NICHD
NEONATAL RESEARCH NETWORK

Darbepoetin Trial to Improve Red Cell Mass and Neuroprotection in Preterm Infants

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Disclosures

- I have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved
- This presentation will involve discussion of off-label, investigational use of darbepoetin (IND #100138)

Thank you to the families of the participating infants, the research coordinators who performed the study, and NHLBI/NICHD for funding the study

Erythropoiesis Stimulating Agents

- Erythropoiesis stimulating agents (ESAs) erythropoietin and darbepoetin stimulate red cell production
- Hematopoietic doses: higher hematocrit, decreased transfusions, decreased donor exposures
- Darbepoetin half life allows for weekly dosing
- ESAs have non-hematopoietic effects

Neuroprotective Effects of ESAs

- Decreased apoptosis, decreased inflammation, increased neurogenesis and oligodendrogenesis
- Hematopoietic doses show neurodevelopmental improvements into school age (Neubauer et al, Ann Neurol 2010; Ohls et al, Pediatrics 2013; Song et al, Ann Neurol 2016; Ohls et al, Curr Pediatr Rev 2023)
- Multicenter RCT of high dose erythropoietin (PENUT): decreased transfusions, similar developmental outcomes (Juul et al, New Engl J Med 2020)
- Darbepoetin might result in better developmental outcomes (Ohls et al, Pediatrics 2014; Ohls et al, Pediatrics 2016)

Hypothesis and Objectives

Hypothesis: Preterm infants given darbepoetin weekly, starting within 36 hours of birth and continuing to 35 weeks gestational age, will have improved neurocognitive outcome at 22-26 months compared to placebo recipients.

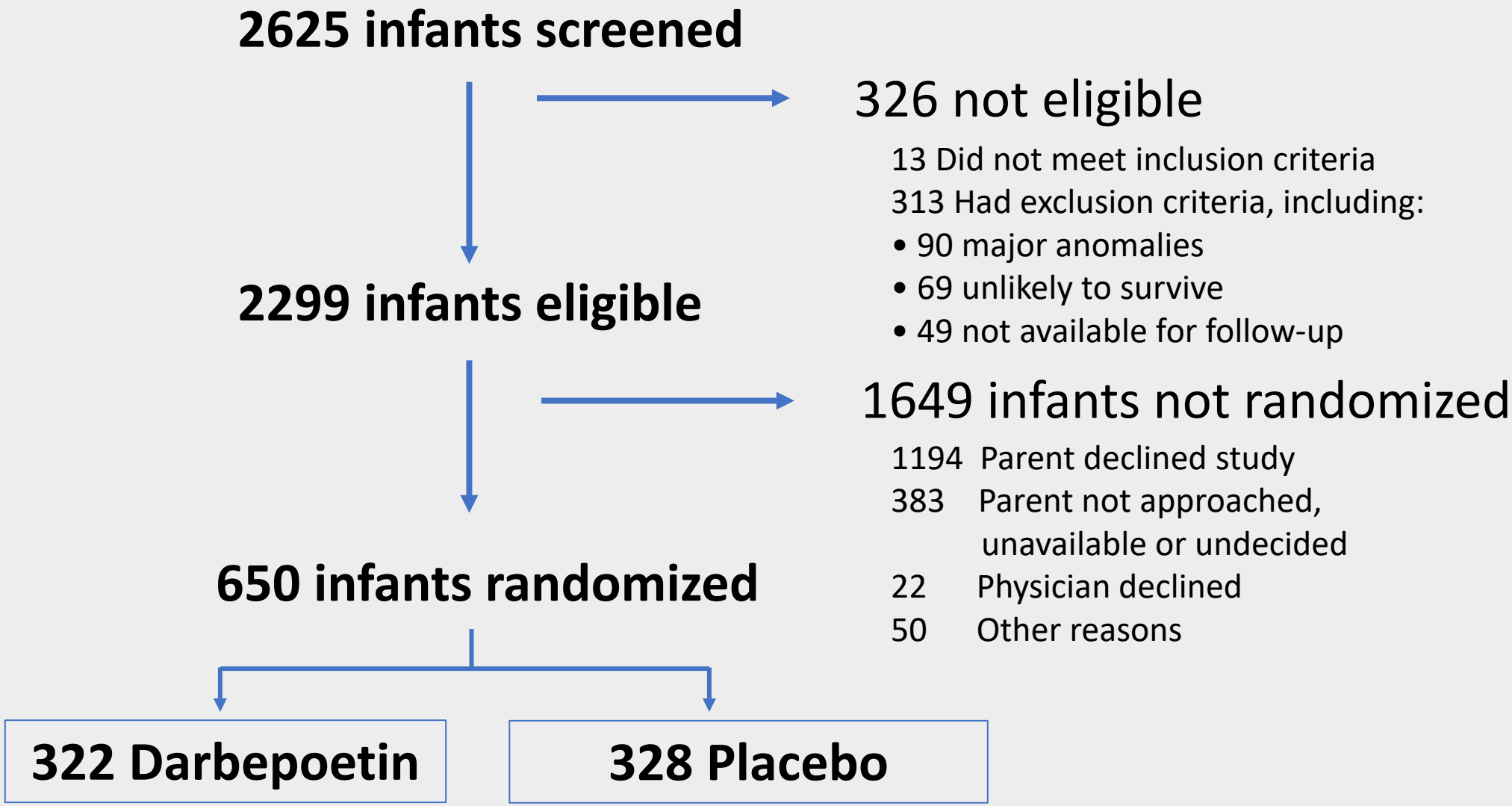
Objective: Evaluate the effects of darbepoetin on red cell mass, transfusions, donor exposures and neurodevelopment.

Primary Outcome: Bayley III composite cognitive score

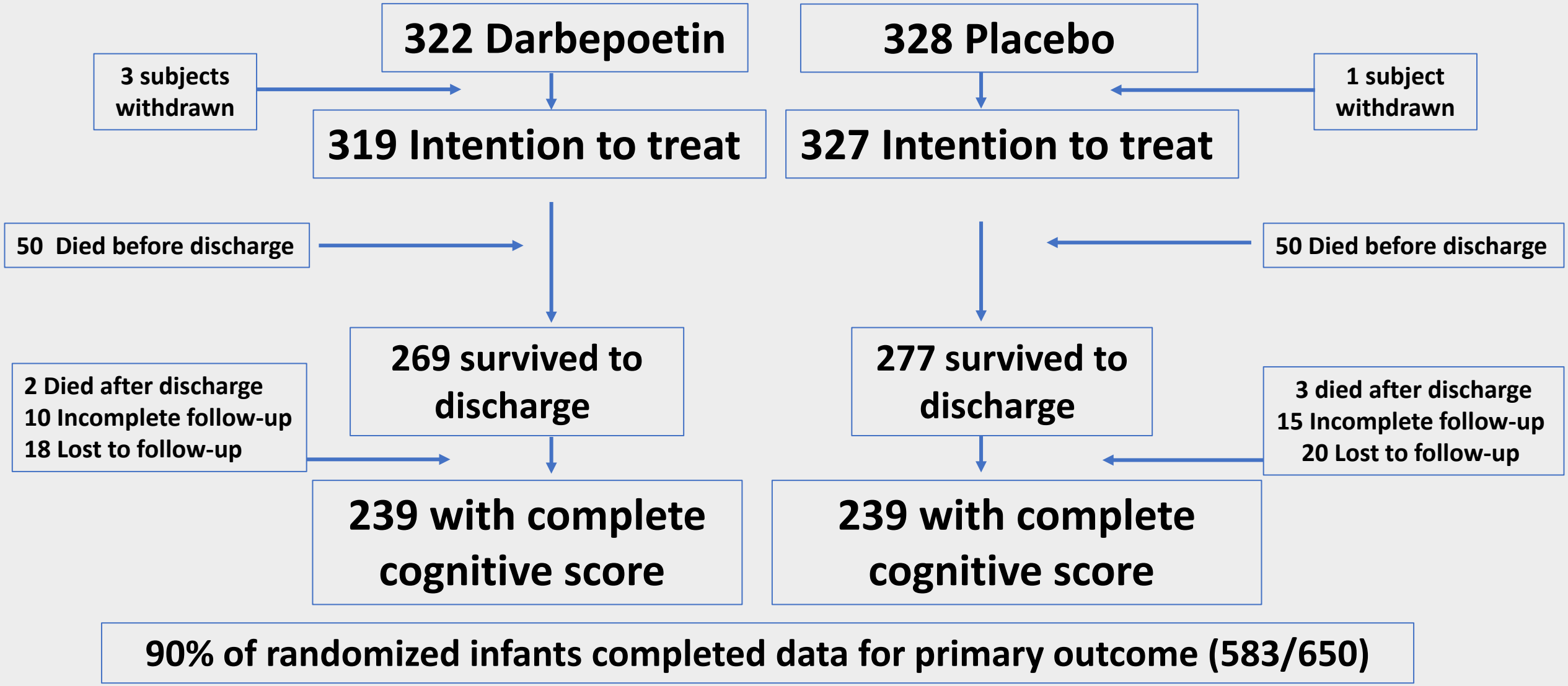
Methods

- **Population:** Infants born 23 $^{0/7}$ to 28 $^{6/7}$ weeks gestation
- **Randomization**: Stratified by gestation (23-25$^{6/7}$; 26-28 $^{6/7}$) and center
- **Intervention**:
  - **darbepoetin** 10 micrograms/kg once a week (IV or SC) or placebo (IV or sham dosing), through 35 completed weeks
  - **Iron:** parenteral and enteral supplementation guidelines
  - **Transfusions:** restrictive protocol
- **Primary outcome:** Bayley Scales of Infant Development, third edition (Bayley III) composite cognitive score evaluated at 22-26 months corrected gestation (deaths assigned score of 54)

Screening and Enrollment



Study Flow


322 Darbepoetin
328 Placebo
3 subjects withdrawn
1 subject withdrawn
319 Intention to treat
327 Intention to treat
50 Died before discharge
50 Died before discharge
269 survived to discharge
277 survived to discharge
2 Died after discharge
10 Incomplete follow-up
18 Lost to follow-up
3 died after discharge
15 Incomplete follow-up
20 Lost to follow-up
239 with complete cognitive score
239 with complete cognitive score
90% of randomized infants completed data for primary outcome (583/650)

Maternal and Infant Characteristics

	Darbe (n=322)	Placebo (n=328)
Antenatal Steroids (%)	93	93
Multiple births (%)	24	29
Outborn, (%)	8	7
Delayed cord clamping (%)	44	41
5 minute Apgar score (median, 25/75)	7 (5, 8)	7 (6, 8)
Birth weight (grams; mean, SD)	838 (253)	822 (238)
Gestation (weeks; mean, SD)	25.8 (1.7)	25.7 (1.6)
Female (%)	52	49
SGA (%)	13	11
Age at randomization (hours; mean, SD)	16 (6)	17 (6)
Hematocrit (mean, SD)	43 (7)	43 (7)

Primary outcome: Bayley III cognitive scores

	Darbe (N=291)	Placebo (N=292)	Adjusted Mean Difference (95% CI)
Cognitive Score Mean (SD)	81 (19)	80 (19)	-0.2 (-3.1 to 2.6)

The 52 deaths in the Darbe group and the 53 deaths in the Placebo group were assigned the lowest possible score of 54

Bayley III cognitive scores by low and high gestation

	Darbe (N=291)	Placebo (N=292)	Adjusted Mean Difference (95% CI)
Gestation 23 $^{0/7}$-25 $^{6/7}$ weeks: N	**131**	**129**	
Cognitive Score Mean (SD)	**72 (19)**	**74 (18)**	**-3.2 (-7.6 to 1.3)**
Gestation 26 $^{0/7}$-28 $^{6/7}$ weeks: N	**160**	**163**	
Cognitive Score Mean (SD)	**88 (17)**	**85 (18)**	**2.2 (-1.5 to 5.8)**

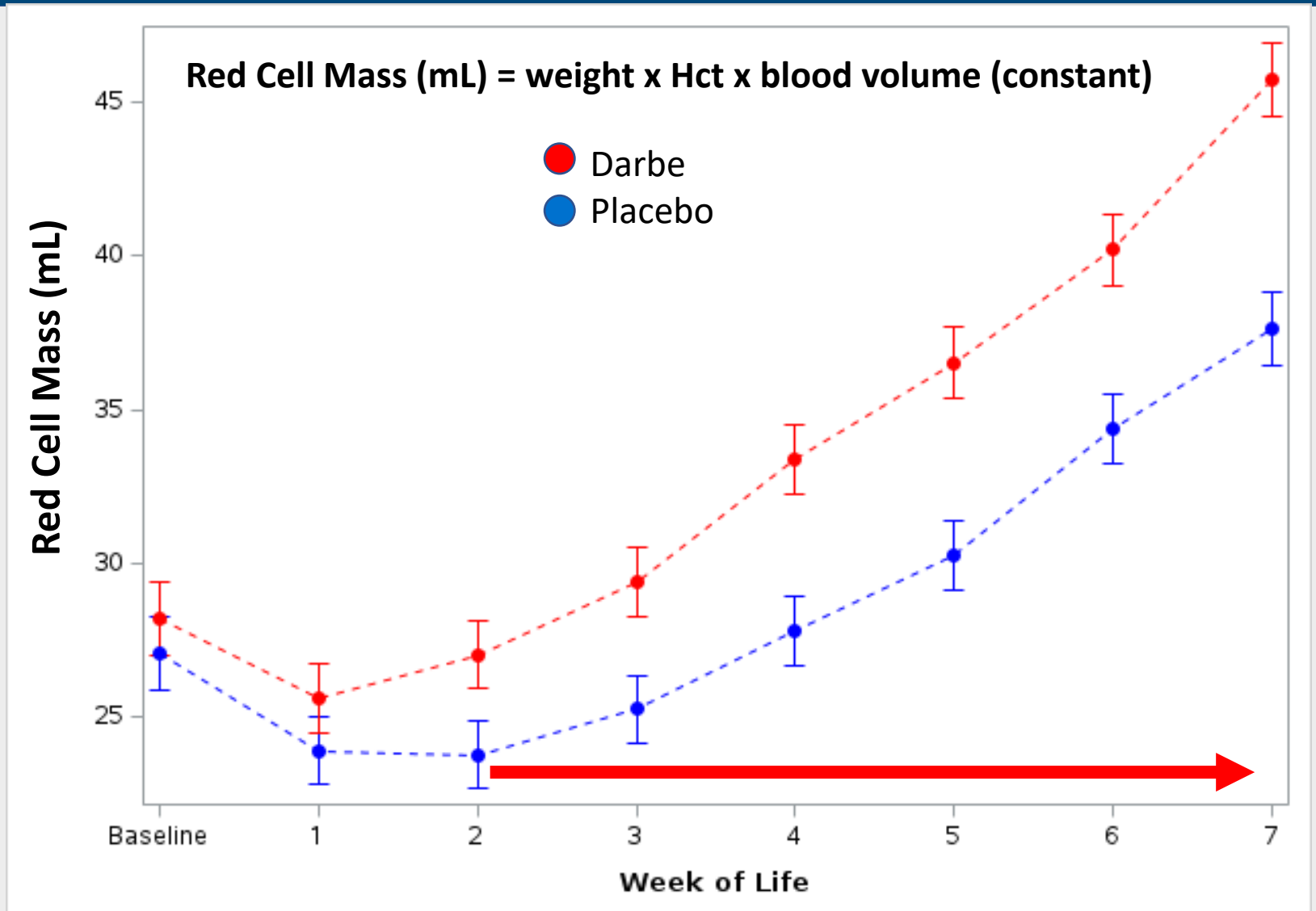
Bayley III cognitive scores in survivors

	Darbe	Placebo	Adjusted Mean Difference (95% CI)
All survivors: N	239	239	
Cognitive Score, Mean (SD)	86 (17)	86 (16)	-0.8 (-3.6 to 2.0)
Median (P25, P75)	90 (75, 95)	85 (75, 95)	
Gestation 23 $^{0/7}$-25 $^{6/7}$ weeks: N	87	93	
Cognitive Score, Mean (SD)	81 (17)	82 (16)	-3.04 (-7.66 to 1.58)
Median (P25, P75)	85 (65, 90)	85 (70, 95)	
Gestation 26$^{0/7}$ -28 $^{6/7}$ weeks: N	152	146	
Cognitive Score, Mean (SD)	90 (15)	88 (15)	0.57 (-2.82 to 3.95)
Median (P25, P75)	90 (80, 100)	85 (80, 100)	

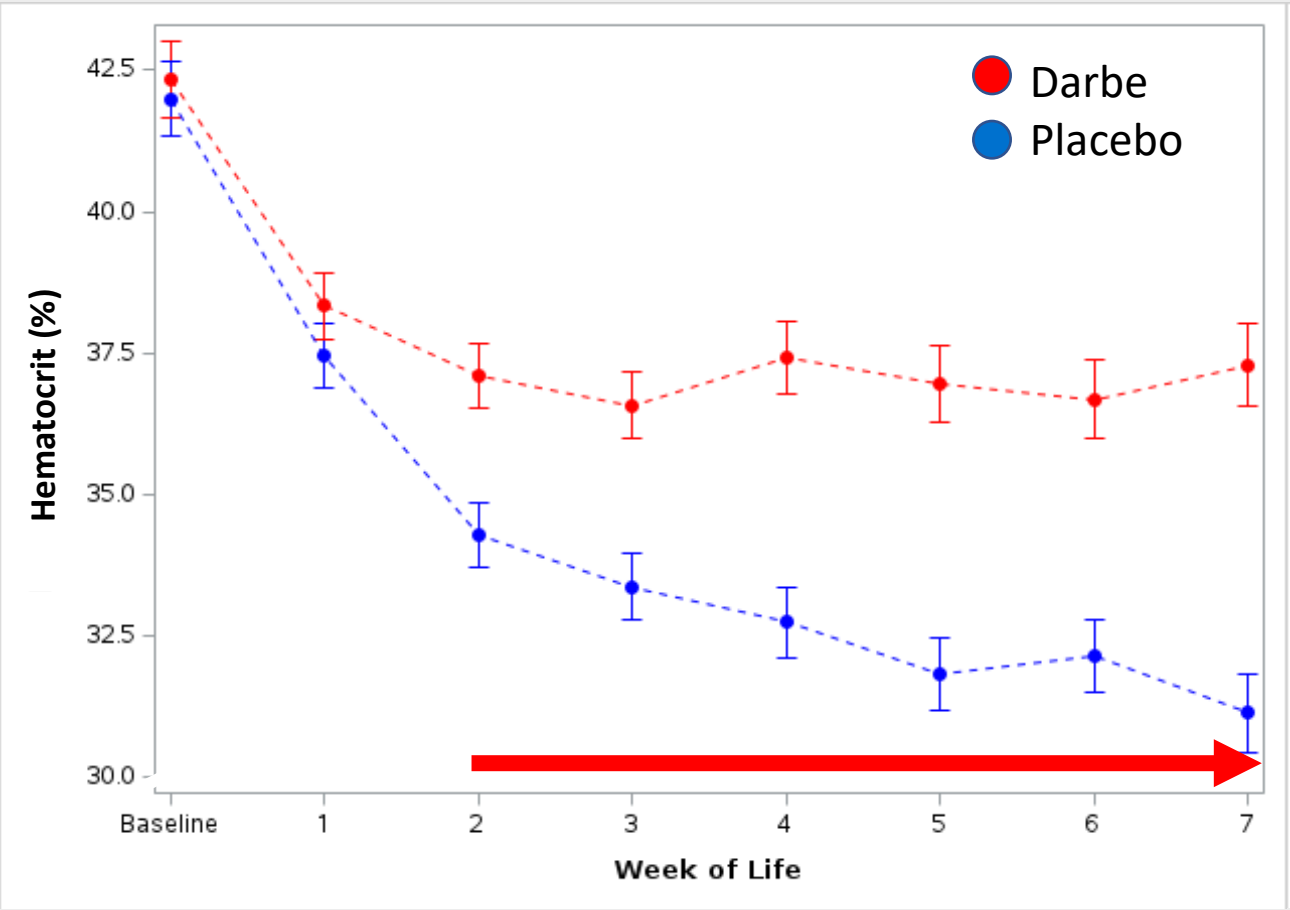
Transfusions and Donors

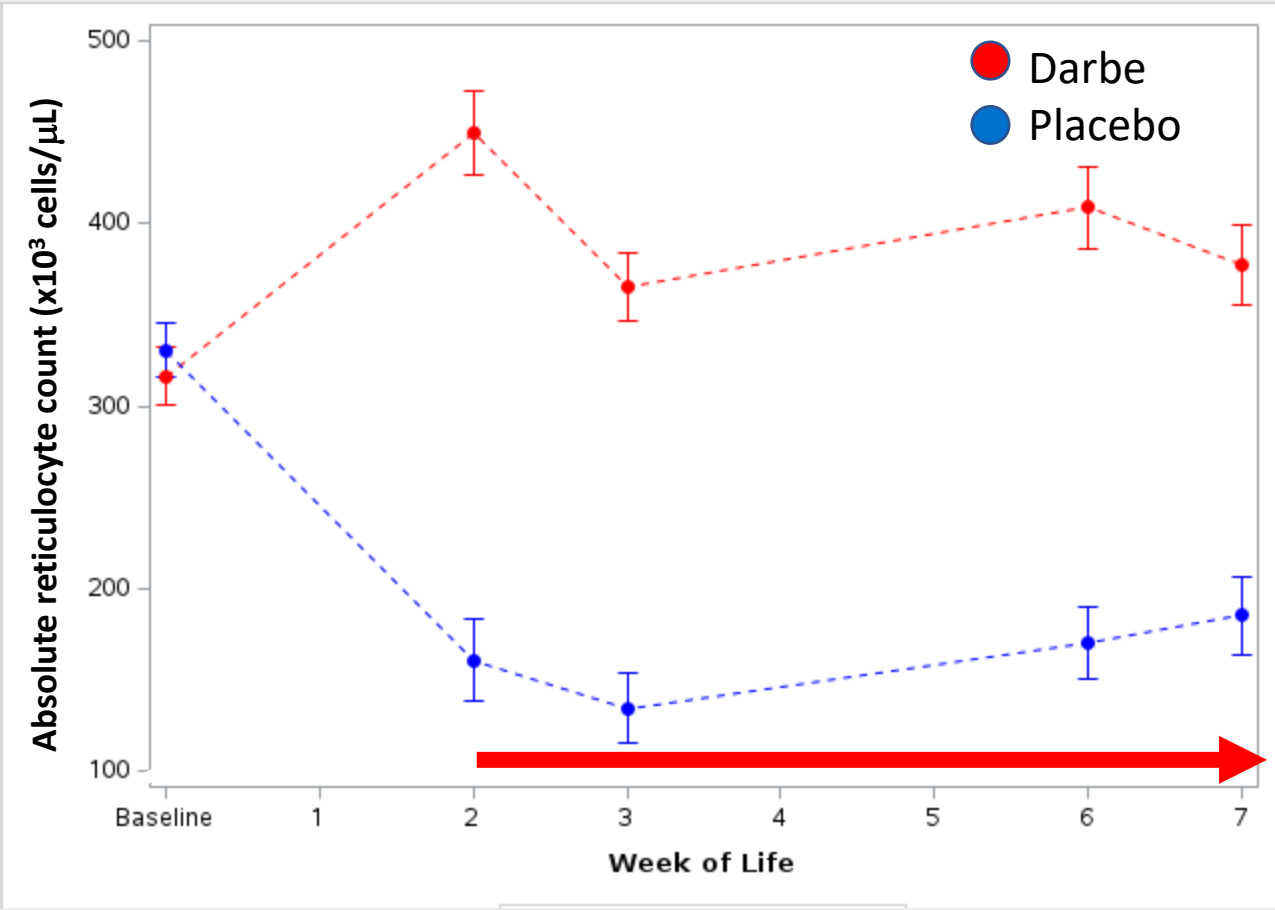
Characteristics	Darbe	Placebo	Adjusted Mean Difference, Relative Risk (95% CI)
Total Subjects	319	327	
Never transfused (%)	40	31	0.7 (0.7 to 0.8)
Number of transfusions mean (SD)	1.3 (2.1)	2.0 (2.4)	-0.5 (-0.7 to -0.3)
Volume of transfusions, mL (if transfused; mean [SD])	54 (52)	69 (51)	-17.3 (-26.7 to -8.9)
Donor exposures mean (SD)	1.6 (2.3)	2.2 (2.3)	-0.3 (-0.5 to -0.2)

Red Cell Mass was greater in Darbe group



Hematocrit and Reticulocyte Count were higher in Darbe group





Hospital Outcomes

Characteristics	Darbe	Placebo	Adjusted Mean Difference, Relative Risk (95% CI)
Death, %	16	15	1.0 (0.7 to 1.4)
Necrotizing Enterocolitis ≥Bells II, % (n/N)	4 (14/319)	4 (13/327)	1.0 (0.5 to 2.1)
Retinopathy of Prematurity ≥Stage 3, % (n/N)	13 (35/273)	16 (45/279)	0.8 (0.5 to 1.2)
Intraventricular Hemorrhage ≥Grade II (%)	24 (77/315)	24 (76/318)	1.0 (0.8 to 1.3)
Bronchopulmonary Dysplasia grades 2 or 3 (%)	35 (91/261)	46 (128/277)	0.8 (0.6 to 0.96)
Length of hospital stay (days; mean, SD)	96 (58)	105 (67)	-9.2 (-19.3 to 1.0)

Safety

No differences noted between treatment groups in

- thromboses
- hypertension
- seizures

Similar incidence in common morbidities of prematurity:

- ROP
- IVH
- NEC

Lower incidence of BPD in darbepoetin group

Summary

- Cognitive scores were similar in both groups
- Greater percentage of infants in the Darbe group were transfusion free
- Infants in the Darbe group had:
  - fewer transfusions
  - fewer donor exposures
  - higher hematocrits
  - increased red cell mass
  - less BPD

Neonatal Research Network Centers (2016-2021)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- University of Utah