Original Article

DE: csolomon
ME: mprince

Colors for Text Alternatives
Print-only text
Web-only text

Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus{q1}

Tim Hundscheid, M.D., Wes Onland, M.D., Ph.D., Elisabeth M.W. Kooi, M.D., Ph.D., Daniel C. Vijlbrief, M.D., Ph.D., Willem B. de Vries, M.D., Ph.D., Koen P. Dijkman, M.D., Anton H. van Kaam, M.D., Ph.D., Eduardo Villamor, M.D., Ph.D., André A. Kroon, M.D., Ph.D., Remco Visser, M.D., Ph.D., Susanne M. Mulder-de Tollenaer, M.D., Barbara De Bisschop, M.D., Peter Dijk, M.D., Ph.D., Daniela Avino, M.D., Catheline Hocq, M.D., Alexandra Zecic, M.D., Marisse Meeus, M.D., Tessa de Baat, M.D., Frank Derriks, M.D., Tine{q2} Brink Henriksen, M.D., Ph.D., Kasper{q3} Jacobsen Kyng, M.D., Ph.D., Rogier Donders, Ph.D., Debbie H.G.M.{q4} Nuytemans, , Bart van Overmeire, M.D., Ph.D., Antonius L. Mulder, M.D., Ph.D., and Willem P. de Boode, M.D., Ph.D., for the BeNeDuctus Trial Investigators*

The authors' affiliations are as follows:From the Department of Pediatrics,{q5} Division of Neonatology (T.H., W.P.B.), and the Department for Health Evidence (R.D.), Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, the Department of Neonatology, Amsterdam Reproduction and Development, Emma Children's Hospital, Amsterdam University Medical Centers (W.O., W.B.V., A.H.K., T.B.), and Neonatology Network Netherlands (D.N.{q6}), Amsterdam, University Medical Center Groningen, Beatrix Children's Hospital, and the Department of Pediatrics, Division of Neonatology, University of Groningen (E.M.W.K., P.D.), Groningen, the Division of Woman and Baby, Department of Neonatology, University Medical Center Utrecht, Utrecht University, Wilhelmina Children's Hospital, Utrecht (D.V.{q7}, W.B.V.), the Department of Neonatology, Maxima Medical Center Veldhoven, Veldhoven (K.P.D.), Maastricht University Medical Center, the Department of Pediatrics, Division of Neonatology, School for Oncology and Reproduction, University of Maastricht, Maastricht (E.V.), the Department of Pediatrics, Division of Neonatology, Erasmus Medical Center Rotterdam, Sophia Children's Hospital, Rotterdam (A.A.K.), the Department of Pediatrics, Division of Neonatology, Leiden University Medical Center, Willem Alexander Children's Hospital, Leiden (R.V.), and the Department of Pediatrics, Division of Neonatology, Isala Women's and Children's Hospital Zwolle, Zwolle (S.M.M.-T.) — all in the Netherlands; the Department of Neonatology, Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel (B.D.B.), the Department of Pediatrics, Division of Neonatology, Hôpital Universitaire des Enfants Reine Fabiola (D.A.), the Department of Pediatrics, Division of Neonatology, Cliniques Universitaires St. Luc (C.H.), the Department of Neonatology, Cliniques Universitaires de Bruxelles, Hôpital Erasme (F.D.), and Opgroeien — Kind en Gezin, Flemish Government, Sint-Gillis (B.O.), Brussels, the Department of Pediatrics, Division of Neonatology, Ghent University Hospital, Ghent (A.Z.), and the Department of Pediatrics, Division of Neonatology, Antwerp University Hospital, Edegem (A.L.M., M.M.) — all in Belgium; and the Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark (T.B.H., K.J.K.).

Dr. de Boode can be contacted at willem.deboode@radboudumc.nl or at the Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands.{q8}

*A list of the investigators in the BeNeDuctus trial is provided in the Supplementary Appendix, available at NEJM.org.

Abstract{q9}

Background

Cyclooxygenase inhibitors are commonly used in infants with patent ductus arteriosus (PDA), but the benefit of these drugs is uncertain.

Methods

In this multicenter, noninferiority trial involving infants with echocardiographically confirmed PDA (diameter, >1.5 mm, with left-to-right shunting) who were extremely preterm (<28 weeks' gestational age) to receive either expectant management or early ibuprofen treatment. The primary composite outcome included necrotizing enterocolitis (Bell's stage IIa or higher), moderate to severe bronchopulmonary dysplasia, or death at 36 weeks' {q10} postmenstrual age. The noninferiority of expectant management was defined as an absolute between-group difference of 10 percentage points or less.

Results

A total of 273 infants underwent randomization. The median gestational age was 26 weeks, and the median birth weight was 845 g. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 (63.5%) in the early-ibuprofen group (adjusted risk difference [ARD], −17.2 {q11}percentage points; one-sided 95% confidence interval [CI], −7.4; P<0.001 for noninferiority). Necrotizing enterocolitis occurred in 24 of 136 infants (17.6%) in the expectant-management group and in 21 of 137 (15.3%) in the early-ibuprofen group (ARD, 2.3 percentage points; two-sided 95% CI, −6.5 to 11.1); bronchopulmonary dysplasia occurred in 39 of 117 infants (33.3%) and in 57 of 112 (50.9%), respectively (ARD, −17.6 percentage points; two-sided 95% CI, −30.2 to −5.0). Death occurred in 19 of 136 infants (14.0%) and in 25 of 137 (18.2%), respectively (ARD, −4.3 percentage points; two-sided 95% CI, −13.0 to 4.4). Rates of other adverse outcomes were similar in the two groups.

Conclusions

Expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to the primary composite outcome of necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' {q12}postmenstrual age. (Funded by the Netherlands Organization for Health Research and Development and the Belgian Health Care Knowledge Center; BeNeDuctus Dutch Trial Register number, NTR5479; ClinicalTrials.gov number, NCT02884219.{q13})

Patent ductus arteriosus (PDA) is common in preterm infants,[1] and its management is a subject of debate.[2-5] This heart defect, which occurs when the opening between the aorta and the pulmonary artery does not close normally, is associated with increased neonatal mortality and morbidity, including bronchopulmonary dysplasia,[6] necrotizing enterocolitis,[7] and intraventricular hemorrhage.[8]

Meta-analyses of randomized, controlled trials showed that pharmacologic treatment with cyclooxygenase inhibitors induced PDA closure but had no beneficial effect on clinical outcomes.[9,10] The lack of evidence supporting a causal relationship between PDA and neonatal morbidity and mortality and the potential adverse effects of pharmacologic treatment have led to more frequent

expectant (i.e., nonintervening) management of PDA.[11] However, the evidence to support this strategy is limited and contradictory.[12]

We performed the {q14}Early Treatment Versus Expectative Management of PDA in Preterm Infants (BeNeDuctus) trial in extremely preterm infants with echocardiographically confirmed PDA to assess whether expectant management would be noninferior to early ibuprofen treatment for the composite primary outcome of necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a {q15}postmenstrual age of 36 weeks.

Methods

Trial Design

The trial was an international, multicenter, randomized, controlled noninferiority trial conducted at 17 neonatal intensive care units in the Netherlands, Belgium, and Denmark and was {q16}funded by the Netherlands Organization for Health Research and Development and the Belgian Health Care Knowledge Center. Approval was granted by {q17}the ethics committees at Radboud University, Cliniques Universitaires de Bruxelles–Hôpital Erasme, and the Central Denmark Region.

The trial protocol and statistical analysis plan have been published previously[13,14] and are available in the protocol document with the full text of this article, available at NEJM.org. Written {q18}informed consent was obtained from the parents or guardians of all the infants who were included in the trial.

Patients

Infants with extremely premature birth (gestational age, <28 weeks) who had echocardiographically confirmed PDA with a diameter of more than 1.5 mm at the smallest point and who had a transductal left-to-right shunt between 24 and 72 hours postnatal age were eligible.[13] Exclusion criteria were contraindications to the administration of ibuprofen, the use of a cyclooxygenase inhibitor before randomization, persistent pulmonary hypertension (defined as a transductal right-to-left shunt during ≥33% of the cardiac cycle), a congenital heart defect (other than PDA or patent foramen ovale), a life-threatening congenital defect or chromosomal abnormality, or a congenital anomaly that was associated with an abnormal neurodevelopmental outcome.[13]

Randomization

As part of the consent process, parents were informed of the uncertainty as to whether PDA plays a causal role in neonatal morbidity and mortality or whether the condition is simply a marker of immaturity and that the best approach to management thus remains unclear{q19}. After provision of consent, the infants were randomly assigned to receive either expectant management or early ibuprofen treatment. Randomization was coordinated centrally with the use of a Web-based system and was stratified according to trial center and gestational age (<26 weeks or ≥26 weeks). Block sizes varied within a range of 4 to 8.

Multiple-birth infants underwent independent randomization, unless the parents explicitly requested that all siblings be enrolled in the same trial group.

Intervention

In the expectant-management group, no treatment was initiated with the intention of closing the PDA. Unblinded echocardiography was allowed if indicated by the local pediatric cardiologist {q20}or after a primary-outcome event had occurred. Open-label pharmacologic treatment could be considered only if prespecified criteria had been met for clinical and echocardiographic findings of cardiovascular failure associated with a clinically significant left-to-right shunt (Table {q21}S1A in the Supplementary Appendix, available at NEJM.org).[13]

In the early-ibuprofen group, ibuprofen was administered according to the local protocol, preferably within 3 hours after randomization. After a complete course of ibuprofen, echocardiographic evaluation was performed at least 12 hours after the last dose. Closure was defined as a ductus arteriosus that either could not be visualized with the use of color Doppler imaging or had a transductal diameter of less than 0.5 mm.[13] If closure had not been achieved, a second course of ibuprofen was given. After two failed courses, a third course of ibuprofen or ductal ligation could be considered if prespecified criteria had been met for clinical and echocardiographic findings of cardiovascular failure associated with a clinically significant left-to-right shunt (Table S1B).[13]

Outcomes

The primary outcome was a composite of necrotizing enterocolitis (defined as Bell's stage IIa or higher),[15] moderate-to-severe bronchopulmonary dysplasia, or death as assessed at a {q22}postmenstrual age of 36 weeks. In accordance with the international standard criteria of Bancalari{q23} and Claure,[16] bronchopulmonary dysplasia was defined as the need for supplemental oxygen or positive-pressure ventilatory support at a postmenstrual age of 36 weeks after at least 28 cumulative days of supplemental oxygen. This diagnosis included the performance of an oxygen reduction test according to the criteria of Walsh et al.,[17] if indicated (see the Supplementary Methods{q24}). If the indicated oxygen reduction test was not performed, a committee of three investigators who had extensive clinical expertise and who were unaware of trial-group assignments assessed the severity of bronchopulmonary dysplasia as mild or moderate. All outcome measures and their definitions (including cause of death) are summarized in Table S2.

Information was also collected from the electronic medical record regarding adverse events and serious adverse events that were not among the secondary outcomes, as well as protocol deviations.[14]

Statistical Analysis

For the {q25}primary analysis, we prespecified a noninferiority margin of 10 percentage points. Noninferiority would be established if the one-sided 95% confidence interval for the observed difference in the percentage of patients

in the expectant-management group and the early-ibuprofen did not exceed 10 percentage points. With an estimated a priori risk for a primary-outcome event of 35%, a type I error of 5%, and a power of 80%, we determined that a sample size of 564 patients (282 per group) would be required to exclude the noninferiority margin. Trial enrollment ended on December 15, 2020, before the anticipated sample size had been reached after the randomization of 273 patients (48.4% of the powered sample size), owing to the discontinuation of funding and slower-than-anticipated recruitment.[14]

We performed both an intention-to-treat analysis that included all the patients who had undergone randomization and a per-protocol analysis that included infants in the expectant-management group who had received open-label pharmacologic treatment after meeting the criteria but that excluded those who did not fulfill the criteria. We also excluded infants in the early-ibuprofen group who had not receive any ibuprofen. We also performed five predefined exploratory subgroup analyses and four sensitivity analyses for the primary outcome. Details regarding these analyses are provided in the Supplementary Methods.

Treatment effects for components of the primary outcome and for secondary dichotomous clinical outcomes are reported as an absolute risk difference and relative risk with two-sided 95% confidence intervals for the expectant-management group as compared with the early-ibuprofen group. No adjustment was made for multiple testing, so the widths of the 95% confidence intervals should not be used in place of hypothesis testing. Normally distributed data are presented as means and standard deviations, and unevenly distributed data are presented as medians with interquartile ranges.

Results

Patients

Between December 2016 and December 2020, a total of 1600 infants who had been born at less than 28 weeks' gestation were admitted to the neonatal intensive care units at the participating centers (Fig. 1). Written informed consent was obtained for 442 infants, of whom 273 (61.8%) underwent randomization (136 to the expectant-management group and 137 to the early-ibuprofen group).

In the early-ibuprofen group, ibuprofen was initiated at a median postnatal age of 63 hours (interquartile range, 55 to 70) at a median dose of 10 mg per kilogram of body weight (interquartile range{q26}, 10 to 10), followed by two subsequent doses of 5 mg per kilogram (interquartile range, 5 to 5) (Table S3). The baseline characteristics of the infants and their mothers were similar, except for a greater incidence of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) among mothers in the expectant-management group (Table 1 and Table S4). All the infants were included in the intention-to-treat analysis (Fig. S1). The representativeness of the included cohort is shown in Table S5.

Primary Outcome

At 36 weeks' {q27}postmenstrual age, data regarding the primary composite outcome were available for all 273 infants. In 6 infants, the indicated oxygen reduction test had not been performed, so the severity of bronchopulmonary dysplasia was classified by the committee. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 infants (63.5%) in the early-ibuprofen group (adjusted risk difference, –17.2 percentage points; one-sided 95% CI, –7.4; P<0.001) (Table 2).

Secondary Outcomes

No material between-group differences in the incidence of necrotizing enterocolitis and death were observed (Table 2). Distributions of reported causes of death were similar in the two groups (Table S6). Moderate-to-severe bronchopulmonary dysplasia was diagnosed in 39 of 117 infants (33.3%) in the expectant-management group and in 57 of 112 infants (50.9%) in the early-ibuprofen treatment group (adjusted risk difference, –17.6 percentage points; 95% CI, –30.2 to –5.0). Other secondary outcome measures and cointerventions are shown in Table 3 and Tables S7 and S8.

Adverse Events and Per-Protocol Analysis

The frequencies of adverse events and serious adverse events were similar in the two groups (Table 4).

In the per-protocol analysis, the primary composite outcome was observed in 60 of 133 infants (45.1%) in the expectant-management group and in 83 of 132 (62.9%) in the early-ibuprofen group (adjusted risk difference, –17.8 percentage points; one-sided 95% CI, –7.9; P<0.001) (Table 2). Excluded from the per-protocol analysis were 3 infants in the expectant-management group and 5 infants in the early-ibuprofen group (Fig. 1 and Table S9).

The results of secondary outcomes in the per-protocol analysis were similar to those obtained in the intention-to-treat analysis (Tables S8 and S10).

Subgroup Analyses

Results for the primary outcome in predefined subgroups are provided Table S11. The results of subgroup analyses were consistent with the overall findings, with the exception of a potential difference according to sex that suggested a better outcome for expectant management in male infants than in female infants.

Sensitivity Analyses

In the predefined sensitivity analysis with a modified classification of bronchopulmonary dysplasia,[18] a primary-outcome event was observed in 53 of 136 infants (39.0%) in the expectant-management group and in 68 of 137 infants (49.6%) in the early-ibuprofen group (adjusted risk difference, –10.7 percentage points; one-sided 95% CI, –0.8) (Table S12).

The adjusted odds ratios after adjustment for multiple births and for the stratification variables of trial center and gestational age were similar to those

obtained in the intention-to-treat, per-protocol, and auxiliary sensitivity analyses (Table S12).

Discussion

In this international, randomized, controlled trial, expectant management of PDA in preterm infants was noninferior to early-ibuprofen treatment at a postnatal age of 24 to 72 hours with respect to the primary composite outcome of necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death, as assessed at 36 weeks' postmenstrual age. This observation is in line with previous evidence regarding the lack of beneficial effects of pharmacologic PDA treatment on clinical outcomes reported in meta-analyses[9,10] and in the most recent placebo-controlled randomized, controlled trials investigating various strategies for the management of PDA.[19-22]

A placebo-controlled pilot trial showed that early targeted ibuprofen treatment in preterm infants did not reduce the incidence of the combined outcome of bronchopulmonary dysplasia or death.[19] Another study showed that among infants with a mean postnatal age of 8.3 days, nonintervention was noninferior to late ibuprofen treatment with regard to the combined outcome of bronchopulmonary dysplasia or death.[20]

In contrast to previous studies with a high incidence of open-label treatment,[19] our trial had a true nonintervention control group, which allowed for a clearer comparison between expectant management and ibuprofen treatment. In another study, investigators did not evaluate any open-label treatment and reported only the results of their per-protocol analysis; in their nonintervention group, judicious fluid restriction, use of diuretics, and changes in ventilatory settings targeting the PDA were allowed.[20]

In our trial, the primary-outcome results suggest harm associated with early ibuprofen exposure, largely driven by a higher incidence of moderate-to-severe bronchopulmonary dysplasia in the early-ibuprofen group than in the expectant-management group. This result contrasts with the general hypothesis that pulmonary hyperperfusion associated with transductal left-to-right shunting is the plausible pathophysiological mechanism for the occurrence of bronchopulmonary dysplasia. According to this hypothesis, PDA closure is expected to normalize pulmonary perfusion, as supported by data from a baboon model showing improved alveolarization after ibuprofen treatment.[23] The suggestion of a higher risk of bronchopulmonary dysplasia in the ibuprofen group is consistent with observational data showing associations between ibuprofen use and the development of bronchopulmonary dysplasia[24,25] and is supported by in vitro and in vivo studies suggesting that angiogenesis may be inhibited by ibuprofen.[26,27] A recent prospective study showed decreased vascular growth factors in preterm infants with PDA after exposure to ibuprofen.[28] Of note, previous randomized trials have not shown an increase in the risk of bronchopulmonary dysplasia with ibuprofen treatment. It is possible that this

discrepancy can be explained by the high percentage of infants who received open-label treatment in the expectant-management group in these trials.[9,13]

Our exploratory analyses raise the possibility of a sex-related difference in the effects of the intervention on the primary outcome, which suggests a benefit specifically for male infants who received expectant management. However, this analysis was one of several secondary and subgroup analyses that were performed without adjustment for multiplicity, so the results may be explained by chance. Effect modification according to sex has not been reported in other trials, and further study is needed to confirm this finding.

Our trial focused on the short-term effects of PDA management in the neonatal period and cannot inform management beyond this period, including whether neonatal follow-up should include routine echocardiographic screening for potentially prolonged exposure to transductal left-to-right shunting. Although spontaneous closure of untreated PDA before discharge occurs in up to 85% of patients,[29] in a cohort of patients who had been discharged home with a PDA, 8.4% underwent assisted PDA closure at a median postnatal age of 349 days.[30]

Our trial has several limitations. The main limitation is that even though the investigators recruited infants at 17 centers for almost 4 years, enrollment was stopped after only 48% of the planned sample size had undergone randomization. However, we found that expectant management was noninferior to early ibuprofen, and indeed outcomes appeared to be worse in the ibuprofen group. The PDA diameter, which was used as an inclusion criterion, is an imperfect indicator of hemodynamically significant PDA,[31] even though it is the most commonly used measure to guide management.[11] Our trial was unblinded because it was designed to compare the two most commonly used strategies for PDA management. However, we consider bias to be unlikely in the assessment of the components of the primary composite outcome{q28}; in the six cases in which the classification of the severity of bronchopulmonary dysplasia involved clinician judgment because the indicated oxygen reduction test had not been performed, assessment was made by experts who were unaware of treatment assignments. In addition, the majority of enrolled infants were White and had a gestational age of more than 24 weeks at randomization. Because infants were recruited soon after birth, they did not have prolonged exposure to a moderate-to-large shunt, to invasive ventilation, or both, so the results may not be generalizable to infants of different races or gestational ages or to those receiving prolonged invasive ventilation. In the intervention group, ibuprofen was administered according to local protocols. Although most centers used an initial intravenous ibuprofen dose of {q29}10 mg per kilogram, followed by 5 mg per kilogram at 24 and at 48 hours after the first dose, higher-dose ibuprofen (15/7.5/7.5 to 20/10/10 mg per kilogram) may be more effective in inducing PDA closure.[10,32] However, the closure rate in our trial after a first course was similar to that in earlier randomized, controlled trials of ibuprofen treatment.[19,32,33]

The results of this trial should not be interpreted to suggest that there is no causal relationship between PDA and neonatal morbidity in extremely preterm

infants. Pathophysiologically, a high transductal left-to-right shunt volume with subsequent pulmonary hyperperfusion and systemic hypoperfusion may indeed have adverse consequences; evidence suggests that prolonged shunt exposure is associated with development of bronchopulmonary dysplasia.[34,35] Rather, it is plausible that an attempt to close the PDA with ibuprofen may be more harmful than the condition itself. Safer and more effective treatments for a PDA with a high left-to-right shunt volume warrant study.

In this international multicenter trial involving extremely preterm infants with a gestational age below 28 weeks, expectant management for a PDA measuring more than 1.5 mm in diameter was noninferior to early ibuprofen treatment with regard to a composite outcome of necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death, and results suggested a lower risk of this outcome in the expectant-management group.

Published/updated

This article was published on December 6, 2022, at NEJM.org.

Data sharing

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.{q30}

Supported by

Supported by the Netherlands Organization for Health Research and Development (project number, 843002622) and the Belgian Health Care Knowledge Center (project number, KCE-16013{q31}).

Financial disclosure

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org{q32}.

Acknowledgments

We thank {q33}the parents who consented to have their infants participate in the trial; the members of the data and safety monitoring board: Anne van Kempen (neonatologist), Caroline van Baal (biostatistician), and Hans Breur (pediatric cardiologist); research coordinators Karin Deckers and Wendy Jansen; and all the research nurses at the trial sites for their support.

References

1. Lee JA, Kim M-J, Oh S, Choi BM. Current status of therapeutic strategies for patent ductus arteriosus in very-low-birth-weight infants in Korea. J Korean Med Sci 2015;30:Suppl 1:S59-S66. [PMID: 26566359]
2. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241-52. [PMID: 20182439]
3. Benitz WE. Hey, doctor, leave the PDA alone. Pediatrics 2017;140(2):e20170566. [PMID: 28701391]
4. Sankar MN, Bhombal S, Benitz WE. PDA: to treat or not to treat. Congenit Heart Dis 2019;14:46-51. [PMID: 30811796]
5. Hundscheid T, El-Khuffash A, McNamara PJ, de Boode WP. Survey highlighting the lack of consensus on diagnosis and treatment of patent ductus arteriosus in prematurity. Eur J Pediatr 2022;181:2459-68. [PMID: 35305143]
6. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr 1979;95:865-6. [PMID: 490263]
7. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr 2005;40:184-8. [PMID: 15699694]
8. Lipman B, Serwer GA, Brazy JE. Abnormal cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatrics 1982;69:778-81. [PMID: 7079043]
9. Jansen EJS, Hundscheid T, Onland W, Kooi EMW, Andriessen P, de Boode WP. Factors associated with benefit of treatment of patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. Front Pediatr 2021;9:626262. [PMID: 33634058]
10. Mitra S, Florez ID, Tamayo ME, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA 2018;319:1221-38. [PMID: 29584842]
11. Ngo S, Profit J, Gould JB, Lee HC. Trends in patent ductus arteriosus diagnosis and management

for very low birth weight infants. Pediatrics 2017;139(4):e20162390. [PMID: 28562302]
12. Hundscheid T, Jansen EJS, Onland W, Kooi EMW, Andriessen P, de Boode WP. Conservative management of patent ductus arteriosus in preterm infants — a systematic review and meta-analyses assessing differences in outcome measures between randomized controlled trials and cohort studies. Front Pediatr 2021;9:626261. [PMID: 33718300]
13. Hundscheid T, Onland W, van Overmeire B, et al. Early treatment versus expectative management of patent ductus arteriosus in preterm infants: a multicentre, randomised, non-inferiority trial in Europe (BeNeDuctus trial). BMC Pediatr 2018;18:262. [PMID: 30077184]
14. Hundscheid T, Donders R, Onland W, et al. Multi-centre, randomised non-inferiority trial of early treatment versus expectant management of patent ductus arteriosus in preterm infants (the BeNeDuctus trial): statistical analysis plan. Trials 2021;22:627. [PMID: 34526095]
15. Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996;43:409-32. [PMID: 8614608]
16. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol 2006;30:164-70. [PMID: 16860155]
17. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics 2004;114:1305-11. [PMID: 15520112]
18. Onland W, Merkus MP, Nuytemans DH, et al. Systemic hydrocortisone to prevent bronchopulmonary dysplasia in preterm infants (the SToP-BPD study): statistical analysis plan. Trials 2018;19:178. [PMID: 29523175]
19. El-Khuffash A, Bussmann N, Breatnach CR, et al. A pilot randomized controlled trial of early targeted patent ductus arteriosus treatment using a risk based severity score (The PDA RCT). J Pediatr 2021;229:127-33. [PMID: 33069668]
20. Sung SI, Lee MH, Ahn SY, Chang YS, Park WS. Effect of nonintervention vs oral ibuprofen in patent ductus arteriosus in preterm infants: a randomized clinical trial. JAMA Pediatr 2020;174:755-63. [PMID: 32539121]
21. Rozé JC, Cambonie G, Le Thuaut A, et al. Effect of early targeted treatment of ductus arteriosus with ibuprofen on survival without cerebral palsy at 2 years in infants with extreme prematurity: a randomized clinical trial. J Pediatr 2021;233:33-42.e2. [PMID: 33307111]
22. Clyman RI, Liebowitz M, Kaempf J, et al. PDA-TOLERATE trial: an exploratory randomized controlled trial of treatment of moderate-to-large patent ductus arteriosus at 1 week of age. J Pediatr 2019;205:41-48.e6. [PMID: 30340932]
23. McCurnin D, Seidner S, Chang L-Y, et al. Ibuprofen-induced patent ductus arteriosus closure: physiologic, histologic, and biochemical effects on the premature lung. Pediatrics 2008;121:945-56. [PMID: 18450898]
24. Chen X, Qiu X, Sun P, et al. Neonatal ibuprofen exposure and bronchopulmonary dysplasia in extremely premature infants. J Perinatol 2020;40:124-9. [PMID: 31391526]
25. Termerova J, Kubena AA, Paslerova R, Liska K. Worse outcomes of early targeted ibuprofen treatment compared to expectant management of patent ductus arteriosus in extremely premature infants. J Clin Neonatol 2021;10:209-15.
26. Beharry KD, Modanlou HD, Hasan J, et al. Comparative effects of early postnatal ibuprofen and indomethacin on VEGF, IGF-I, and GH during rat ocular development. Invest Ophthalmol Vis Sci 2006;47:3036-43. [PMID: 16799050]
27. Akrami H, Aminzadeh S, Fallahi H. Inhibitory effect of ibuprofen on tumor survival and angiogenesis in gastric cancer cell. Tumour Biol 2015;36:3237-43. [PMID: 25542229]
28. Huang X, Han D, Wei Y, et al. Decreased plasma levels of PDGF-BB, VEGF-A, and HIF-2α in preterm infants after ibuprofen treatment. Front Pediatr 2022;10:919879. [PMID: 35958170]
29. Semberova J, Sirc J, Miletin J, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics 2017;140(2):e20164258. [PMID: 28701390]
30. Tolia VN, Powers GC, Kelleher AS, et al. Low rate of spontaneous closure in premature infants discharged with a patent ductus arteriosus: a multicenter prospective study. J Pediatr 2022;240:31-36.e2. [PMID: 34293369]
31. El-Khuffash A, James AT, Corcoran JD, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr 2015;167(6):1354-1361.e2. [PMID: 26474706]
32. Pourarian S, Takmil F, Cheriki S, Amoozgar H. The effect of oral high-dose ibuprofen on patent ductus arteriosus closure in preterm infants. Am J Perinatol 2015;32:1158-63. [PMID: 26007314]
33. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674-81. [PMID: 10974130]
34. Mirza H, Garcia J, McKinley G, et al. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. J Perinatol 2019;39:1648-55. [PMID: 31554913]
35. Schena F, Francescato G, Cappelleri A, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr 2015;166:1488-92. [PMID: 25882876]

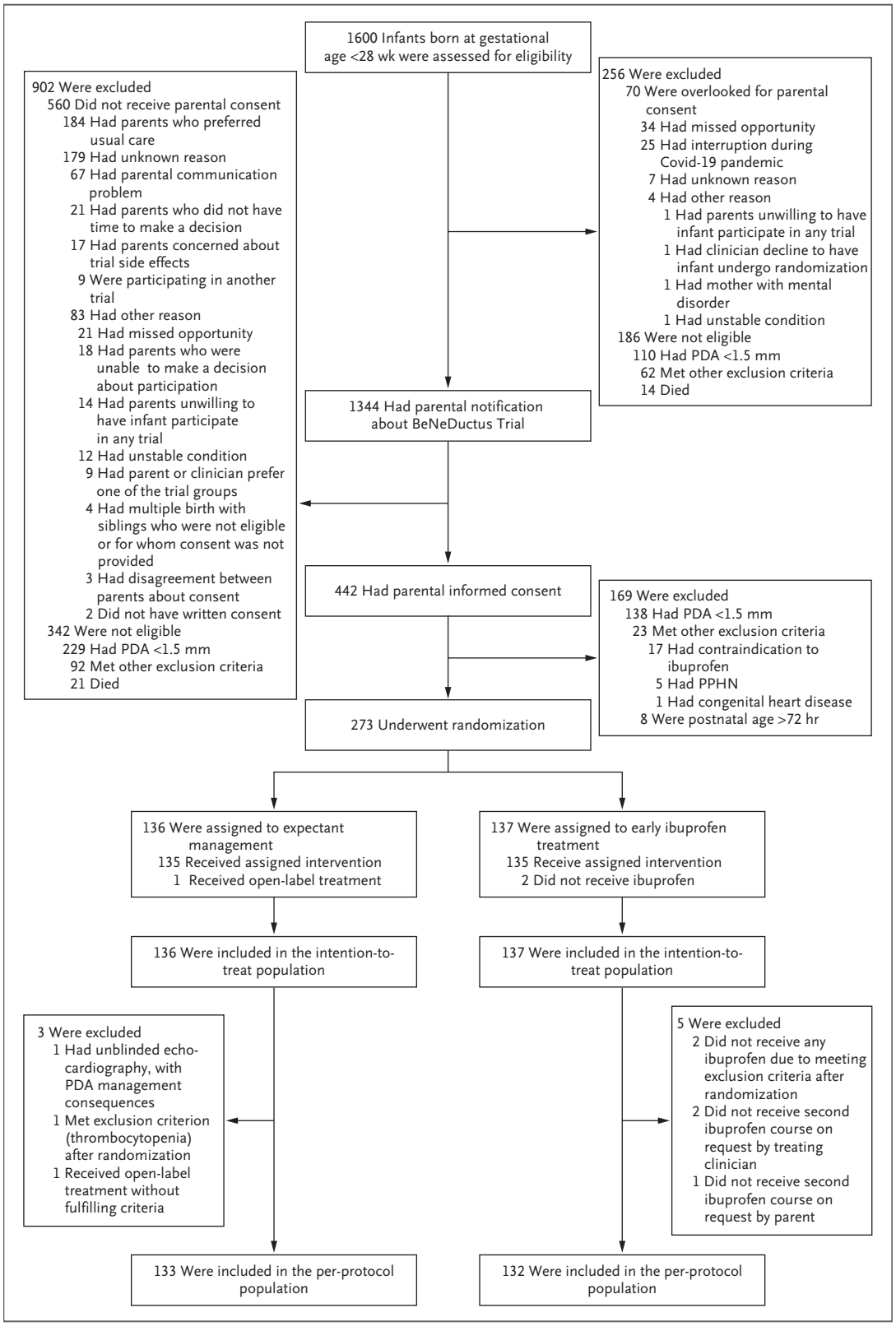

Figure 1. Randomization and{q34} Outcomes.

At trial sites in which echocardiography was performed as common practice, informed consent could be obtained after echocardiographic assessment of eligibility, whereas at sites in which echocardiography was considered to be a trial procedure, informed consent had to be obtained before eligibility could be assessed. Covid-19 denotes coronavirus disease 2019, PDA patent ductus arteriosus, and PPHN persistent pulmonary hypertension of the newborn.

Table 1. Maternal and Neonatal Characteristics at Baseline.*

Characteristic	Expectant Management (N=136)	Early Ibuprofen (N=137)
Maternal		
Age — yr	30.4±5.4	31.0±5.1
Race or ethnic group — no. (%)†		
White	102 (75.0)	110 (80.3)
Mediterranean	10 (7.4)	9 (6.6)
African	12 (8.8)	7 (5.1)
Asian	2 (1.5)	4 (2.9)
Latin American	2 (1.5)	3 (2.2)
Unknown	8 (5.9)	4 (2.9)
Obstetrical condition — no. (%)		
Preeclampsia	15 (11.0)	18 (13.1)
HELLP syndrome	7 (5.1)	1 (0.7)
Placental abruption	6 (4.4)	3 (2.2)
PPROM	36 (26.5)	40 (29.2)
Clinical chorioamnionitis	52 (38.2)	53 (38.7)
Medication history — no./total no. (%)	88/136 (64.7)	92/137 (67.2)
NSAID	15/136 (11.0)	19/137 (13.9)
Magnesium sulfate	86/136 (63.2)	85/137 (62.0)
Antenatal {q35}glucocorticoid		
Any	119/X (88.1)	126/X (93.3)
Course completed	73/X (54.1)	76/X (56.3)
Tocolysis	79/X (58.1)	{q36}84/X (62.2)
Type of delivery — no. (%)		
Vaginal	86 (63.2)	76 (55.5)
Cesarean section	50 (36.8)	61 (44.5)
Multiple birth — no. (%)	47 (34.6)	50 (36.5)
Neonatal		
Median{q37} gestational age (IQR) — wk	26.1 (25.4–27.0)	26.0 (25.1–27.0)
Median birth weight (IQR) — g	863 (748–984)	825 (715–970)
Outborn — no. (%)	10 (7.4)	8 (5.8)
Male sex — no. (%)	70 (51.5)	70 (51.1)
Median Apgar score at 5 min (IQR)	7 (6–8)	8 (7–8)
Support during fetal–neonatal transition — no. (%)	133 (97.8)	137 (100)
Noninvasive respiratory support	101 (74.3)	103 (75.2)
Invasive respiratory support	32 (23.5)	34 (24.8)
Circulatory support	0	0
Respiratory distress syndrome — no. (%)	117 (86.0)	116 (84.7)
Surfactant {q38}administration		
Infants — no./total no. (%)	103/X (88.0)	106/X (91.4)
Median no. of surfactant doses (IQR)	1 (1–2)	1 (1–2)
Median postnatal age at time of echocardiography (IQR) — hr	57 (47–65)	57 (44–64)
Median diameter of patent ductus arteriosus (IQR) — mm	2.1 (1.8–2.5)	2.1 (1.8–2.6)

* Plus–minus values are means ±SD. IQR denotes interquartile range; HELLP hemolysis, elevated liver enzymes, and low platelets; NSAID nonsteroidal antiinflammatory drug; and PPROM preterm premature rupture of membranes.
† Race or ethnic group was reported by the mothers.

Table 2. Primary Outcome{q39} and Its Components.*

Outcome	Intention-to-Treat Analysis				Per-Protocol Analysis			
	Expectant Management (N=136)	Early Ibuprofen (N=137)	ARD (95% CI)†	Risk Ratio (95% CI)	Expectant Management (N=133)	Early Ibuprofen (N=132)	ARD (95% CI)†	Risk Ratio (95% CI)
	number (percent)		*percentage points*		*number (percent)*		*percentage points*	
Primary composite outcome								
Necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death‡	63 (46.3)	87 (63.5)	−17.2 (−7.4)§	0.73 (0.59 to 0.91)	60 (45.1)	83 (62.9)	−17.8 (−7.9)§	0.72 (0.57 to 0.90)
Components of primary outcome¶								
Necrotizing enterocolitis	24 (17.6)	21 (15.3)	2.3 (−6.5 to 11.1)	1.15 (0.67 to 1.97)	23 (17.3)	21 (15.9)	1.4 (−7.6 to 10.3)	1.09 (0.63 to 1.87)
Moderate-to-severe bronchopulmonary dysplasia‖	39 (33.3)	57 (50.9)	−17.6 (−30.2 to −5.0)	0.66 (0.48 to 0.90)	37 (32.2)	55 (50.5)	−18.3 (−31.0 to −5.6)	0.64 (0.46 to 0.88)
Death	19 (14.0)	25 (18.2)	−4.3 (−13.0 to 4.4)	0.77 (0.44 to 1.32)	18 (13.5)	23 (17.4)	−3.9 (−12.6 to 4.8)	0.78 (0.44 to 1.37)

* ARD{q40} denotes adjusted risk difference.
† For the primary composite outcome, {q41}the 95% confidence intervals are one-sided. For the components of the primary outcome, the 95% confidence intervals are two-sided.
‡ The primary outcome and its components were measured at 36 weeks' {q42}postmenstrual age. Necrotizing enterocolitis was defined as Bell's stage IIa or higher.
§ P<0.001 for noninferiority in the prespecified primary analysis.
¶ The 95% confidence intervals for the components of the primary outcome have not been adjusted for multiplicity and should not be used in place of hypothesis testing.
‖ Moderate-to-severe bronchopulmonary dysplasia was measured in 117 infants in the expectant-management group and in 112 in the early-ibuprofen group in the intention-to-treat analysis and in 115 and 109 infants, respectively, in the per-protocol analysis.

Table 3. Secondary Outcome Measures (Intention-to-Treat Analysis).*

Secondary Outcome	Expectant Management (N=136)	Early Ibuprofen (N=137)	ARD (95% CI)†	Risk Ratio (95% CI)†
	number (percent)		*percentage points*	
Surgical patent ductus arteriosus ligation	0	3 (2.2)	−2.2 (−4.6 to 0.3)	NA
Death at 28 days	13 (9.6)	25 (18.2)	−8.7 (−16.8 to −0.5)	0.52 (0.28 to 0.98)
Pulmonary hemorrhage	4 (2.9)	1 (0.7)	2.2 (−1.0 to 5.4)	4.03 (0.46 to 35.59)
Pulmonary air leakage	6 (4.4)	16 (11.7)	−7.3 (−13.7 to −0.9)	0.38 (0.15 to 0.94)
Pneumothorax	2 (1.5)	3 (2.2)	−0.7 (−3.9 to 2.5)	0.67 (0.11 to 3.96)
Pulmonary interstitial emphysema	5 (3.7)	13 (9.5)	−5.8 (−11.7 to 0.0)	0.39 (0.14 to 1.06)
Cardiovascular support	60 (44.1)	57 (41.6)	−2.5 (−9.2 to 14.2)	1.06 (0.81 to 1.40)
Volume expansion	45 (33.1)	48 (35.0)	−1.9 (−13.2 to 9.3)	0.94 (0.68 to 1.31)
Inotropes or vasopressors	44 (32.4)	40 (29.2)	−3.2 (−7.8 to 14.1)	1.11 (0.78 to 1.58)
Glucocorticoids	18 (13.2)	15 (10.9)	2.3 (−5.4 to 10.0)	1.21 (0.64 to 2.30)
Renal failure‡	13 (9.6)	13 (9.5)	0.0 (−6.9 to 7.0)	1.01 (0.49 to 2.09)
Intraventricular hemorrhage	51 (37.5)	54 (39.4)	−1.9 (−13.5 to 9.6)	0.95 (0.71 to 1.29)
Grade I or II	40 (29.4)	45 (32.8)	−3.4 (−14.4 to 7.5)	0.90 (0.63 to 1.28)
≥Grade III	11 (8.1)	9 (6.6)	1.5 (−4.7 to 7.7)	1.23 (0.53 to 2.88)
Sepsis	49 (36.0)	60 (43.8)	−7.8 (−19.3 to 3.8)	0.82 (0.61 to 1.10)
Retinopathy of prematurity treatment§	14 (12.2)	12 (10.8)	1.4 (−6.9 to 9.7)	1.13 (0.55 to 2.33)
Cointerventions	86 (63.2)	99 (72.3)	−9.0 (−20.1 to 2.0)	0.88 (0.74 to 1.03)
Glucocorticoids	52 (38.2)	63 (46.0)	−7.8 (−19.4 to 3.9)	0.83 (0.62 to 1.10)
Paracetamol‡	34 (25.0)	52 (38.0)	−13.0 (−23.9 to −2.0)	0.66 (0.46 to 0.95)
Diuretics‡	68 (50.0)	57 (41.6)	8.4 (−3.4 to 20.2)	1.20 (0.93 to 1.56)
	median no. of days (IQR)			**Median Difference¶**
Other support{q43}				
Supplemental oxygen	41 (13 to 66)	40 (14 to 69)	—	−1.0 (−9.0 to 6.0)
Respiratory support	55 (34 to 72)	56 (36 to 76)	—	−1.0 (−8.0 to 6.0)
Invasive	3.5 (0 to 11.5)	5 (1 to 14)	—	0 (−1.0 to 1.0)
Noninvasive	47 (30 to 63)	49 (28 to 62)	—	−1.0 (−7.0 to 5.0)
Time until full enteral feeding	10 (9 to 14)	12 (10 to 19)	—	−2.0 (−3.0 to −1.0)

* All listed outcomes{q44} were measured before discharge home unless otherwise specified. NA denotes{q45} not applicable.
† This confidence interval is two-sided. The 95% confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.
‡ This analysis was not prespecified in the trial protocol.
§ This analysis includes survivors{q46} at the time of assessment, which consisted of X patients in the expectant-management group and X in the early-ibuprofen group.
¶ The values in this category are Hodges–Lehmann estimates.

Table 4. Adverse Events.*

Event	Expectant Management (N=136)	Early Ibuprofen (N=137)
Adverse event		
Patients with at least one adverse event — no. (%)	7 (5.1)	8 (5.8)
Medical specialty — no. of events		
Cardiology		
Pulmonary stenosis	1	1
Ductus arteriosus reopening	0	1
Respiratory or ear, nose, and throat		
Glottic edema	1	0
Stridor	0	1
Vocal cord paralysis	0	1
Dermatology		
Wrist abscess	1	1
Cellulitis	1	0
Necrosis caused by extravasation	1	0
Surgical complication: wound dehiscence	0	2
Pharmacology: caffeine toxicity	1	0
Neurology: West syndrome†	0	1
Nephrology: severe dehydration from tubulopathy	1	0
Hematology: thrombus vena cava inferior	2	0
Serious adverse event		
Patients with at least one serious adverse event — no. (%)	3 (2.2)	4 (2.9)
Medical specialty — no. of events		
Respiratory: subglottic stenosis	0	1
Circulatory		
Pulmonary-vein stenosis	0	1
Aortic coarctation	1	0
Gastrointestinal		
Volvolus	1	0
Meconium ileus	0	2
Hematology: renal-vein thrombosis	0	1
Surgical: liver hemorrhage during laparotomy	1	0

* Participants could have more than one adverse event or serious adverse event.
† West syndrome is frequently associated with infantile spasms, hypsarrhythmia, and intellectual disability

Queries

q1. AU: Your article has been edited for grammar, consistency, readability, adherence to Journal style, and clarity for nonspecialist readers. To expedite publication, we do not ask authors for specific approval of routine changes; please read the entire article to make sure your meaning has been retained. Note that we may be unable to make changes that conflict with Journal style or create grammatical or other problems. Finally, please note that a delayed or incomplete response may delay publication of your article. Thank you!

q2. AU: Correct that Brink is a middle name, which we would initial, per style? Or part of a double surname?

q3. AU: Correct that Jacobsen is a middle name, which we would initial, per style? Or part of a double surname?

q4. AU: Please provide any post-secondary degree here.

q5. AU: The affiliations have been revised per style. Please check for accuracy.

q6. AU: Is this Nuytemans? If so, we would include initials D.H.G.M.N.

q7. AU: Is this Dr. Vijlbrief? If so, we would include initials D.C.V.

q8. AU: Okay to publish postal and e-mail addresses?

q9. AU: Please confirm that all the numbers and terms in the abstract also appear in the body of the article (in the text or in a table or figure).

q10. AU: Is postmenstrual correct? Not gestational age?

q11. AU: Note the use of percentage points for the difference between two percentages. Throughout.

q12. AU: Is the following correct? Not gestational?

q13. AU: Please verify trial registration number(s).

q14. AU: Trial spellout correct?

q15. AU: Correct with postmenstrual? Not gestational age?

q16. AU: Correct to add funding information here?

q17. AU: Is this sentence OK as moved up from the end of the article?

q18. AU: Correct consent was written?

q19. AU: Dr. Solomon comments: OK as revised?

q20. AU: Is the following correct as revised?

q21. AU: Please check all callouts to the Supp App for accuracy. Throughout.

q22. AU: The term “gestational age” was used earlier. OK to revise here?

q23. AU: Correct to add Claure?

q24. AU: Please confirm that none of the material in the Supplementary Appendix is under copyright by a third party.

q25. AU: Is this paragraph correct as revised? Or otherwise clarify?

q26. AU: Please clarify same values for IQR in this sentence.

q27. AU: Is postmenstrual age correct here?

q28. AU: Dr. Solomon comments: OK as added to further clarify?

q29. AU: Is the following spellout correct? Or otherwise clarify?

q30. AU: The final page of this proof is the data sharing statement for your article. The statement was generated from your responses to questions asked by our system during the manuscript

submission process. The PDF statement will be posted along with your article at NEJM.org. Please confirm that it is accurate.

q31. AU: Correct that this is also a project number? Or grant number? Please verify source(s) of funding.

q32. AU: Please confirm that the disclosure forms you submitted are accurate, complete, and current for each author. If any of the information changes before publication, please update the forms.

q33. AU: Is the "thank" statement correct as tweaked? Note that we include academic titles for all the thankees or for none, so we have deleted honorific titles here.

q34. AU: Please clarify the exclusion criterion "Missed".

q35. AU: Please provide denominators of patients in each group, as marked. Note that listed numbers don't compute for tocolysis as marked.

q36. AU: Calculated percentage is '61.3'.

q37. AU: Correct that this is median? Also for birth weight and Apgar score below?

q38. AU: Please provide total no. in each group as indicated below.

q39. AU: Note that Table 2 would not fit horizontally on a print page in the original format, so we deleted the two-sided 95% CIs for the primary outcome and included footnotes to clarify whether the remaining 95% CIs are one-sided or two-sided. If so desired, you could include the two-sided 95% CIs for the primary outcome in the footnotes.

q40. AU: Footnotes have been revised per style, so please check for accuracy.

q41. AU: Is this footnote correct to clarify the two CI categories shown here?

q42. AU: Correct? Not gestational age?

q43. AU: Note that values have been rounded to whole numbers for consistency. Please check for accuracy.

q44. AU: The footnotes have been revised, so please check the placement of citations in the table and accuracy of the footnotes.

q45. AU: Correct? Or not available?

q46. AU: Please provide denominators of patients in this category.