long-Term Evaluation

Neurodevelopmental Assessment Tool	Age Range	Measures Assessed
Mullen Scale of Early Learning (MSEL)	Birth – 6 years	General developmental
Bayley Scales of Infant and Toddler Development (BSID)	1 – 42 months	Cognitive and motor development
Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	2 – 7 years	General cognitive ability
Receptive-Expressive Emergent Language Test (REEL)	0 – 36 months	Language
Child Behavior Checklist (CBCL)	1 – 16 years	Problem behaviors

No Difference in Direction of Advantage: Bayley Scales of Infant Development at 18 Months



No Significant Differences in Receptive/Expressive Language Between Groups at 18 Months (REEL Study 01C-3W)

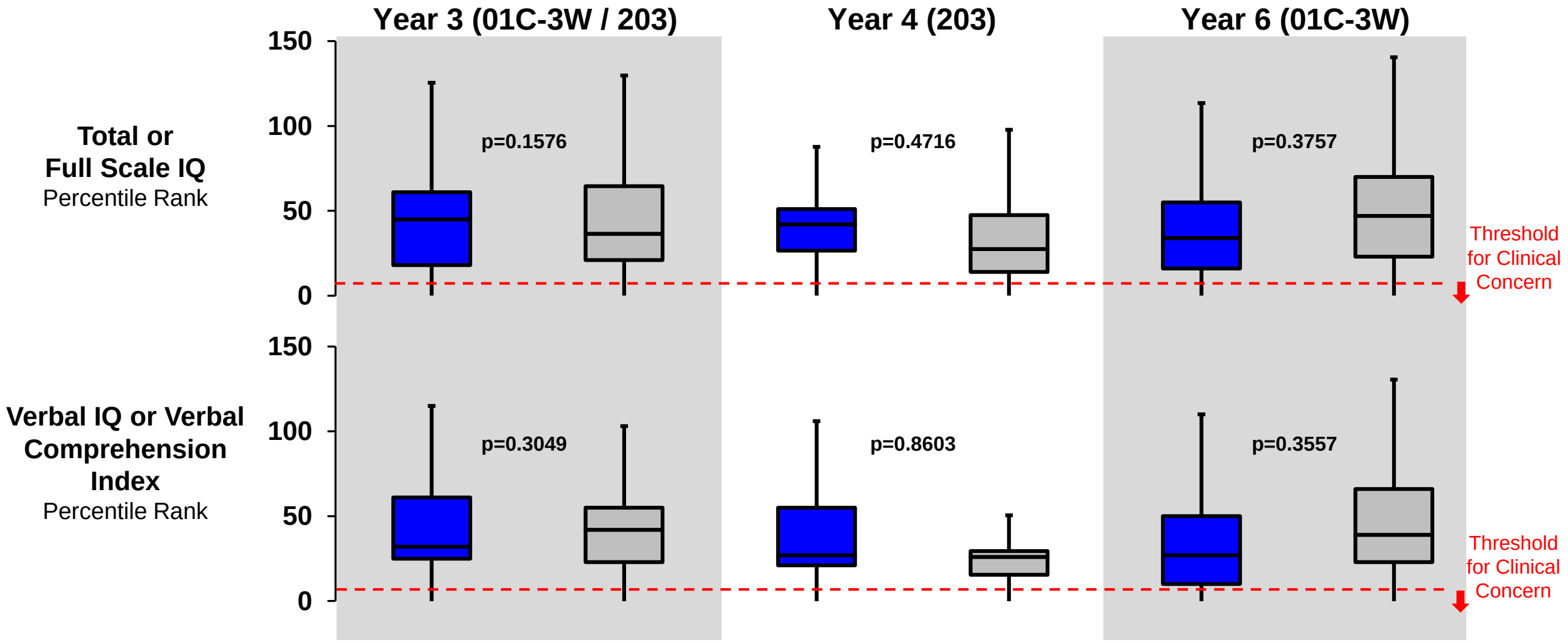
	T-Score	
	Stanns 4.5 mg/kg N=44	Placebo N=43
N	29	26
Receptive Language, mean (SD)	54 (14)	53 (9)
	p=0.63	
Expressive Language, Mean (SD)	54 (9)	51 (9)
	p=0.15	

Long-Term Safety: Wechsler Preschool and Primary Scale of Intelligence (WPPSI)

- Most widely used assessment of intelligence in preschoolers
- Represents a common transition from the BSID
- WPPSI and Bayley have strong concurrent validity
  - Low Bayley scores (18 months) have predictive validity in identifying low WPPSI scores (60 months)[1]

1. Lung, et. al. 2012

Long-Term Extension Studies 01C-3W and 203: WPPSI



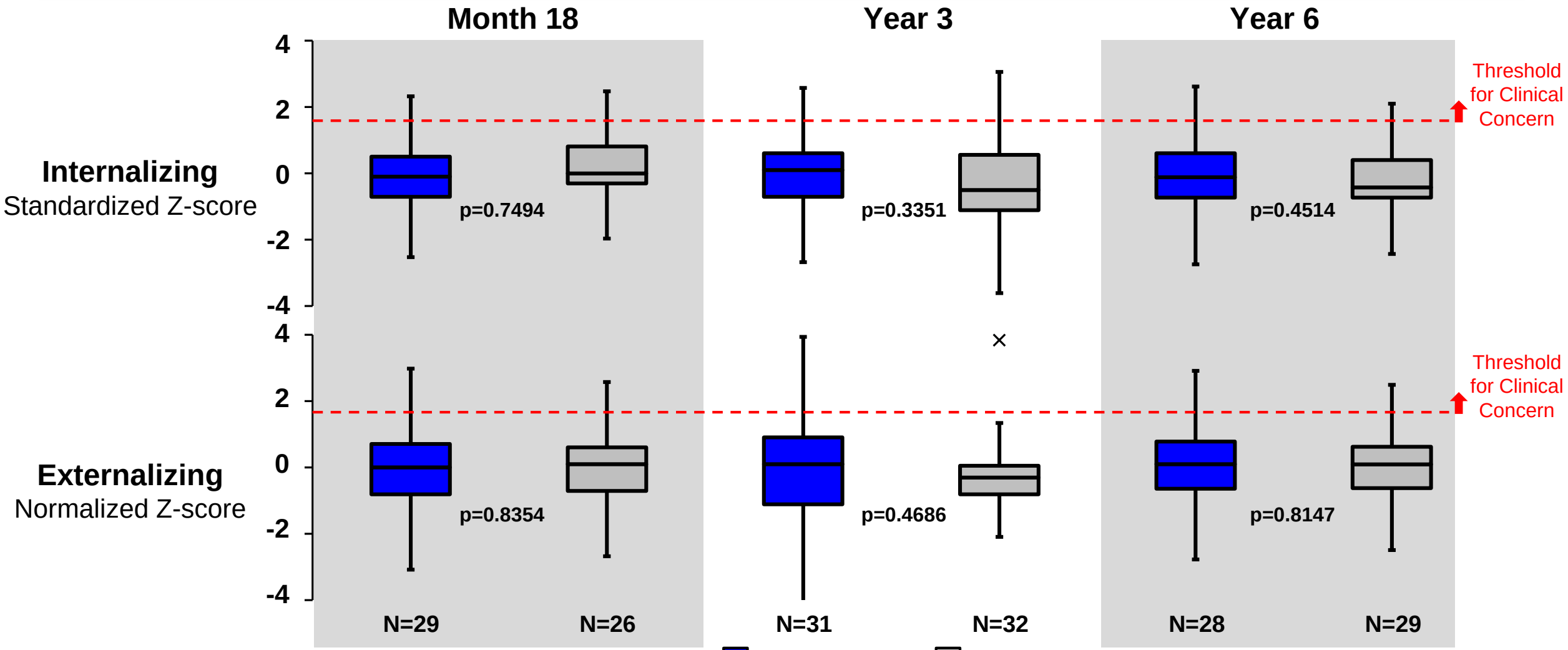
Study 01C-3W: 4.5 mg/kg dose at year 3 and year 6
Study 203: 1.5 mg/kg, 3.0 mg/kg and 4.5 mg/kg doses at year 3

No Consistent Relationship Between Speech Disorder and Abnormal WPPSI Score

Sex	Preferred Term	Severity	Onset	Status	Mother's Age	Confounding Factors	WPPSI V. IQ
4.5 mg/kg Dose							
M	Speech Disorder	Mod	23m	LTFU	17	Otitis media	-
M	Speech Disorder	Mod	18m	LTFU	18	Atopic dermatitis	-
M	Speech Disorder Language Disorder Dyspraxia	Mild Mild Mild	2y,4m 2y,6m 2y,6m	Resolved LTFU LTFU	32	Deafness	32
M	Speech Disorder	Mild	3y	Resolved	39	Contusion head, Bilateral ear infection; Bilateral otitis media (5x); Ear disorder; Otitis media (2X); Head injury (3X)	32
M	Speech Disorder	Mild	3y,1m	LTFU	19	None reported	14
M	Speech Disorder	Mild	3y,2m	LTFU	21	Otitis media	8
F	Speech Disorder Speech Disorder	Mild Mod	3y 3y,11m	Resolved Ongoing	17	Otitis media (2X), Bilateral otitis media, Hand/foot/mouth disease (10d before speech disorder), Abnormal WPPSI	6
M	Speech Disorder Speech Disorder	Mod Mod	4y,7m	Ongoing	20	Otitis media, Bilateral otitis media, Left head bump, Iron deficiency anemia, Eczema	42
M	Speech Disorder	Mod	4y	Ongoing	18	Child neglect, Otitis media (2X), Bilateral otitis media, Febrile seizure, Eczema	25
Placebo							
M	Language Disorder	Mild	22m	LTFU	24	Eczema	10
F	Speech Disorder	Mild	5y,6m	Ongoing	40	None reported	68
M	Speech Disorder Learning Disability	Mild Mild	5y,9m 6y	Resolved Ongoing	24	Eczema, Otitis media	18

Unique patients; LTFU = Lost To Follow Up

Long-Term Extension Studies 01C-3W and 203: Child Behavior Checklist



Study 01-C3W: 4.5 mg/kg dose at month 18 and year 6
Study 203: 1.5 mg/kg, 3.0 mg/kg and 4.5 mg/kg doses at year 3

No Consistent Signal of Safety Concern Among Children Receiving Stannsoporfin

Factors	Conclusions
1. Consistency in adverse events across studies	▪ No consistent presentation of speech/language adverse events across studies
2. Severity of adverse events	▪ Adverse events not severe
3. Plausibility of alternative explanation for adverse events	▪ Existence of plausible alternative explanations
4. Persistence of adverse events	▪ Data inconclusive to support safety concern
5. Evidence that standardized neurodevelopmental outcomes are comparable to typically developing children and consistent across studies	▪ Values of neurodevelopmental assessments within normal range and consistent across studies
6. Hierarchy of evidence	▪ Highest level of evidence: Standardized assessments by trained professionals

Risk Management Plan (RMP)

Lawrence A. Hill, PharmD, MBA

Vice President, Clinical Development

Mallinckrodt Pharmaceuticals

Common Long-Term Risk Management Goals

- Ensure that stannsoporfin used in hemolyzing term, near-term infants who meet AAP guidelines for PT
- Collect additional safety data to confirm long-term safety profile

Comparison Between Mallinckrodt's RMP and FDA's REMS

Action	FDA Plan (REMS)	Mallinckrodt Plan (RMP)
Restricted Access	Certification of facility experience and ability to treat at-risk neonates	Restrict to hospitals with NICUs
Prescriber Education	Confirm HCP education and training on use and potential long-term neurodevelopmental risk	Confirm HCP education and training on use consistent with approved label
Parent / Guardian Education	Document receipt of Patient Fact Sheet and counseling on potential long-term neurodevelopment risk	Provide Patient Fact Sheet on photosensitivity and undetermined developmental risks
Registry	Enrollment before treatment	Enrollment after treatment

Mallinckrodt Plan Restricts Access to Hospitals with NICUs

- HCPs experienced with PT population and have knowledge on administration of IM drug
  - Site certification not required
- Targeted health care providers
  - Neonatologists, pediatric intensivists, pediatricians, neonatal nurse practitioners, clinical pharmacists, fellows/residents
- Training documented and required before prescribing stannsoporfin

Mallinckrodt Plan to Educate and Train NICU Prescribers and Health Care Providers

- Prescriber brochure to reinforce correct application of AAP guideline and decisions on treatment initiation
- Website provides accessibility to educational materials anytime
  - Use as resources for hospital in-services

Mallinckrodt Parent Education Materials Modeled After Vaccination Brochures

- Parent brochures: provided to parents at time of use
  - Inform on potential risks in approved label
- Website for parents to house all educational materials

Mallinckrodt Plan Proposes a Prospective, Open-Label, Long-Term Study

- Examines long-term development in indicated population
- Between 800-1000 babies
- Follow patients out to 5 years
- High assay sensitivity for detecting long-term events

Testing Collected by Qualified Professionals at Key Timepoints Measuring Neurodevelopment

	Visits			
	2 year	3 year	4 year	5 year
Bayley (BSID)	✓	✓		
Preschool Language Scales	✓	✓	✓	✓
Child Behavior Checklist (CBCL)	✓	✓	✓	✓
Audiometry	✓	✓	✓	✓
Wechsler (WSPPI)			✓	✓
Vineland Adaptive Behavior Scales	✓	✓	✓	✓
Speech-Language Pathologist	✓	✓	✓	✓

- Combined testing would evaluate children through 5 years
- Data safety monitoring board held annually for review of data

Mallinckrodt Proposed Registry

- Therapeutic setting influences willingness to enroll in registry
- Parents first priority is treating baby's hyperbilirubinemia
  - Not enrolling in a clinical trial
- Proposed registry separates treatment decision from enrollment decision
- Approach to facilitate enrollment, and collect data more rapidly

Mallinckrodt's Proposed Risk Management Plan Supports Safe Use and Collects Long-Term Data

- Risk Management Plan
  - Assure use in appropriate population
  - Add significantly to long-term safety database in a timely manner

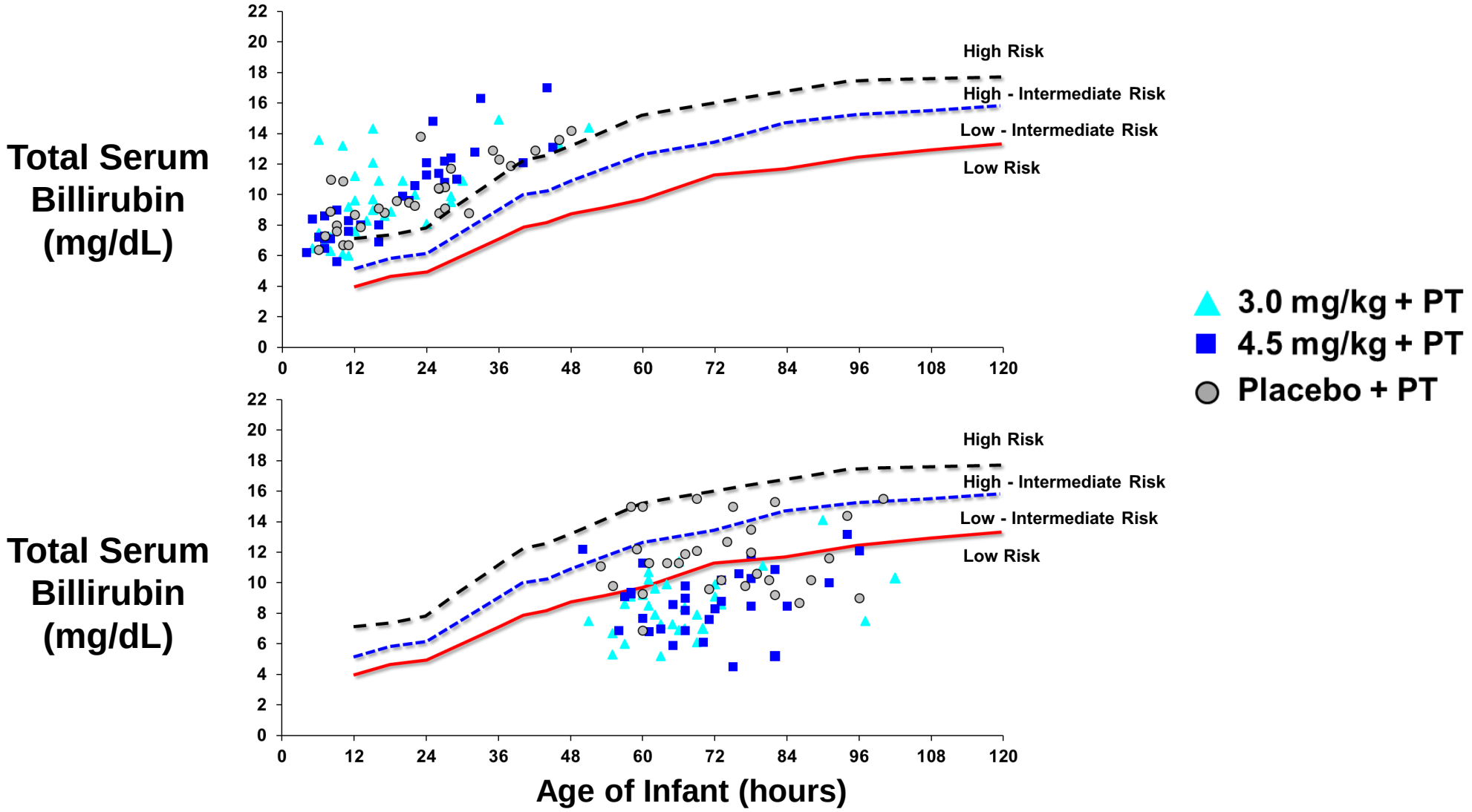
Benefit-Risk

Jeffrey Maisels, MD, DSc
Chair Emeritus and Professor
Department of Pediatrics
Oakland University William Beaumont School of Medicine

Stannsoporfin Effectively and Predictably Inhibits Bilirubin Production – A First for Hyperbilirubinemia

- Clinically meaningful benefits
  - ↓ Duration of and failure of phototherapy
  - ↓ Rebound, rehospitalization and restarts of phototherapy
  - ↓ Need for exchange transfusion
  - ↓ Separation of mother from baby

Study 204: 87% of Neonates on Stannsoporfin 4.5 mg/kg Shifted from High to Low Risk at 48 Hours



Stannsoporfin is Well-Tolerated With Favorable Safety Profile

- Photosensitivity
  - Self-limiting
  - Manageable
  - Resolved with minor intervention
- Registry to confirm observed, long-term safety profile

Benefits of 4.5 mg/kg Stannsoporfin Outweigh Risks

- Unique, meaningful addition to options for preventing, treating hyperbilirubinemia
- Benefits outweigh risks for neonates ≥ 35 weeks at risk for developing severe hyperbilirubinemia

Stannsoporfin for Neonatal Hyperbilirubinemia

InfaCare, A Mallinckrodt Pharmaceuticals Company

Gastrointestinal Drugs Advisory Committee and

Pediatric Drugs Advisory Committee

May 3, 2018

ONSCREEN BACK-UP SLIDES

No Safety Signals in 4 Years of Long-term Data

- Clinical laboratory assessments (hematology, clinical chemistry, and urinalysis)
  - 18 months and 3 years in 01-C3W
  - 3, 6, and 18 months and 1, 2, 3, and 4 years in 203
  - not required in 205
- Vital signs, height, weight, and head circumference
- Physical examinations and overall assessment findings
- No safety signals seen in 4 years of assessments

Biliary Elimination and Induction of HO-1 Counteracts Heme Accumulation after Treatment with Stannsoporfin

- Total serum bilirubin levels drop and biliary excretion is decreased after treatment with Stannsoporfin
- Biliary heme excretion is increased for 48-hours after a single dose of SnPP in healthy volunteers
- Heme is a potent inducer of HO-1 in liver after 24 hours
- Compensatory increase in heme elimination and induction of HO-1 counteracts heme accumulation

Berglund et al, 1988

Biological Effects of Excess Heme in Patients

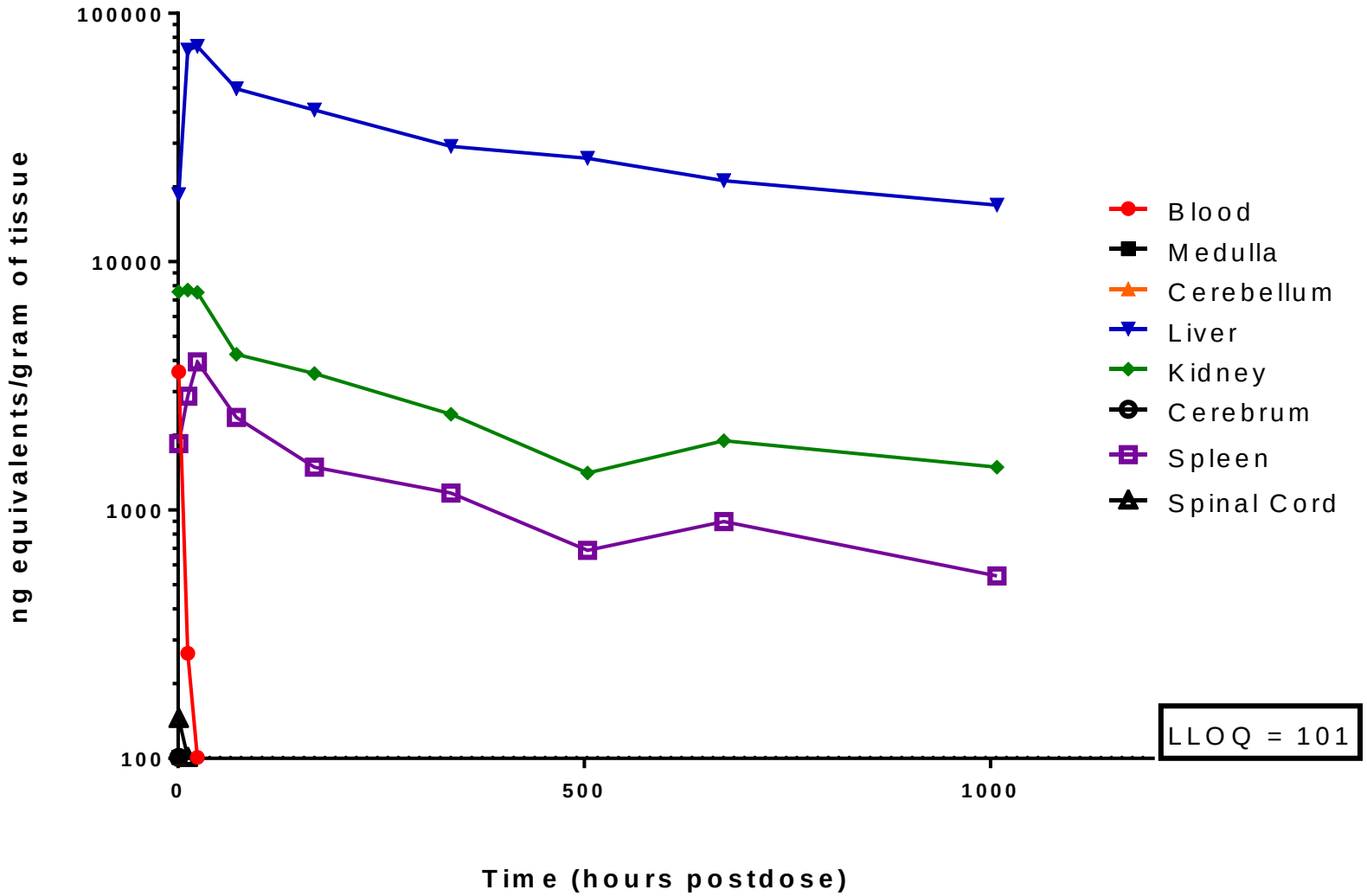
- Intravenous hemin used for acute attacks of porphyria in EU[1]
- Heme arginate rescue therapy prevents further neuronal injury in porphyria patients (3 mg/kg IV, up to 3 months)[1]
- Intravenous heme arginate increases HO-1 protein levels and enzyme activity by 4-5 fold and 15-fold in PBMCs in volunteers[2]
- Mechanism of heme neuroprotection not known in patients[2]
- Stannsoporfin transiently increases heme and induces HO-1

1. Stein et al, 2013. Ann Clin Biochem. 2013 May;50(Pt 3):217-23
2. Doberer et al, 2010, Br J Pharmacol. 2010 Dec;161(8):1751-62

Stannsoporfin Excretion and Mass Balance

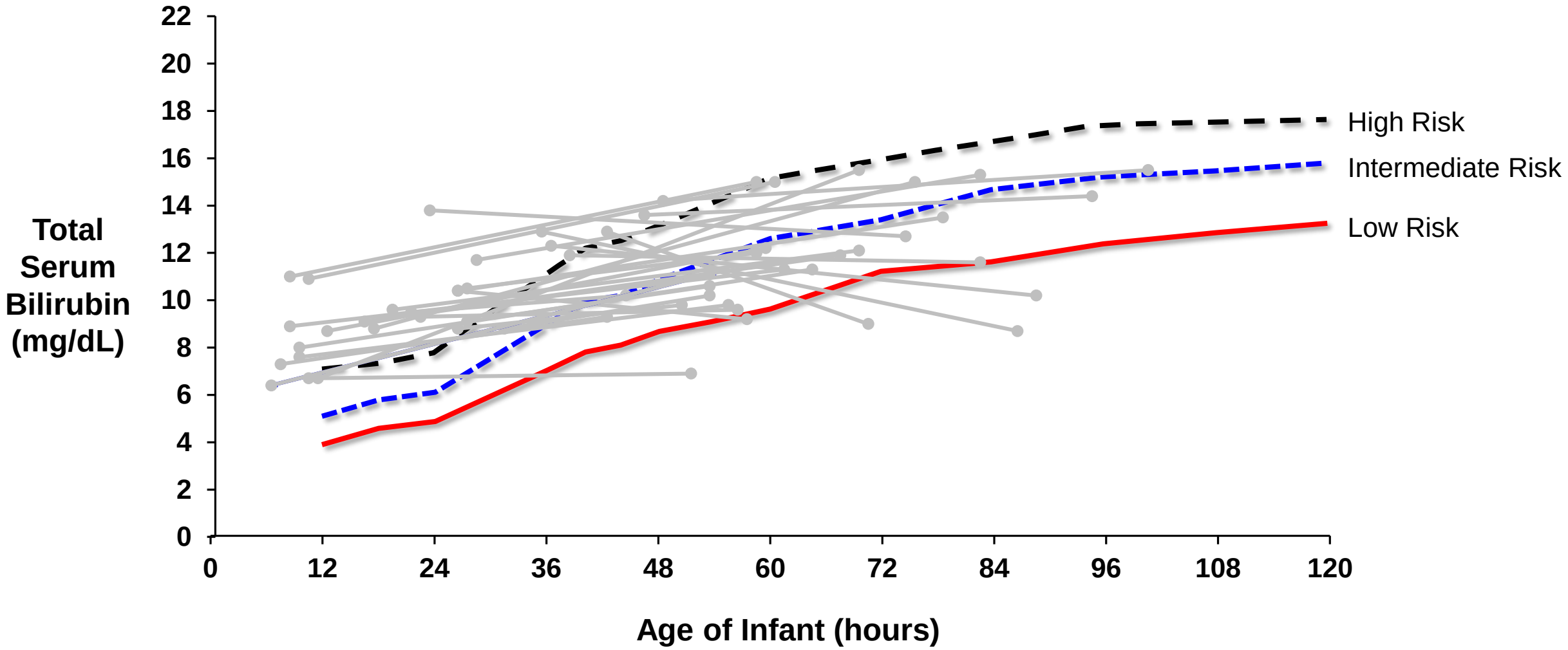
- Dogs: Overall recovery of 44.5 to 48.7% in M, F
  - 15.5% to 19.8% in urine, 24.5 to 33.1% in feces
  - Low recovery due to tissue retention, incomplete elimination
  - Major metabolites M5 and M6 identified in feces
- Rats: Overall recovery of 66.1 and 64.3% after IV, IM
  - 11.9% in urine, 51.1% in feces – most elimination in 72 hrs
  - Low recovery due to tissue retention, incomplete elimination
  - Major metabolites M6 and M7 identified in feces

Radiolabeled Stannsoporfin Distribution in Organs of Clearance in Neonatal Dogs (6 mg/kg IM)



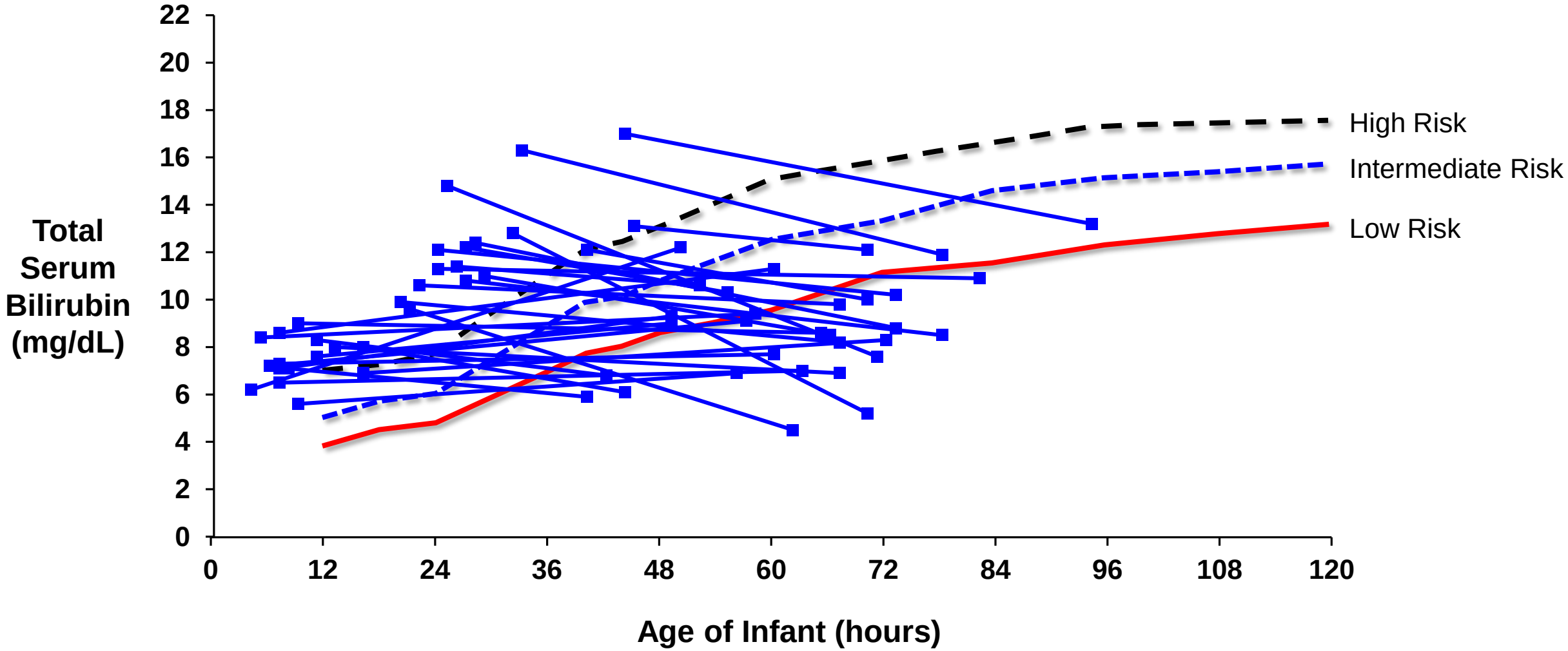
Study 7611-105

Study 204: Baseline and 48-Hour Placebo TSB Levels on Bhutani Nomogram



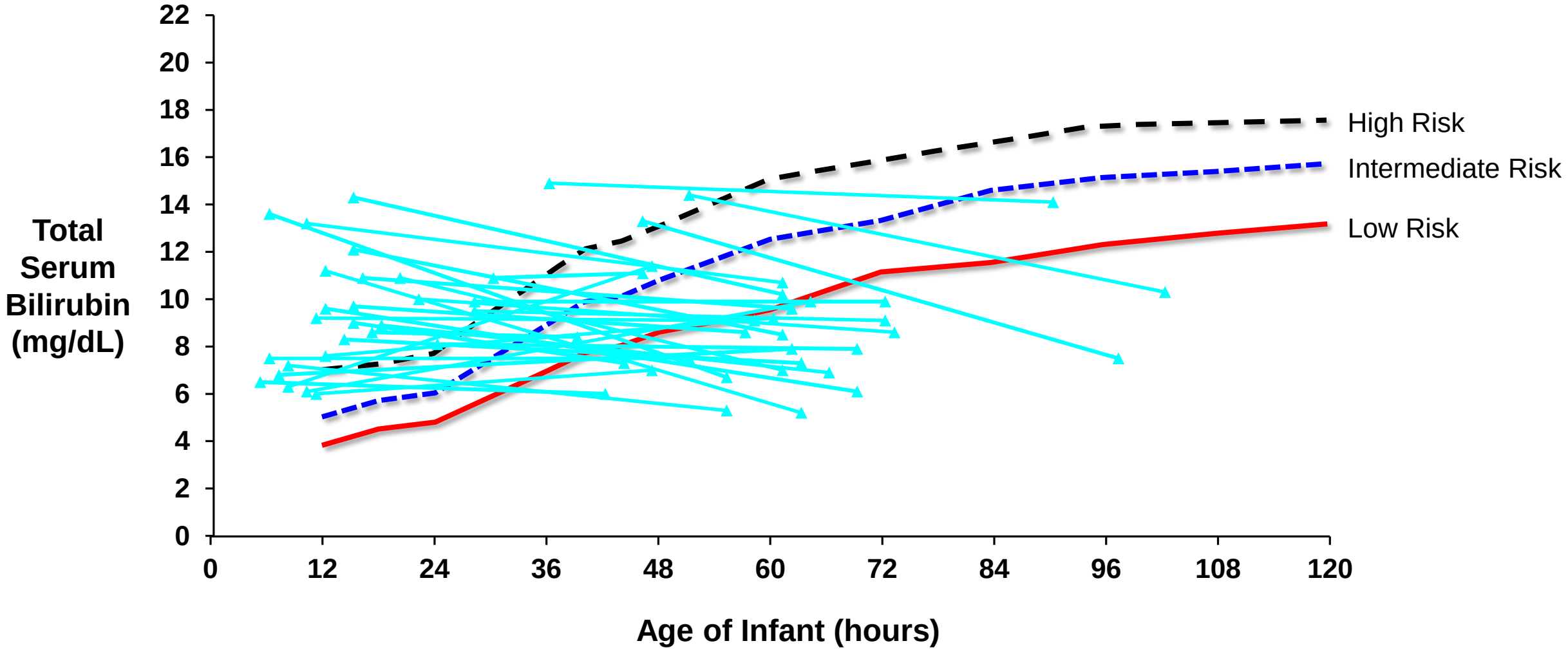
Adapted from Bhutani nomogram

Study 204: Baseline and 48-Hour 4.5 mg/kg TSB Levels on Bhutani Nomogram



Adapted from Bhutani nomogram

Study 204: Baseline and 48-Hour 3.0 mg/kg TSB Levels on Bhutani Nomogram



Adapted from Bhutani nomogram