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ORIGINAL ARTICLE

Long-Term Effects of Inhaled Budesonide for Bronchopulmonary Dysplasia

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ABSTRACT

BACKGROUND

The long-term effects on neurodevelopment of the use of inhaled glucocorticoids in extremely preterm infants for the prevention or treatment of bronchopulmonary dysplasia are uncertain.

METHODS

We randomly assigned 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) to receive early (within 24 hours after birth) inhaled budesonide or placebo. The prespecified secondary long-term outcome was neurodevelopmental disability among survivors, defined as a composite of cerebral palsy, cognitive delay (a Mental Development Index score of <85 [1 SD below the mean of 100] on the Bayley Scales of Infant Development, Second Edition, with higher scores on the scale indicating better performance), deafness, or blindness at a corrected age of 18 to 22 months.

RESULTS

Adequate data on the prespecified composite long-term outcome were available for 629 infants. Of these infants, 148 (48.1%) of 308 infants assigned to budesonide had neurodevelopmental disability, as compared with 165 (51.4%) of 321 infants assigned to placebo (relative risk, adjusted for gestational age, 0.93; 95% confidence interval [CI], 0.80 to 1.09; P=0.40). There was no significant difference in any of the individual components of the prespecified outcome. There were more deaths in the budesonide group than in the placebo group (82 [19.9%] of 413 infants vs. 58 [14.5%] of 400 infants for whom vital status was available; relative risk, 1.37; 95% CI, 1.01 to 1.86; P=0.04).

CONCLUSIONS

Among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between infants who received early inhaled budesonide for the prevention of bronchopulmonary dysplasia and those who received placebo, but the mortality rate was higher among those who received budesonide. (Funded by the European Union and Chiesi Farmaceutici; ClinicalTrials.gov number, NCT01035190.)

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Bronchopulmonary dysplasia is the most common chronic complication of extremely preterm birth, and rates of this complication have remained stable or increased among extremely preterm infants in the past two decades.[1] Bronchopulmonary dysplasia is associated with higher mortality rates, and among survivors it confers a predisposition to chronic respiratory and cardiovascular impairment, growth failure, and neurodevelopmental delay.[2-5] Neonatal pharmacologic therapies are an important tool for reducing the burden of bronchopulmonary dysplasia. Systemic glucocorticoids are effective for the prevention of bronchopulmonary dysplasia but can increase the risk of neurodevelopmental impairment.[6,7] Administration of inhaled glucocorticoids may have beneficial effects on the pulmonary system, with a lower risk of adverse effects. Many preterm infants receive inhaled glucocorticoids for the prevention or treatment of bronchopulmonary dysplasia during routine clinical care.[8-12] Despite their widespread use, inhaled glucocorticoids have been evaluated in only a few small, short-term studies.[8] We conducted this large, international, randomized, placebo-controlled trial to study the short-term and long-term efficacy and safety of inhaled budesonide for the prevention of bronchopulmonary dysplasia in extremely preterm infants. With respect to the primary composite outcome — bronchopulmonary dysplasia or death at 36 weeks of postmenstrual age — we found a nonsignificant difference (P=0.05) between infants randomly assigned to inhaled budesonide and those assigned to placebo. Budesonide treatment resulted in a significantly lower risk of bronchopulmonary dysplasia than placebo; however, mortality was higher in the budesonide group, although the between-group difference was not significant.[13] We further aimed to determine whether inhaled budesonide for the prevention of bronchopulmonary dysplasia alters the rate of neurodevelopmental disability at a corrected age of 18 to 22 months.

METHODS

INITIAL TRIAL PERIOD

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 respiratory support were eligible for this trial. The exclusion criteria and the randomization procedure are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. The primary outcome — bronchopulmonary dysplasia or death at a postmenstrual age of 36 weeks — and other short-term outcomes have been reported previously.[13,14] In summary, 863 infants were enrolled during the period from April 2010 through August 2013 at 40 trial centers in nine countries and were randomly assigned to receive early (within 24 hours after birth) inhaled budesonide or placebo. Randomization was stratified according to gestational age (23 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Metered-dose inhalers containing budesonide or placebo were supplied free of charge by Chiesi Farmaceutici, and Trudell Medical International supplied the spacers (AeroChamber mini) free of charge. Neither company had any 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. The research ethics board at each of the clinical centers approved the protocol. Written informed consent was obtained from a parent or guardian of each infant, and appropriate regulatory approvals were obtained in participating countries. Six of the authors vouch for the accuracy and completeness of the data and analyses, and all the authors vouch for the fidelity of the trial to the protocol. The trial protocol and statistical analysis plan are available at NEJM.org.

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 infants no longer required supplemental oxygen and positive-pressure support or until they reached a postmenstrual age of 32 weeks, regardless of ventilatory status. The mean total duration of budesonide use was 33.9 days.[13] Infants received the first dose of the trial drug within 12 hours after random assignment, which occurred at a median of 6.7 hours after birth in the budesonide group and 6.6 hours after birth in the placebo group.

All adverse events in the trial were related to the initial hospital stay of the participants and have been reported previously.[13] An external data and safety monitoring committee reviewed the

trial safety data four times and the results of the interim analysis for efficacy after 50% of infants had been enrolled. After the last safety review, when patient enrollment had already been completed, the committee recommended that the trial drugs be withheld because of a rate of death that was higher, although nonsignificantly higher, in the budesonide group than in the placebo group, according to the data available for review at that time. However, at the time of this recommendation, trial drugs had already been discontinued in all the patients in accordance with the protocol.

PRESPECIFIED LONG-TERM OUTCOME

Overall, our trial protocol lists 13 prespecified secondary outcomes. The only prespecified secondary long-term outcome was neurodevelopmental disability among survivors, defined as a composite of cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 22 months. Neurodevelopmental assessment was performed by trained and experienced examiners who were unaware of the treatment assignments. Documentation of the presence of the prespecified composite long-term outcome required confirmation that the infant had survived with one or more of the four types of disability. Documentation of the absence of the prespecified composite outcome required confirmation that the infant had survived without any disability. The composite long-term outcome was designated as "missing" if one or more of its four components were not successfully tested and the successfully tested component or components did not reveal any impairment. Follow-up was targeted for a corrected age of 18 to 22 months, but efforts to conduct assessments continued beyond a corrected age of 22 months when necessary. Cerebral palsy was diagnosed if the patient had nonprogressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. The level of gross motor function was determined with the use of the Gross Motor Function Classification System.[15] Cognitive delay was defined as a Mental Development Index score of less than 85 (1 SD below the mean of 100) on the Bayley Scales of Infant Development, Second Edition, on which the minimum score is 50 and the maximum score is 150 and higher scores indicate better performance.[16] The score was assumed to be less than 85 if the child could not be tested because of severe developmental delay. Audiometry was performed to determine the presence or absence of sensorineural hearing loss. Blindness was defined as a corrected visual acuity of less than 20/200.

EXPLORATORY OUTCOMES

Data for the following exploratory outcomes were collected prospectively in case-report forms that were designed at the onset of the trial: height percentile; weight percentile; head circumference percentile; mean Psychomotor Development Index scores on the Bayley scales; mean Mental Development Index scores; Mental Development Index score of less than 70; cerebral palsy with a gross motor function level of 3 to 5 (on a scale of 1 [mild impairment] to 5 [most severe impairment]); hospital admission after initial discharge for any medical reason or any surgical procedure; use of inhaled glucocorticoids, systemic glucocorticoids, leukotriene antagonists, or bronchodilators for at least 2 months after initial discharge; use of supplemental oxygen or positive-pressure ventilation for more than 1 week after initial discharge; and diagnosis of hypertrophic obstructive cardiomyopathy at any time after birth. We also analyzed mortality and a composite outcome of death or neurodevelopmental disability at the time of the follow-up assessment. Documentation of the presence of the composite long-term outcome required confirmation that the infant had died or had survived with one or more of the four types of disability included in the prespecified secondary composite long-term outcome. Documentation of the absence of this composite exploratory long-term outcome required confirmation that the infant had survived without any disability. The criteria to constitute adequate evidence for this assessment were the same as for the prespecified composite long-term outcome.

STATISTICAL ANALYSIS

Comparisons of secondary outcomes were performed with the use of stratified and nonstratified Cochran–Mantel–Haenszel tests for dichotomous outcomes and the Wilcoxon test for continuous outcomes. We did not adjust for multiple comparisons. 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. We performed the analysis on the basis of the intention-to-treat

principle, and we included infants who were tested later than a corrected age of 22 months. We conducted post hoc sensitivity analyses with imputation of missing data (see the Supplementary Appendix).

RESULTS

TRIAL PARTICIPANTS

Figure 1 shows the number of infants who were screened for the trial, who were randomly assigned to receive inhaled budesonide or placebo, and who were assessed for follow-up. Follow-up assessment began on February 23, 2012, and ended on March 10, 2016. The primary outcome was analyzed in an intention-to-treat population of 856 infants (437 in the budesonide group and 419 in the placebo group); 43 infants (5%) were lost to follow-up, and 140 infants died before the follow-up assessment. Of these 140 infants, 131 died before 36 weeks of postmenstrual age and were included in our previous analysis of short-term trial outcomes.[13] The baseline characteristics and the short-term outcomes of the 43 infants who were lost to follow-up are shown in Table S2 in the Supplementary Appendix. A follow-up assessment was performed in 673 infants, but in the case of 44 infants, this assessment was incomplete and neurodevelopmental disability could not be evaluated. (The individual test results of these 44 infants are provided in Table S3 in the Supplementary Appendix.) Therefore, adequate data were available for 629 infants for the analysis of neurodevelopmental disability among survivors, for 769 infants for the composite of death or neurodevelopmental disability, and for 813 infants for mortality up to the completion of follow-up.

Among infants with adequate data for the assessment of the prespecified composite outcome, characteristics were similar between the two groups at birth and at the time of randomization. The rate of bronchopulmonary dysplasia at 36 weeks of postmenstrual age was lower in the budesonide group than in the placebo group. The ages of the patients at follow-up and the characteristics of their caregivers were similar in the two groups (Table 1).

PRESPECIFIED SECONDARY LONG-TERM OUTCOME

Results regarding the prespecified secondary long-term outcome and its components are shown in Table 2. The rate of neurodevelopmental disability did not differ significantly between the budesonide group and the placebo group. Among infants for whom adequate data on the prespecified secondary outcome were available, 148 (48.1%) of 308 infants assigned to budesonide had neurodevelopmental disability, as compared with 165 (51.4%) of 321 infants assigned to placebo (relative risk, adjusted for gestational age, 0.93; 95% confidence interval [CI], 0.80 to 1.09; P=0.40). There were no significant differences between the two groups in the rates of the four components of the composite outcome — cerebral palsy, blindness, hearing loss, and cognitive delay (Mental Development Index score <85) (Table 2).

EXPLORATORY OUTCOMES

Death or neurodevelopmental disability occurred in 59.0% of the infants in the budesonide group (230 of 390 infants) and in 58.8% in the placebo group (223 of 379) (relative risk, 1.00; 95% CI, 0.89 to 1.13; P=0.97). The mortality rate was higher in the budesonide group than in the placebo group (19.9% vs. 14.5%; relative risk, 1.37; 95% CI, 1.01 to 1.86; P=0.04) (Table 3). Nine infants died after 36 weeks of postmenstrual age; of these infants, 8 (7 in the budesonide group and 1 in the placebo group) died before the initial hospital discharge. No single cause of death recorded on death certificates or on autopsy reports explained the difference in mortality between the two groups (Table S1 in the Supplementary Appendix). No information about the survival status is available for the 43 infants who were lost to follow-up (24 assigned to budesonide and 19 assigned to placebo).

The groups did not differ significantly with respect to the rate of severe cognitive delay (Mental Development Index score <70) or of severe cerebral palsy; the median Mental Development Index and the Psychomotor Development Index scores on the Bayley scales; the rate of hypertrophic cardiomyopathy; the average percentiles for height, weight, and head circumference; hospital readmission rates; and receipt of pulmonary medications at a follow-up of 18 to 22 months (Table 3). At the discretion of the local clinicians, 162 (24.2%) of 670 infants — 74 in the budesonide group and 88 in the placebo group — received inhaled glucocorticoids for at least 2 months after discharge from the hospital;

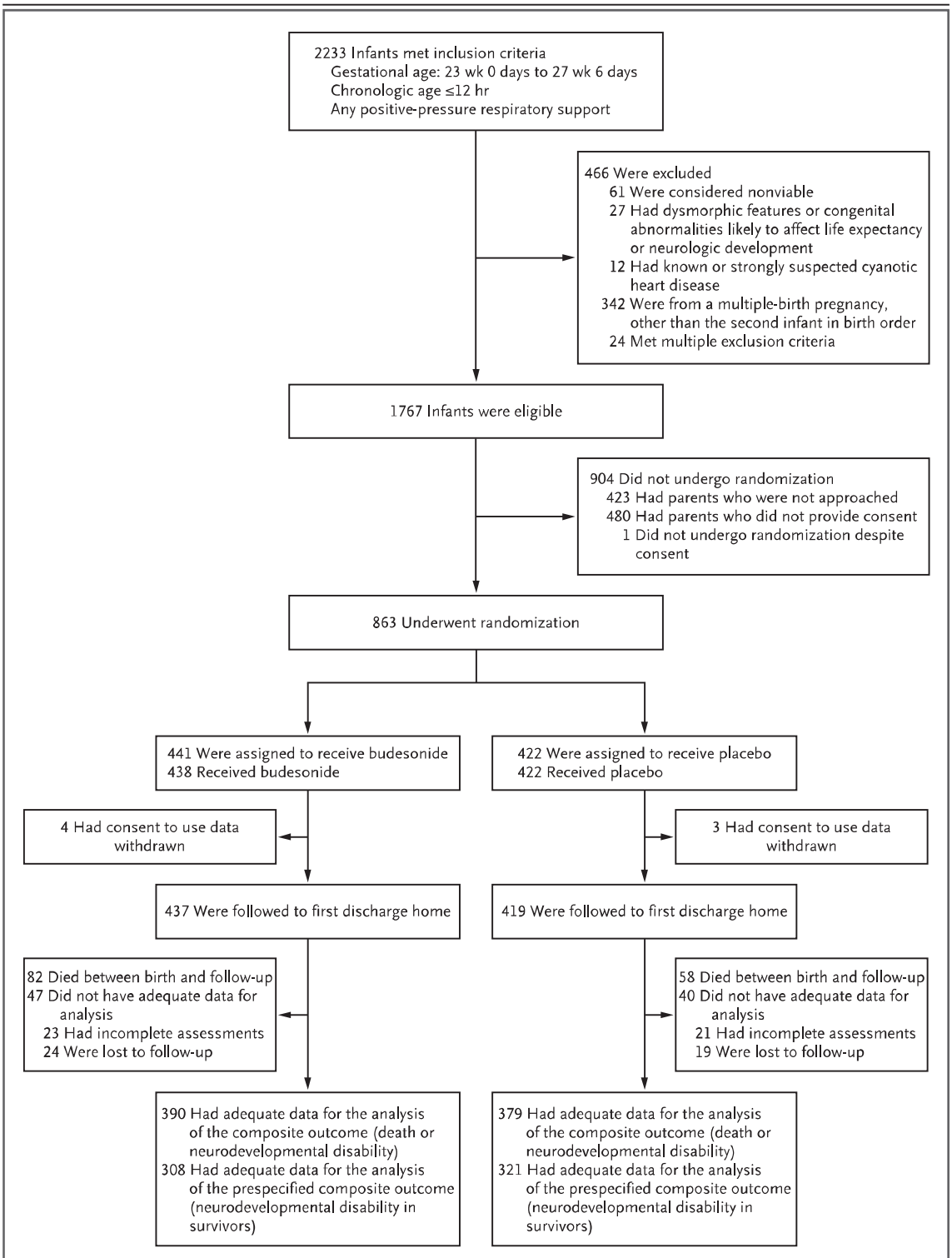

Figure 1. Eligibility, Randomization, and Follow-up.

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

Table 1. Characteristics of the Infants and Their Caregivers and Neonatal Outcomes at 36 Weeks of Postmenstrual Age.*

Characteristic	Budesonide Group	Placebo Group
Infants†		
No. with data	308	321
Birth weight — g	827±188	822±181
Gestational age — wk	26.2±1.2	26.2±1.1
Male sex — no. (%)	157 (51.0)	166 (51.7)
Receipt of antenatal glucocorticoids — no. (%)	278 (90.3)	295 (91.9)
Singleton birth — no. (%)	247 (80.2)	257 (80.1)
Age at randomization — hr		
Median	6.2	6.5
Interquartile range	3.8–10.2	3.8–10.4
Receipt of caffeine or other methylxanthines — no. (%)	306 (99.4)	319 (99.4)
Outcome at 36 wk of postmenstrual age — no. (%)		
Bronchopulmonary dysplasia‡	87 (28.2)	120 (37.4)
Brain injury§	57 (18.5)	45 (14.0)
Cystic periventricular leukomalacia	12 (3.9)	11 (3.4)
Corrected age at follow-up — mo		
Median	21.4	21.3
Interquartile range	20.7–22.8	20.4–22.5
Caregivers		
At randomization		
No. with data	437	419
Chorioamnionitis — no. (%)		
Antibiotics received	229 (52.4)	220 (52.5)
Histologic diagnosis	90 (20.6)	76 (18.1)
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)
Level of education — 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)
At follow-up†		
No. with data	308	321
Relationship to child — no. (%)		
Biologic mother	278 (90.3)	292 (91.0)
Adoptive parent	2 (0.6)	0 (0.0)
Foster parent	4 (1.3)	1 (0.3)
Other or unknown	24 (7.8)	28 (8.7)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. There were no significant differences between the treatment groups, except for a higher rate of bronchopulmonary dysplasia in the placebo group than in the budesonide group (P=0.01).
† These data are for the 629 infants with sufficient information for the ascertainment of the composite long-term outcome of neurodevelopmental disability among survivors at a corrected age of 18 to 22 months.
‡ Bronchopulmonary dysplasia was defined as the need for positive-pressure respiratory support; the need for supplemental oxygen at a fraction of inspired oxygen exceeding 0.30; or, in infants receiving low amounts of supplemental 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).
§ Brain injury was defined as ventriculomegaly with or without intraventricular hemorrhage.
¶ Race was reported by the caregiver.

Table 2. Neurodevelopmental Disability at a Corrected Age of 18 to 22 Months.

Outcome	Budesonide Group	Placebo Group	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)*	Adjusted P Value
	no./total no. (%)				
Composite outcome	148/308 (48.1)	165/321 (51.4)	0.93 (0.80–1.09)	0.93 (0.80–1.09)	0.40
Component†					
Cerebral palsy	24/330 (7.3)	21/340 (6.2)	1.18 (0.67–2.07)	1.18 (0.67–2.07)	0.57
Blindness	3/331 (0.9)	6/337 (1.8)	0.51 (0.13–2.02)	0.51 (0.13–2.02)	0.33
Hearing loss	1/330 (0.3)	4/337 (1.2)	0.26 (0.03–2.27)	0.26 (0.03–2.28)	0.19
Cognitive delay‡	139/303 (45.9)	152/315 (48.3)	0.95 (0.80–1.12)	0.95 (0.80–1.12)	0.56

* The relative risk has been adjusted for gestational age.
† Data for these outcomes exclude infants who died before the scheduled tests and those who were alive but were not tested.
‡ Cognitive delay was defined as a Mental Development Index score of less than 85, assessed relative to a standardized mean of 100, on the Bayley Scales of Infant Development, Second Edition, on which the minimum score is 50 and the maximum score is 150, with higher scores indicating better performance.

69 (42.6%) of these 162 patients were classified as having bronchopulmonary dysplasia at 36 weeks of postmenstrual age.

DISCUSSION

In this large, multinational trial involving very-high-risk, extremely preterm infants, we found no significant difference in the prespecified composite long-term outcome of neurodevelopmental impairment among survivors at a corrected age of 18 to 22 months between infants randomly assigned to early treatment with budesonide and those assigned to placebo. There were no significant differences between the budesonide group and the placebo group with respect to the frequencies of the components of neurodevelopmental impairment, including cognitive delay, cerebral palsy, hearing impairment, and blindness.

A Cochrane Collaboration systematic review of randomized trials of intravenous or oral glucocorticoids administered within the first 7 days of life to prevent chronic lung disease in preterm infants suggested that the early administration of dexamethasone may compromise brain development and increase the risk of cerebral palsy.[7] These findings underline the need for long-term follow-up of preterm infants who are enrolled in studies investigating glucocorticoids, regardless of the method of administration. Among the 10 trials included in a recent Cochrane systematic review of the administration of inhaled glucocorticoids within 2 weeks after birth, only 2 trial reports included information about long-term outcomes.[17]

One of these 2 trials, a randomized, controlled trial of inhaled fluticasone as compared with placebo in infants with extremely low birth weight, showed no significant difference in the rate of death or neurodevelopmental impairment at 18 months of postmenstrual age among 187 infants who were available for follow-up (relative risk with fluticasone vs. placebo, 1.09; 95% CI, 0.70 to 1.70).[18] The other randomized, controlled trial compared inhaled beclomethasone with placebo and assessed neurodevelopmental outcomes in all 56 survivors to the age of 3 years.[19] There was no significant difference between those assigned to beclomethasone and those assigned to placebo in the incidence of cerebral palsy (relative risk, 1.33; 95% CI, 0.33 to 1.42) or in the incidence of Mental Development Index scores less than 2 SD below the mean (relative risk, 1.25; 95% CI, 0.37 to 4.17). The results of our trial, which included a larger sample, are consistent with these findings.

When we designed the trial, we did not anticipate an effect of inhaled budesonide on mortality, and thus our prespecified long-term composite outcome did not include mortality as a component.[13,14] However, at the time of assessment of the primary outcome, budesonide was associated with a nonsignificant excess in mortality.[13] This unexpected finding prompted us to assess additional exploratory long-term outcomes,

Table 3. Exploratory Outcomes at a Corrected Age of 18 to 22 Months.*

Outcome	Budesonide Group	Placebo Group	Relative Risk (95% CI)	P Value
Death or disability — no./total no. (%)	230/390 (59.0)	223/379 (58.8)	1.00 (0.89–1.13)	0.97
Death — no./total no. (%)†	82/413 (19.9)	58/400 (14.5)	1.37 (1.01–1.86)	0.04
Mental Development Index score‡				0.22
Median (IQR)	88 (74–102)	86 (70–99)		
Score <70: severe cognitive delay — no./total no. (%)§	60/303 (19.8)	78/315 (24.8)	0.80 (0.59–1.08)	0.14
Psychomotor Development Index score — median (IQR)¶	89 (78–102)	90 (76–100)		0.70
Severe cerebral palsy — no./total no. (%)§‖	11/329 (3.3)	10/339 (2.9)	1.13 (0.49–2.63)	0.77
Height percentile — median (IQR)**	29.5 (8–62)	24 (5–60)		0.14
Weight percentile — median (IQR)††	30 (9–60)	26 (5–58)		0.24
Head circumference percentile — median (IQR)‡‡	16 (<3–60)	13 (<3–59.5)		0.52
Hypertrophic obstructive cardiomyopathy — no./total no. (%)§	6/331 (1.8)	3/340 (0.9)	0.99 (0.97–1.01)	0.30
Hospital admission — no./total no. (%)				
For medical reason	152/331 (45.9)	163/340 (47.9)	1.04 (0.90–1.20)	0.60
For surgical reason	69/331 (20.8)	70/340 (20.6)	1.00 (0.92–1.08)	0.93
Glucocorticoids — no./total no. (%)§§				
Inhaled	74/330 (22.4)	88/340 (25.9)	0.87 (0.66–1.13)	0.30
Systemic	14/330 (4.2)	7/340 (2.1)	2.06 (0.84–5.04)	0.11
Leukotriene antagonists — no./total no. (%)§§	4/330 (1.2)	7/340 (2.1)	0.59 (0.17–1.99)	0.39
Bronchodilators — no./total no. (%)§§	75/330 (22.7)	89/340 (26.2)	0.87 (0.66–1.13)	0.30
Supplemental oxygen — no./total no. (%)¶¶	29/330 (8.8)	33/340 (9.7)	0.91 (0.56–1.46)	0.68
Positive airway pressure — no./total no. (%)¶¶	9/330 (2.7)	7/340 (2.1)	1.32 (0.50–3.52)	0.57

* IQR denotes interquartile range.
† Data are for infants whose vital status was known at the time of the follow-up assessment.
‡ Data were available for 303 infants in the budesonide group and 315 infants in the placebo group.
§ Data for this outcome exclude infants who died before the scheduled tests and those who were alive but were not tested.
¶ The Psychomotor Development Index score is assessed relative to a standardized mean of 100 on the Bayley Scales of Infant Development, Second Edition, on which the minimum score is 50 and the maximum score is 150, with higher scores indicating better performance. Data on this index were available for 287 infants in the budesonide group and 299 infants in the placebo group.
‖ Severe cerebral palsy was described as a gross motor function level of 3 to 5 as determined with the use of the Gross Motor Function Classification System (on a scale of 1 [mild impairment] to 5 [most severe impairment]).
** Data were available for 328 infants in the budesonide group and 335 infants in the placebo group.
†† Data were available for 328 infants in the budesonide group and 337 infants in the placebo group.
‡‡ Data were available for 325 infants in the budesonide group and 332 infants in the placebo group.
§§ These patients received this therapy for at least 2 months after initial discharge.
¶¶ These patients received this therapy for more than 1 week after initial discharge.

including mortality at the time of the follow-up assessment and a composite outcome of death or severe neurodevelopmental disability. At a corrected age of 18 to 22 months, there was no significant difference between the budesonide group and the placebo group with respect to the composite outcome of death or neurodevelopmental disability, but the results of our analyses suggest higher mortality with budesonide. This finding was of nominal statistical significance and may have been due to chance; no adjustment was made in our analyses for multiple comparisons. Most infants had died in the first weeks of life; thus, the difference in mortality observed at a corrected age of 18 to 22 months largely reflected the differences in mortality before hospital discharge that were reported previously[13]; among the 43 infants who were lost to follow-up, survival status is unknown.

A recent Cochrane meta-analysis of six ran-

domized trials, involving a total of 1285 preterm infants, that assessed the early use of inhaled glucocorticoids as compared with placebo or no intervention did not show an increased risk of death by 36 weeks of postmenstrual age among all randomly assigned infants (pooled relative risk, 1.07; 95% CI, 0.82 to 1.40).[17] Similarly, no significantly higher mortality with inhaled glucocorticoids was reported in another systematic review that included randomized, placebo-controlled trials of inhaled glucocorticoids for either the prevention or the treatment of bronchopulmonary dysplasia.[20] In an editorial accompanying the publication of our primary outcome results, respiratory infections were suggested as a potential explanation for any excess in mortality in the glucocorticoid group,[21] but a post hoc analysis of our data did not support this hypothesis.[22] The causes of death in our trial did not differ considerably between the groups.

Budesonide was not associated with a significantly lower or higher risk of any outcome assessed at follow-up except for mortality. Bronchopulmonary dysplasia is predictive of a poor long-term outcome,[2,23] but although inhaled budesonide started in the first 24 hours of life resulted in a lower rate of bronchopulmonary dysplasia than placebo, there was no significant difference between the groups in adverse long-term outcomes in our study. However, the fact that fewer infants died in the placebo group than in the budesonide group complicates the interpretation of the treatment effect of budesonide.[21]

In summary, we found no effect of budesonide on the risk of neurodevelopmental disability among surviving extremely preterm infants at 18 to 22 months of age. However, the mortality rate was higher in the budesonide group.

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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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