Supplemental Table 1 Randomized clinical trial: paracetamol vs. indomethacin

References	Drug	Admin	Dosage	N	Closure rate %	Renal impairment			
						Renal dysfunction %	Urine output mL/kg/h	BUN mg/dL	Creatinine mg/dL
Davidson 2021	Paracetamol Indomethacin	IV IV	15 mg/kg/6 h 0.2–0.2 –0.2 mg/kg 0.2–0.25–0.25 mg/kg	17 21	N/A	N/A	No difference	N/A	No difference
El-Mashad 2017	Paracetamol Indomethacin Ibuprofen	IV IV IV	15 mg/kg/6 h 0.2–0.2–0.2 mg/kg 10–5–5 mg/kg	100 100 100	88 87 83	N/A	2.24 ± 0.37 1.10 ± 0.37 1.69 ± 0.60	20.60 ± 2.80 32.00 ± 3.62 22.10 ± 3.04	0.55 ± 0.05 0.90 ± 0.19 0.69 ± 0.16
Meena 2020	Paracetamol Indomethacin Ibuprofen	IV Oral Oral	15 mg/kg/6 h 0.2–0.1 –0.1 mg/kg 0.2–0.2 –0.2 mg/kg 0.2–0.25–0.25 mg/kg 10–5–5 mg/kg	35 35 35	71 68 77	N/A	N/A	30.34 ± 10.23 43.42 ± 7.30 34.74 ± 8.59	0.76 ± 0.23 1.01 ± 0.26 0.92 ± 0.34
Dash 2015	Paracetamol Indomethacin	Oral IV	15 mg/kg/6 h 0.2–0.2–0.2 mg/kg	38 39	100 95	3 0	N/A	N/A	N/A

Sipplemental Table 2 Trial synopsis

Study title	**Randomized controlled trial to evaluate the safety and efficacy of *i*ntravenous *PA*racetamol for treatment of *P*atent ductus arteriosus in *P*reterm infants**
Study aims	To examine the safety of intravenous paracetamol therapy for hsPDA in premature infants
Outcomes	***Primary***: Incidence of renal dysfunction from the start of treatment to 48 hours from the last dose of the study drug ***Secondary***: Percentage of DA closure at 24 hours from the last dose of the study drug; Percentage of successful treatment at 24 hours from the last dose of the study drug; Percentage of reopening of DA between 24 and 48 hours from the last dose of the study drug; Adverse events from the start of treatment to 48 hours from the last dose of the study drug; Changes in the laboratory values from the start of treatment to 24 or 48 hours from the last dose of the study drug
Design	Open-label, controlled, parallel, two-arm, randomized, phase III multi-center trial, stratified by GA and history of prophylactic indomethacin for the prevention of IVH
Inclusion criteria	**1.** Born with GA of 24–35 weeks and BW of 500–2,000 g **2.** 24 hours to 7 days old **3.** Diagnosed with hsPDA **4.** Informed parental consent
Exclusion criteria	**1.** History of drug therapy for PDA; **2.** History of systemic administration of steroids; **3.** Congenital heart disease; **4.** Congenital malformation; **5.** Fetal hydrops; **6.** Severe infection; **7.** Pulmonary hypertension; **8.** IVH; **9.** Hyperbilirubinemia; **10.** Necrotizing enterocolitis; **11.** Perforation of the stomach or gastrointestinal tract; **12.** Bleeding tendency; **13.** Serum creatinine level >1.5 mg/dL; **14.** Urine output <1 mL/kg/H for 24 hours before enrollment or <0.5 mL/kg/H for 24 hours after birth; **15.** Platelet count <50,000/ul; **16.** Increase in ALT or AST; **17.** Judged to be ineligible for participation in this study by the investigators
Intervention	***Intervention*:** Intravenous paracetamol 15 mg/kg every 6 hours for 3 days ***Control*:** Intravenous indomethacin 0.1–0.2 mg/kg intravenous every 24 hours for 3 days
Study product	***Active*:** Paracetamol 10 mg/mL ***Control*:** Indomethacin 1 mg
Schedule	Vital signs to be measured during the screening period and on Days 1, 2, 3, 4, 5, 7, and 14 Urine output (24 hours) will be measured for Days 1, 2, and 3 Patient to be weighed during the screening period and on Day 1 Ultrasound examinations to be performed during the screening phase, Day 1, 2, 3, and 24 and 48 hours from the last dose of the study drug Chest x-ray examinations to be performed during the screening phase Laboratory tests to be performed during the screening phase and on Days 1, 2, 3, 4, 5, 7, and 14 Acetaminophen blood levels to be measured 24 hours from the last dose of the study drug NTproBNP measurements to be performed on Day 1 and 24 hours from the last dose of the study drug
Preparation	Paracetamol (10 mg/mL) to be administered without dilution

	Indomethacin (1 mg) to be diluted to 0.1 mg/mL in 10 mL of solutions
Sample size	**n = 110**; 55/group; assuming that approximately 25% of infants would have renal dysfunction by intravenous indomethacin, a sample size of at least 49 infants per group would be required to detect a 20% reduction in the rate of renal dysfunction, with 95% CI and power of 80%

DA, ductus arteriosus; PDA, patent ductus arteriosus; hsPDA, hemodynamically significant PDA; GA, gestational age; BW, birth weight; IVH, intraventricular hemorrhage; ALT, alanine aminotransferase; AST, aspartate aminotransferase