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Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia

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ABSTRACT

BACKGROUND

Systemic glucocorticoids reduce the incidence of bronchopulmonary dysplasia among extremely preterm infants, but they may compromise brain development. The effects of inhaled glucocorticoids on outcomes in these infants are unclear.

METHODS

We randomly assigned 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) to early (within 24 hours after birth) inhaled budesonide or placebo until they no longer required oxygen and positive-pressure support or until they reached a postmenstrual age of 32 weeks 0 days. The primary outcome was death or bronchopulmonary dysplasia, confirmed by means of standardized oxygen-saturation monitoring, at a postmenstrual age of 36 weeks.

RESULTS

A total of 175 of 437 infants assigned to budesonide for whom adequate data were available (40.0%), as compared with 194 of 419 infants assigned to placebo for whom adequate data were available (46.3%), died or had bronchopulmonary dysplasia (relative risk, stratified according to gestational age, 0.86; 95% confidence interval [CI], 0.75 to 1.00; P=0.05). The incidence of bronchopulmonary dysplasia was 27.8% in the budesonide group versus 38.0% in the placebo group (relative risk, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; P=0.004); death occurred in 16.9% and 13.6% of the patients, respectively (relative risk, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; P=0.17). The proportion of infants who required surgical closure of a patent ductus arteriosus was lower in the budesonide group than in the placebo group (relative risk, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; P=0.004), as was the proportion of infants who required reintubation (relative risk, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96; P=0.03). Rates of other neonatal illnesses and adverse events were similar in the two groups.

CONCLUSIONS

Among extremely preterm infants, the incidence of bronchopulmonary dysplasia was lower among those who received early inhaled budesonide than among those who received placebo, but the advantage may have been gained at the expense of increased mortality. (Funded by the European Union and Chiesi Farmaceutici; ClinicalTrials.gov number, NCT01035190.)

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About one half of preterm infants (gestational age, <28 weeks) have bronchopulmonary dysplasia,[1,2] which is a major cause of early death.[1,3] Infants with bronchopulmonary dysplasia who survive have increased risks of neurodevelopmental impairment[4] and respiratory problems later in life.[5,6]

Bronchopulmonary dysplasia results from ongoing lung injury and simultaneous repair[7,8]; inflammation related to chorioamnionitis, postnatal infections, or iatrogenic causes (such as the use of ventilation or oxygen) contributes to lung fibrosis and arrested lung development.[7,9] Systemic glucocorticoids have been shown to reduce the incidence of bronchopulmonary dysplasia, but they may cause short-term and long-term adverse effects, including intestinal perforation and cerebral palsy.[10]

A plausible alternative to systemic administration of glucocorticoids is delivery of glucocorticoids by inhalation.[11] Unfortunately, most trials in which this method has been used have been small or did not initiate administration of glucocorticoids promptly after birth,[12] which may be important since the pulmonary inflammatory response in preterm infants in whom bronchopulmonary dysplasia develops starts very early in life and may even appear prenatally.[13-15] We therefore conducted a multinational, randomized trial to test the hypothesis that in preterm infants born before 28 weeks of gestation, inhaled budesonide administered within 24 hours after birth would decrease the incidence of bronchopulmonary dysplasia and death at 36 weeks of postmenstrual age.[16]

METHODS

STUDY PATIENTS

Infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronologic age of 12 hours or less who required any form of positive-pressure support were eligible. Figure 1 shows the reasons for exclusion.

STUDY OVERSIGHT

The trial was approved by the research ethics board at University Hospital, Tübingen, and at each of the participating centers. Appropriate regulatory approvals and written informed consent from parents or guardians were obtained before randomization. All the authors vouch for the accuracy and completeness of the data and the fidelity of the report to the study protocol, which is available with the full text of this article at NEJM.org. Metered-dose inhalers containing the study drugs were supplied free of charge by the manufacturer, Chiesi Farmaceutici, and Trudell Medical International supplied spacers (AeroChamber mini) free of charge; these companies had no role in the design or conduct of the trial, the analysis of the data, the reporting and interpretation of the results, or the writing of the manuscript.

RANDOMIZATION

A computer-generated randomization scheme with a fixed block size of 8 was used to assign infants, in a 1:1 ratio, to a study group, with stratification according to gestational age (23 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). The manufacturer of the study drug received the sequence of study-drug assignments from a statistician at the coordinating center and prepared drug packages, each of which contained eight sequentially numbered metered-dose inhalers that were identical in appearance. Packages of coded inhalers containing the study drugs were delivered to each participating center to ensure concealment of randomization. Infants were considered to have been randomly assigned at the time of the first signing of a prescription for the study drug.

STUDY DESIGN

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygen-saturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask.

The dose of budesonide was two puffs (200 μg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered. The placebo contained only hydrofluoroalkane propellant.

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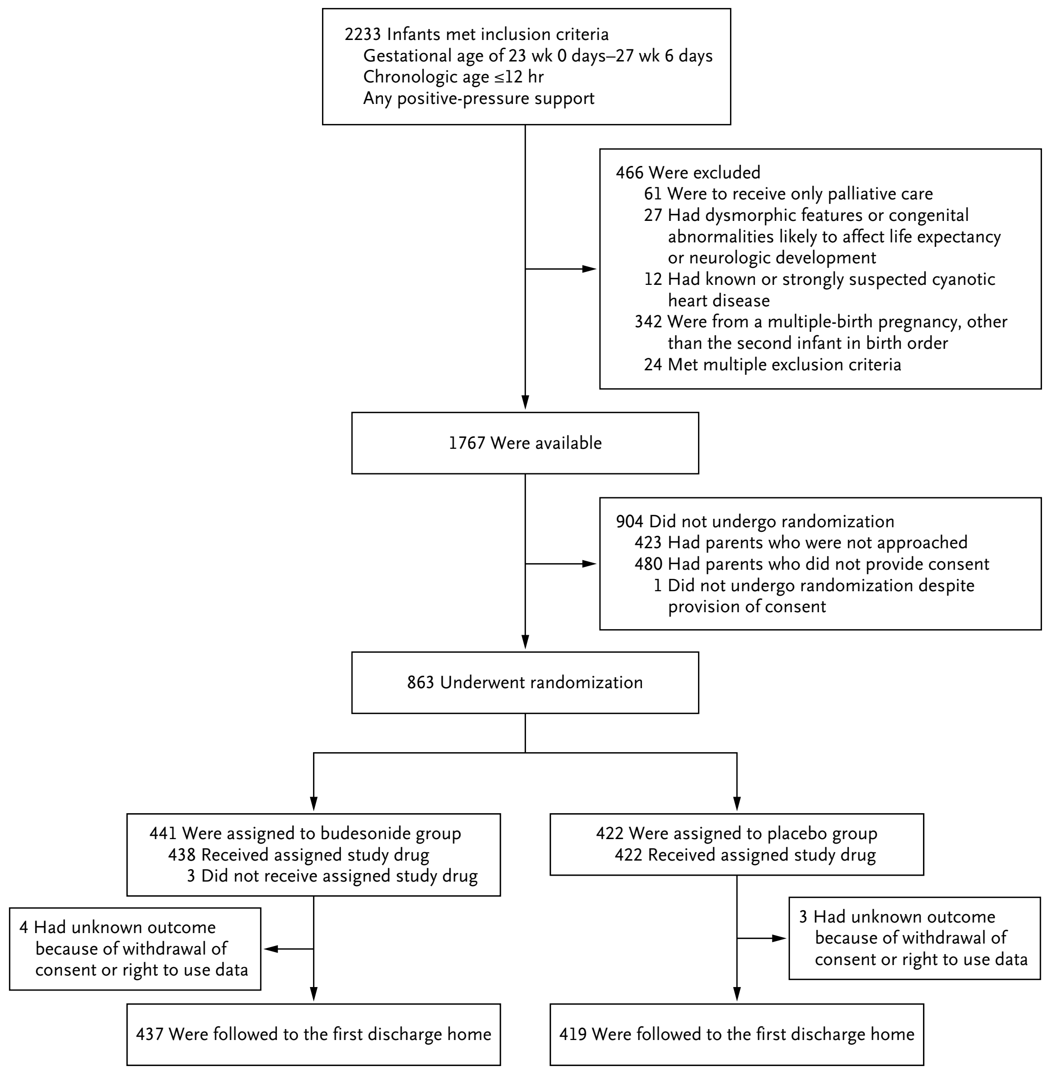

Figure 1. Eligibility, Randomization, and Follow-up.

In case of a multiple-birth pregnancy, only one of the multiples (the second in birth order, when possible) was considered eligible for the study, to prevent a correlated data problem.

Study drugs were administered until infants no longer needed supplemental oxygen and positive-pressure support or reached a postmenstrual age of 32 weeks 0 days, regardless of ventilator status. Attending physicians could withhold or decrease doses of study drugs at their discretion. To minimize contamination, the study protocol strongly discouraged the use of open-label inhaled glucocorticoids. All other interventions were prescribed at the discretion of the local clinicians. No one involved in patient care or in the assessment and analysis of outcomes was aware of the individual study-group assignments before completion of the analysis.

Primary Outcome

The primary outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. Bronchopulmonary dysplasia was defined as the requirement for positive-pressure support, the requirement for supplemental oxygen at a fraction of inspired oxygen

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exceeding 0.30, or, in infants receiving low amounts of oxygen, an inability to maintain an oxygen-saturation value above 90% during a structured, short period of saturation monitoring coupled with gradual weaning from oxygen to ambient air (the oxygen-reduction test).[17]

SECONDARY OUTCOMES

Prespecified secondary outcomes were the following: death for any reason at 36 weeks of postmenstrual age; bronchopulmonary dysplasia (defined in the same way as for the primary outcome) in survivors at 36 weeks of postmenstrual age[17]; the duration of positive-pressure respiratory support or supplemental oxygen; ventriculomegaly with or without intraventricular hemorrhage[18] (diagnosed on the basis of the worst finding on cranial ultrasonography performed at or before 36 weeks of postmenstrual age); patent ductus arteriosus requiring drug treatment or surgery; and intestinal perforation or necrotizing enterocolitis (diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on abdominal radiography).

Additional prespecified secondary outcomes were retinopathy of prematurity (stage 2 or higher according to the international classification[19] or requiring treatment), culture-proven infections (defined as episodes of sepsis or meningitis confirmed by blood or cerebrospinal fluid culture growing bacteria, fungi, or viruses), increases in weight and head circumference from birth to day 28, the length of hospitalization, a need for reintubation after the last dose of study drug had been administered, and the occurrence of oral candidiasis requiring treatment, hyperglycemia requiring insulin treatment, or hypertension requiring treatment. The results of neurodevelopmental disability testing at 18 to 22 months of corrected age are not reported here.

STATISTICAL ANALYSIS

Assuming a rate of death or bronchopulmonary dysplasia of 50% in the placebo group, we calculated that 808 infants would have to be enrolled for the study to have 80% power (at a two-sided alpha level of 5%) to detect a 20% lower risk in the budesonide group. With an anticipated loss to follow-up, we aimed to recruit 850 infants.

We assessed the primary outcome by means of a Mantel–Haenszel chi-square test stratified according to gestational age (23 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days), at a two-sided alpha rate of 0.05. The analysis was performed on the basis of the intention-to-treat principle. We performed a secondary analysis using a logistic-regression model adjusted for gestational age, maternal age, family structure (single vs. two-parent family at the time of delivery), antenatal glucocorticoid use (yes vs. no), presence or absence of chorioamnionitis (defined histologically), intubation status, birth weight (<750 g vs. ≥750 g), sex, multiple vs. singleton gestation, and caffeine use (yes vs. no). The final model was checked for colinearities and interactions and includes, besides therapy, only factors with P values of less than 0.05. For the primary outcome, we also conducted prespecified analyses in subgroups defined according to intubation status, gestational age, and the presence or absence of chorioamnionitis.

Comparisons of secondary outcomes were performed with the use of stratified and nonstratified Cochran–Mantel–Haenszel tests for dichotomous outcomes. Continuous outcomes were checked for normal distribution and analyzed with the use of Student's t-test and analysis of variance, with posterior tests if they were normally distributed and Wilcoxon and Kruskal–Wallis tests with posterior tests if they were nonnormally distributed.[20] Censored data were analyzed with the use of Kaplan–Meier estimates and the log-rank test. Hazard ratios were calculated with the use of Cox regression. Two-sided P values of less than 0.05 were considered to indicate statistical significance. SAS software, version 9.2 (SAS Institute) was used for analyses.

An independent statistician conducted one planned interim analysis for efficacy after 50% of the infants had been enrolled; an external data and safety monitoring committee reviewed the analysis. A Haybittle–Peto stopping boundary was set at a P value of less than 0.001. The external data and safety monitoring committee reviewed safety data four times. After the last review, when patient enrollment had already been completed, the committee recommended that the study drugs be withheld because of a borderline significant between-group difference in the rate of death according to the data available for review at that time. However, at the time of this recommendation, study drugs had already been discontinued in all patients according to the protocol.

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RESULTS

STUDY PATIENTS

A total of 863 infants at 40 study centers in nine countries underwent randomization from April 1, 2010, to August 3, 2013 (Fig. 1). The study population included 10 infants who were part of a multiple birth and who were not the second in birth order (in 9 cases, the second multiple had died prenatally, was not considered viable at birth, or died before randomization; in 1 case, both infants in a set of twins underwent randomization by mistake). The outcome for 7 infants was unknown owing to withdrawal of consent or of the right to use the data, leaving 856 in the analysis population. The baseline characteristics of the infants and of the mothers were similar in the two groups (Table 1).

COINTERVENTIONS

Twelve infants, seven in the budesonide group (1.6%) and five in the placebo group (1.2%), received at least one puff of open-label inhaled glucocorticoids before 32 weeks of postmenstrual age, either because of an administrative error or intentionally. Clinicians administered systemic glucocorticoids, inhaled bronchodilators, intramuscular vitamin A, and methylxanthines similarly in the two groups, but they administered diuretics more frequently in the placebo group (Table 2).

PRIMARY OUTCOME

A total of 856 infants were evaluated for the primary outcome. Overall, 131 infants died before 36 weeks of postmenstrual age, and 239 infants were classified as having bronchopulmonary dysplasia. In 52 of the infants with bronchopulmonary dysplasia (21.8%), the diagnosis was based on the results of the oxygen-reduction test; this test was performed at 36 weeks 0 days±1 day in all but 3 infants (2 of whom underwent testing at 36 weeks 2 days and 1 of whom underwent testing at 36 weeks 3 days of postmenstrual age). The observed rate of death or bronchopulmonary dysplasia was 40.0% (175 of 437 infants) in the budesonide group and 46.3% (194 of 419 infants) in the placebo group (relative risk, stratified according to gestational age, 0.86; 95% confidence interval [CI], 0.75 to 1.00; P=0.05) (Table 3).

In a secondary analysis that included adjustment for other covariates, the odds ratio for the primary outcome in the budesonide group, as compared with the placebo group, was 0.71 (95% CI, 0.53 to 0.97; P=0.03). The treatment effect was not significantly influenced by intubation status, gestational age, or the presence or

Table 1. Baseline Characteristics of the Mothers and Infants.*

Characteristic	Budesonide Group (N=437)	Placebo Group (N=419)
Mothers		
Age — yr	30.7±6.0	30.8±5.9
Race — no. (%)†		
White	369 (84.4)	359 (85.7)
Black	36 (8.2)	30 (7.2)
Asian	8 (1.8)	7 (1.7)
Other or unknown	24 (5.5)	23 (5.5)
Use of antenatal glucocorticoids — no. (%)	388 (88.8)	383 (91.4)
Cesarean section — no. (%)	299 (68.4)	282 (67.3)
Chorioamnionitis — no. (%)		
Antibiotics received	229 (52.4)	220 (52.5)
Histologic diagnosis	90 (20.6)	76 (18.1)
Educational level — no. (%)		
High school or less	155 (35.5)	162 (38.7)
High-school graduate	130 (29.7)	129 (30.8)
Some college or university	127 (29.1)	113 (27.0)
Unknown	25 (5.7)	15 (3.6)
Single-parent family — no. (%)	39 (8.9)	39 (9.3)
Infants		
Birth weight — g	798±193	803±189
Gestational age at birth — wk	26.1±1.3	26.1±1.2
Male sex — no. (%)	222 (50.8)	213 (50.8)
Born at study hospital — no. (%)	423 (96.8)	410 (97.9)
Singleton birth — no. (%)	357 (81.7)	325 (77.6)
Apgar score at 5 min‡		
Median	7	7
Interquartile range	6–8	6–8
Age at randomization — hr		
Median	6.7	6.6
Interquartile range	4.0–10.3	3.8–10.6
Intubated at randomization — no. (%)	301 (68.9)	287 (68.5)
Supplemental oxygen at randomization — no. (%)	212 (48.5)	193 (46.1)

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups in any characteristic.
† Race was self-reported.
‡ Apgar scores range from 0 to 10, with higher scores indicating better function.

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Table 2. Use of Study Drug and Cointerventions.*

Variable	Budesonide Group (N=437)	Placebo Group (N=419)	P Value
Study drug			
Duration of use — days†	33.9±15.9	35.6±15.4	0.07
Temporary discontinuation — no. (%)	69 (15.8)	81 (19.3)	0.17
Cointervention — no. (%)			
Systemic glucocorticoids‡	127 (29.1)	134 (32.0)	0.35
Bronchodilators	116 (26.5)	122 (29.1)	0.40
Vitamin A	62 (14.2)	49 (11.7)	0.28
Loop and other diuretics	231 (52.9)	254 (60.6)	0.02
Caffeine or other methylxanthines	414 (94.7)	398 (95.0)	0.87

* Plus–minus values are means ±SD.
† The use of the study drug was measured from the first to the last day of scheduled administration; temporary discontinuation of study drugs and reductions in the dosage were not considered.
‡ Infants were considered to have received systemic glucocorticoids if they received at least one single dose for the prevention or treatment of bronchopulmonary dysplasia.

absence of chorioamnionitis (Fig. S3 and Table S5 in the Supplementary Appendix, available at NEJM.org).

The net treatment effect on the composite outcome was explained by a decrease in the incidence of bronchopulmonary dysplasia. A diagnosis of bronchopulmonary dysplasia was made in 101 of the 363 infants (27.8%) assigned to budesonide who were alive at a postmenstrual age of 36 weeks, as compared with 138 of the 363 infants (38.0%) assigned to placebo (relative risk, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; P=0.004). This benefit was offset by a nonsignificant excess in mortality with budesonide as compared with placebo (16.9% vs. 13.6%; relative risk, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; P=0.17). (The survival curves are shown in Fig. S1 and S2 in the Supplementary Appendix.) No single cause of death recorded on death certificates or on autopsy reports explained the difference in mortality between the two groups (Tables S1.1 and S1.2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The frequency of a patent ductus arteriosus that was considered by clinical staff to require surgical ligation was significantly lower among the infants assigned to budesonide than among those assigned to placebo (31 patients vs. 54 patients; relative risk, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; P=0.004), as was the frequency of the need for reintubation after the last administration of the study drug (23 patients vs. 38 patients; relative risk, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96: P=0.03). The median postmenstrual age at the last use of supplemental oxygen was 31.6 weeks in the budesonide group and 33.1 weeks in the placebo group (P=0.05) (Table 4).

The groups did not differ significantly with respect to the frequencies of other prespecified outcomes, including retinopathy of prematurity, brain injury, necrotizing enterocolitis, medically treated patent ductus arteriosus, infections, the occurrence of oral candidiasis requiring treatment, hypertension requiring treatment or the occurrence of hyperglycemia requiring insulin treatment, days of hospitalization, increase in weight or head circumference, and age at the last use of respiratory pressure support. Rates of severe adverse events were similar in the two groups (Table S4 in the Supplementary Appendix).

DISCUSSION

In this multinational, randomized trial, we found a difference in the primary composite outcome — bronchopulmonary dysplasia or death — of borderline significance between infants randomly assigned to inhaled budesonide and those assigned to placebo. Budesonide had disparate effects on the individual components of the composite outcome; it was associated with a significantly lower risk of bronchopulmonary dysplasia than that with placebo, which was offset by a nonsignificant excess in mortality.

When we designed the trial, we anticipated that the two components of our primary outcome would move in the same direction. On the basis of a biologic rationale and the available clinical evidence, there was reason to hypothesize that inhaled glucocorticoids might reduce the incidence of bronchopulmonary dysplasia, but there was no indication that they might increase mortality among preterm infants. A Cochrane meta-analysis of five placebo-controlled trials of the administration of inhaled glucocorticoids within 2 weeks after birth showed a risk ratio

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Table 3. Primary Outcome.*

Outcome	Budesonide Group	Placebo Group	Unstratified Relative Risk (95% CI)	Stratified Relative Risk (95% CI)†	P Value	Odds Ratio (95% CI)‡
	no./total no. (%)					
Composite primary outcome	175/437 (40.0)	194/419 (46.3)	0.86 (0.74–1.00)	0.86 (0.75–1.00)	0.05	0.71 (0.53–0.97)
Components of primary outcome						
Death	74/437 (16.9)	57/419 (13.6)	1.24 (0.90–1.71)	1.24 (0.91–1.69)	0.17	1.39 (0.89–2.18)
Survival with bronchopulmonary dysplasia§	101/363 (27.8)	138/363 (38.0)	0.73 (0.59–0.90)	0.74 (0.60–0.91)	0.004	0.61 (0.44–0.85)
Primary outcome in subgroups						
Intubated at randomization						
No	29/136 (21.3)	48/132 (36.4)	0.59 (0.40–0.87)	0.61 (0.42–0.90)	0.01	0.48 (0.27–0.86)
Yes	146/301 (48.5)	146/287 (50.9)	0.95 (0.81–1.12)	0.94 (0.80–1.10)	0.45	0.84 (0.59–1.20)
Gestational age — wk						
23 wk 0 days to 25 wk 6 days	104/183 (56.8)	109/175 (62.3)	0.91 (0.77–1.08)			0.74 (0.48–1.15)
26 wk 0 days to 27 wk 6 days	71/254 (28.0)	85/244 (34.8)	0.80 (0.62–1.04)			0.72 (0.49–1.08)
Histologic chorioamnionitis¶						
No	55/137 (40.1)	66/143 (46.2)	0.87 (0.66–1.14)	0.89 (0.68–1.16)	0.40	0.75 (0.44–1.26)
Yes	33/90 (36.7)	32/76 (42.1)	0.87 (0.60–1.27)	0.86 (0.60–1.23)	0.42	0.63 (0.31–1.28)

* The primary outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. CI denotes confidence interval.
† Stratification was performed for gestational age.
‡ Odds ratios were adjusted for the covariates of gestational age, intubation status, birth weight (<750 g vs. ≥750 g), and caffeine use with the use of logistic-regression analysis; details are provided in Table S5 in the Supplementary Appendix.
§ The component of bronchopulmonary dysplasia was assessed in 363 infants in each group who were alive at a postmenstrual age of 36 weeks. One infant in the placebo group died 1 day after bronchopulmonary dysplasia was diagnosed.
¶ Histologic examination was performed in 446 infants (227 in the budesonide group and 219 in the placebo group).

for death at 36 weeks (postmenstrual age) of 0.73 (95% CI, 0.44 to 1.21).[12] In two of the trials, as in our trial, glucocorticoids were administered within 24 hours after birth[21,22]; in both of these trials, the risk ratio for death was below 1.

Our dosing regimen of budesonide was based largely on the Open Study of Early Corticosteroid Treatment, which compared early glucocorticoid therapy with late glucocorticoid therapy, as well as dexamethasone with inhaled budesonide[23]; our dose was relatively high as compared with that in other studies.[12] However, we consider it unlikely that increased systemic absorption of the study drug could explain any differences in mortality. A meta-analysis of randomized trials of the early use of systemic postnatal glucocorticoids, as compared with placebo, in preterm infants did not show an increased risk of mortality up to the time of hospital discharge (risk ratio, 1.00; 95% CI, 0.89 to 1.13).[10] The rates of death in our trial are consistent with those in multinational randomized trials involving similar patient populations, including the Surfactant, Positive Pressure, and Oxygenation Randomized Trial[24] and the Benefits of Oxygen Saturation Targeting II trial.[25] The difference between the rate of death in the budesonide group and the rate in the placebo group may be explained by chance.

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Table 4. Secondary Outcomes.*

Outcome	Budesonide Group (N=437)	Placebo Group (N=419)	Unstratified Relative Risk (95% CI)	Stratified Relative Risk (95% CI)†	P Value
Retinopathy of prematurity					
Stage 2 or higher — no./total no. (%)‡	127/363 (35.0)	113/361 (31.3)	1.12 (0.91–1.38)	1.13 (0.93–1.38)	0.23
Treatment administered — no. (%)	33 (7.6)	34 (8.1)	0.93 (0.59–1.47)	0.93 (0.59–1.46)	0.75
Brain injury — no./total no. (%)§	91/428 (21.3)	70/410 (17.1)	1.25 (0.94–1.65)	1.25 (0.94–1.65)	0.12
Necrotizing enterocolitis or intestinal perforation — no. (%)	51 (11.7)	44 (10.5)	1.11 (0.76–1.63)	1.11 (0.76–1.61)	0.58
Necrotizing enterocolitis	29 (6.6)	33 (7.9)	0.84 (0.52–1.36)	0.84 (0.52–1.35)	0.47
Intestinal perforation	36 (8.2)	34 (8.1)	1.02 (0.65–1.59)	1.01 (0.65–1.58)	0.95
Patent ductus arteriosus — no. (%)					
Treated with drugs	189 (43.2)	207 (49.4)	0.88 (0.76–1.01)	0.88 (0.76–1.01)	0.07
Treated by surgical ligation	31 (7.1)	54 (12.9)	0.55 (0.36–0.84)	0.55 (0.36–0.83)	0.004
Culture-proven infection — no. (%)					
Sepsis	148 (33.9)	125 (29.8)	1.14 (0.93–1.38)	1.13 (0.93–1.38)	0.20
Meningitis	5 (1.1)	4 (1.0)	1.20 (0.32–4.43)	1.20 (0.32–4.43)	0.79
Adverse treatment effects — no. (%)¶	95 (21.7)	98 (23.4)	0.93 (0.73–1.19)	0.93 (0.73–1.18)	0.55
Reintubation — no. (%)	23 (5.3)	38 (9.1)	0.58 (0.35–0.96)	0.58 (0.35–0.96)	0.03
Days of hospitalization‖					0.09
Median	91	93			
Range	47–361	50–369			
Change in weight from baseline to day 28 — g	274±118	278±126			0.72
Change in head circumference from baseline to day 28 — cm	1.6±1.2	1.4±1.4			0.21
Postmenstrual age at last use of respiratory support — wk					
Positive-pressure support					0.07
Median	33.1	33.4			
Interquartile range	30.7–35.4	31.4–36.3			
Supplemental oxygen					0.05
Median	31.6	33.1			
Interquartile range	27.9–35.4	28.3–37.1			

* Plus–minus values are means ±SD.
† Stratification was performed according to gestational age.
‡ This outcome was assessed among infants who received retinal examinations. Of the 132 infants who did not receive a retinal examination, 127 infants had died by the time of the examination. In the remaining 5 infants, no retinal examinations were performed.
§ This outcome was assessed among infants who underwent cranial ultrasonography. Of the 18 infants who did not undergo cranial ultrasonography, all had died before the first cranial ultrasonographic examination was performed.
¶ Adverse treatment effects were defined as either oral candidiasis requiring treatment (in 28 patients in the budesonide group and 32 patients in the placebo group), hyperglycemia requiring insulin treatment (in 86 patients in the budesonide group and 85 patients in the placebo group), or hypertension requiring treatment (in 6 patients in the budesonide group and 10 patients in the placebo group).
‖ The duration of hospital stay was measured before the first discharge home.

In the Cochrane Collaboration systematic review of trials of inhaled glucocorticoids administered within the first 2 weeks after birth to prevent chronic lung disease in preterm neonates, the inclusion criteria, intervention, dose, and duration of therapy varied among studies, and none of these trials showed a significant reduction in the incidence of bronchopulmonary

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dysplasia.[12] We speculate that aside from our trial including a large enough sample size to enable us to detect a clinically meaningful treatment effect, our positive finding with respect to the reduced incidence of bronchopulmonary dysplasia may be attributable to the early initiation of therapy and the choice of dose, since it has been shown repeatedly that only a fraction of the administered inhaled dose is deposited in the lungs.[11,26,27]

Budesonide was associated with a significantly lower risk than the risk with placebo of two additional prespecified secondary outcomes — a patent ductus arteriosus considered by clinical staff to require surgical ligation and the requirement for reintubation after the last administration of the study drug. Both results could be explained by the effect of budesonide on the incidence of bronchopulmonary dysplasia. First, infants in whom bronchopulmonary dysplasia develops may have less pulmonary reserve and thus may be more likely to have clinical decompensation in the event of additional neonatal illnesses such as sepsis. Second, since the frequency and timing of echocardiography was left to the discretion of local clinicians, it is possible that clinical staff were more likely to look for and treat a patent ductus arteriosus in the placebo group than in the budesonide group, in which fewer infants had bronchopulmonary dysplasia. This possibility was suggested previously to explain the lower rates of surgical closure of a patent ductus arteriosus in the caffeine group than in the placebo group in a large randomized trial of caffeine for apnea of prematurity.[28] Furthermore, the effect of budesonide on patent ductus arteriosus could be explained by the antiinflammatory effects of budesonide, which might have contributed to early closure of the ductus arteriosus.

The frequencies of other neonatal illnesses and the rate of adverse events did not differ significantly between the groups. However, information on short-term outcomes is insufficient to assess the overall efficacy of inhaled budesonide and its associated risks. Follow-up of our study cohort, including assessment of neurodevelopmental outcomes at 18 to 22 months of corrected age, is currently under way.

In summary, we found a beneficial effect of budesonide on the risk of bronchopulmonary dysplasia, as well as a possible increase in mortality associated with its use.

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

APPENDIX

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