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## OBSTETRICS

# Survival without severe neonatal morbidity after antenatal betamethasone dose reduction: a post hoc analysis of a randomized non-inferiority trial

Olivier Baud, PhD; Loic Sentilhes, MD; Moreno Ursino, PhD; Muriel Doret-Dion, MD; Corinne Alberti, PhD; Camille Aupiais, MD; Thomas Schmitz, MD; On behalf of the BETADOSE trial study group and the GROG (Groupe de Recherche en Obstétrique et Gynécologie)

**BACKGROUND:** Antenatal betamethasone is recommended before preterm delivery to accelerate fetal lung maturation. However, its optimal dose remains unknown. A 50% dose reduction was proposed to decrease the potential dose-related long-term neurodevelopmental side effects, including psychological development, sleep, and emotional disorders. Because noninferiority of the half dose in terms of the need for exogenous surfactant was not shown in the primary analysis, its impact on survival without major neonatal morbidity needs to be investigated.

**OBJECTIVE:** This study aimed to investigate the impact of antenatal betamethasone dose reduction on survival of very preterm infants without severe neonatal morbidity, a factor known to have a strong correlation with long-term outcomes.

**STUDY DESIGN:** We performed a post hoc secondary analysis of a randomized, multicenter, double-blind, placebo-controlled, non-inferiority trial, testing half (11.4 mg once; n=1620) vs full (11.4 mg twice, 24 hours apart; n=1624) antenatal betamethasone doses in women at risk of preterm delivery. To measure survival without severe neonatal morbidity at hospital discharge among neonates born before 32 weeks of gestation, we used the definition of the French national prospective study on preterm children, EPIPAGE 2, comprising 1 of the following morbidities: grade 3 to 4 intraventricular hemorrhage, cystic

periventricular leukomalacia, necrotizing enterocolitis stage  $\geq 2$ , retinopathy of prematurity requiring anti-vascular endothelial growth factor therapy or laser, and moderate-to-severe bronchopulmonary dysplasia.

**RESULTS:** After exclusion of women who withdrew consent or had pregnancy termination and of participants lost to follow-up (8 in the half-dose and 10 in the full-dose group), the rate of survival without severe neonatal morbidity among neonates born before 32 weeks of gestation was 300 of 451 (66.5%) and 304 of 462 (65.8%) in the half-dose and full-dose group, respectively (risk difference, +0.7%; 95% confidence interval, -5.6 to +7.1). There were no significant between-group differences in the cumulative number of neonatal morbidities. Results were similar when using 2 other internationally recognized definitions of severe neonatal morbidity and when considering the overall population recruited in the trial.

**CONCLUSION:** In the BETADOSE trial, severe morbidity at discharge of newborns delivered before 32 weeks of gestation was found to be similar among those exposed to 11.4-mg and 22.8-mg antenatal betamethasone. Additional studies are needed to confirm these findings.

**Key words:** antenatal steroids, betamethasone dose reduction, neonatal morbidities, very preterm neonates

## Introduction

Antenatal corticosteroids given to women at risk of preterm delivery are recommended worldwide to prevent primarily respiratory distress syndrome and neonatal death, but also intraventricular hemorrhage and necrotizing enterocolitis, 2 major complications with long-term consequences.<sup>1</sup> The

current dose regimen of betamethasone derives from a preclinical study and clinical trial reported by Liggins et al<sup>2,3</sup> >50 years ago and has not been revisited in randomized clinical trials, while major improvements in the care of children born preterm have occurred over time.

Preclinical studies support the programming effects of antenatal exposure of the fetus to steroids leading to disturbance in the maturation of several organs and systems including the hypothalamic-pituitary-adrenal axis, pancreas, kidneys, and the central nervous system.<sup>4</sup> In particular, in humans, repeated courses of antenatal corticosteroids have been reported to induce neurodevelopmental side effects including abnormal response to psychosocial stress<sup>5,6</sup> and mental and behavioral disorders in children born at term.<sup>7</sup>

Overall, these data suggest that the current betamethasone dose (11.4 mg plus 11.4 mg, 24 hours apart) might be too high and be associated with a sub-optimal benefit–risk ratio. Because half-dose regimens of antenatal corticosteroids have been shown to be as effective as the full regimen in inducing lung maturation in sheep,<sup>8,9</sup> we asked whether a half dose would be non-inferior to the current full dose for preventing respiratory distress syndrome in human neonates. We recently reported the results of a randomized, multicenter, double-blind, placebo-controlled, non-inferiority trial testing half (11.4 mg) vs full (22.8 mg) antenatal betamethasone doses in women at risk of very preterm delivery.<sup>10</sup> Because the fetal lung is the primary target of antenatal corticosteroids, we chose severe respiratory distress syndrome, defined as the need

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## AJOG at a Glance

**Why was this study conducted?**

A 50% dose reduction was proposed to decrease the potential dose-related long-term neurodevelopmental side effects of antenatal steroids.

**Key findings**

There were no significant differences in survival without neonatal morbidity and in the cumulative number of neonatal morbidities between neonates exposed to half-dose and those exposed to full-dose of antenatal betamethasone.

**What does this add to what is known?**

Our data suggest that reducing the dose of antenatal betamethasone might be safe at hospital discharge. However, assessment of long-term neurodevelopmental outcomes is needed.

for exogenous intratracheal surfactant within 48 hours after birth as the primary outcome. The higher limit of the 95% confidence interval (CI) of the between-group difference (risk difference, 2.4%; 95% CI,  $-0.3$  to  $+5.2$ ) exceeded the predefined 4% margin, and noninferiority was not shown.<sup>10</sup> This primary outcome, chosen ecrot consistency with historical findings by Liggins et al,<sup>3</sup> should be interpreted while taking into consideration survival at discharge and the occurrence of major prematurity-related complications. Indeed, the ultimate goal of antenatal steroids remains to improve long-term outcomes and quality of life of infants born preterm. Because the initial report of the BETADOSE trial analyzed distinct complications only, we further investigated the effect of betamethasone dose reduction on a composite outcome including not only survival and antenatal corticosteroids targets, but also other major complications usually observed in neonates born very preterm, recognized to be better correlated with long-term outcomes.<sup>11–13</sup> We hypothesized that betamethasone dose reduction would have no substantial impact on this composite outcome.

**Materials and Methods****Study design and participants**

We performed a post hoc analysis of the BETADOSE randomized trial, registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02897076) (NCT02897076). Detailed information on the trial design

(noneligibility criteria, sequence generation, allocation concealment mechanism, blinding, and sample size calculation) and principal findings have been previously reported.<sup>10,14</sup> The Île-de-France 1 Committee for the Protection of Research Subjects approved the protocol. I study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Briefly, pregnant women, aged  $\geq 18$  years, at  $< 32$  weeks of gestation with a singleton pregnancy, without chromosomal aberrations or major malformations, at risk of preterm delivery, and already treated with the first 11.4-mg betamethasone (6-mg phosphate plus 5.4-mg acetate) injection were randomly assigned to additionally receive either a placebo injection (half-dose group) or a second 11.4-mg injection (full-dose group).

**Primary and secondary outcomes**

The primary outcome was survival without severe neonatal morbidity at hospital discharge in infants born before 32 weeks of gestation to women enrolled in the BETADOSE trial.

To measure survival, we included all perinatal deaths, both those that occurred in utero and within and after the first 48 hours of life (ie, the end point of the primary outcome of the BETADOSE trial), excluding those due to pregnancy termination. Severe neonatal morbidity was based on the definition from the French national prospective study on preterm children, EPIPAGE 2

(definition A).<sup>15</sup> It comprises 1 of the following morbidities, usually recorded in very preterm infants: severe brain lesions including grade 3 to 4 intraventricular hemorrhage (according to the Papile classification<sup>16</sup>) and cystic periventricular leukomalacia, necrotizing enterocolitis stage  $\geq 2$  (according to Bell's<sup>17</sup> classification), retinopathy of prematurity requiring anti-vascular endothelial growth factor therapy or laser, and moderate-to-severe bronchopulmonary dysplasia, defined as the need for continuous positive airway pressure or supplemental oxygen, or mechanical ventilation after 36 weeks of postmenstrual age.<sup>18</sup>

- Secondary outcomes used 2 other well-recognized definitions of severe neonatal morbidity derived from the following: The Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP), with any proven neonatal infections added to the 4 EPIPAGE 2 study neonatal morbidities, as proposed by Bassler et al<sup>11</sup> (definition B)
- The Victorian Infant Collaborative Study Group,<sup>12</sup> which comprised 1 of the following: severe brain lesions including grade 3 to 4 intraventricular hemorrhage and cystic periventricular leukomalacia, use of postnatal corticosteroids administered by both inhaled and systemic routes, and neonatal surgery for necrotizing enterocolitis or patent ductus arteriosus (definition C)

Outcomes were assessed first in the neonates born before 32 weeks of gestation for whom most of the severe morbidities assessed were recorded, and then in the overall population of infants born to women recruited in the BETADOSE trial.

**Statistical analyses**

The baseline maternal and neonatal characteristics of the trial participants were described with qualitative variables expressed as proportions and quantitative variables expressed as medians with interquartile ranges or means with standard deviations.

For analyses of survival without severe neonatal morbidity considered as a binary outcome, comparisons were performed using 95% CIs for the between-group risk difference (the value in the half-dose group minus the value in the full-dose group). The 2-sided 95% CIs were computed by the Wilson method. With 475 patients per group, our study had an 80% chance of detecting, as significant at the 5% level, a 9% absolute decrease in the primary outcome measure from 66% in the full-dose group to 57% in the half-dose group. Subgroup analyses were performed according to gestational age at randomization (<28 or >28 weeks of gestation), gestational age at birth (<28, 28–32, and >32 weeks of gestation), neonatal sex, and the time interval between the first betamethasone injection and birth (<7 and >7 days).

Then, the number of morbidities were compared between the two groups (half vs full-dose) using the cumulative logit model for ordinal data,<sup>19</sup> both in the population of neonates born <32 weeks of gestation and in the overall population. The results were presented on a log-odds scale, with the parameter indicating the increase or decrease in the log-odds of falling into a higher category associated with the variable (half- vs full-dose). Finally, because of the small sample size and the failure to meet the chi-square assumptions, a chi-square test with a *P* value computed via Monte Carlo simulation (with 10,000 replications) was used to compare the distribution of comorbidity types among patients with 1 and 2 cumulative comorbidities for each criterion. All analyses were performed in the intention-to-treat population. All statistical analyses were conducted with R software, version 4.1 (R Core Team, Vienna, Austria).

## Results

From January 2, 2017 to October 9, 2019, 3244 women underwent randomization: 1620 in the half-dose group (intervention group) and 1624 in the full-dose group (control group). After exclusion of 48 women who withdrew consent, 8 who had pregnancy termination, and 16 who were lost to

follow-up, 1583 and 1589 neonates were born, including 472 and 482 before 32 weeks of gestation, in the half-dose and the full-dose group, respectively (Figure 1). Among the population of neonates born before 32 weeks of gestation, baseline maternal and neonatal characteristics were balanced between the groups (Table).

Survival without severe neonatal morbidity in neonates born before 32 weeks of gestation was recorded as 300 of 451 (66.5%) in the half-dose group and 304 of 462 (65.8%) in the full-dose group (risk difference, +0.7%; 95% CI, -5.6 to +7.1) (Figure 2). There were no significant between-group differences in any of the subgroup analyses, in particular in infants born before 28 weeks of gestation.

A total of 63 deaths occurred in the half-dose group, including 5 in utero and 5 before and 53 after 48 hours of life (ie, the end point of the primary outcome of the BETADOSE trial). In the full-dose group, 62 deaths were recorded, including 10 in utero and 3 before and 49 after 48 hours of life. Therefore, 408 and 419 surviving neonates born very preterm remained in the half-dose and full-dose groups, respectively, for the analysis of cumulative morbidities. No association between treatment groups and the cumulative number of comorbidities was found (parameter estimate, -0.005; standard error, 0.143; *P*=.975) (Figure 3; Supplemental Table 1). The distribution of each comorbidity, according to the total number of comorbidities reported, did not differ between the 2 treatment groups (Supplemental Table 2).

Complementary analyses first extended the primary definition (definition A from EPIPAGE 2) to 2 other internationally recognized definitions of severe neonatal morbidity (definition B from the TIPP trial and definition C from the Victorian Infant Collaborative Study, as described in Materials and Methods). In the comparison between the half dose and the full dose of antenatal betamethasone, the estimated incidence of survival without severe neonatal morbidity in infants born before 32 weeks of gestation ranged from 8.9% lower to 7.1% higher. This range

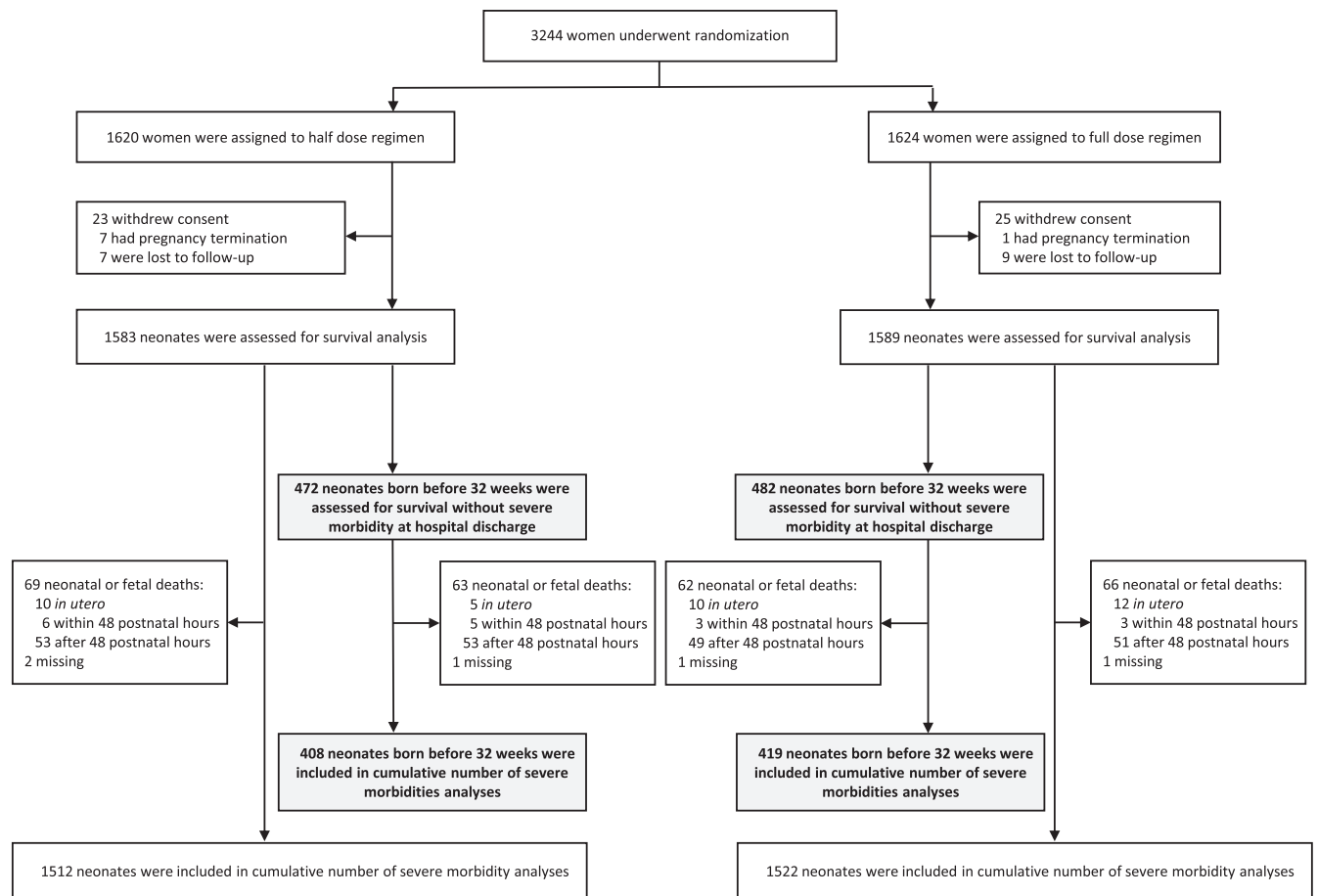
was based on the 95% CI related to the 3 definitions of the composite outcome (Supplemental Figure 1).

We repeated the analysis on the total population randomized in the BETADOSE trial. Maternal and neonatal characteristics were balanced between the groups (Supplemental Table 3). In the comparison between the half dose and the full dose of antenatal betamethasone, the estimated incidence of survival without severe neonatal morbidity ranged from 3.2% lower to 2.1% higher. This range was based on the 95% CI related to the 3 definitions of the outcome (Supplemental Figure 2). In this total population, no between-group difference was found in any of the subgroup analyses, regardless of the definition of severe neonatal morbidity used (Supplemental Figure 3).

No association between treatment groups and the cumulative number of comorbidities both in infants born before 32 weeks of gestation and in the overall population was found, regardless of the definition of severe neonatal morbidity used (Supplemental Table 1; Supplemental Figures 4 and 5). When neonates were exposed to 1 major comorbidity only, their distribution did not differ between the 2 treatment groups (Supplemental Table 2). Subtle between-group changes in distribution were observed when 2 comorbidities were reported, in particular for definition C.

## Comment Principal findings

This post hoc analysis of the BETADOSE randomized trial suggests that survival without severe neonatal morbidity at hospital discharge in infants born before 32 weeks of gestation did not differ between neonates exposed to half doses and those exposed to full antenatal betamethasone doses. In addition, no association between treatment groups and the cumulative number of comorbidities was found. These data suggest that the lack of noninferiority of the half-dose in terms of the need for exogenous surfactant to treat severe respiratory distress syndrome previously shown in the main analysis of the BETADOSE

**FIGURE 1**  
**CONSORT flowchart**

CONSORT, Consolidated Standards of Reporting Trials.

Baud. Betamethasone dose reduction and neonatal health. *Am J Obstet Gynecol* 2024.

trial<sup>10</sup> has no or minimal detectable impact on neonatal health at hospital discharge. Potential explanations for this finding include changes toward less invasive management of respiratory distress syndrome in preterm infants, based on internationally agreed guidelines on early stabilization, respiratory support, and surfactant therapy.<sup>20</sup>

### Results in the context of what is known

Our findings, generated using a definition of neonatal morbidity for the targeted population of very preterm infants, are consistent with the previously reported lack of difference in the incidence of each neonatal complication, considered as distinct variables, between the 2 regimens of antenatal

betamethasone.<sup>10</sup> Moreover, they are consistent with a recent trial showing noninferiority in preventing neonatal respiratory distress syndrome of a 5-mg dexamethasone dose compared with a standard 6-mg dose given to singleton pregnant women at risk of premature delivery at 32 to 36 weeks of gestation.<sup>21</sup> However, because each patient may develop various combinations of morbidities, this previous analysis cannot predict the overall clinical impact of betamethasone dose reduction in infants born very preterm. In addition, herein we used composite definitions of severe neonatal morbidity including bronchopulmonary dysplasia<sup>22</sup> and white matter damage,<sup>23</sup> 2 key risk factors for long-term neurodevelopmental outcomes whose occurrence is not properly

prevented by antenatal steroids. All components of these definitions are important and should be considered because prediction of long-term outcomes in children born preterm remains limited during the first few postnatal days,<sup>24</sup> and specific comorbidities occurring throughout the primary hospitalization increase their discriminative value. Indeed, a simple count of moderate-to-severe bronchopulmonary dysplasia, severe brain injury, and severe retinopathy of prematurity was found to be highly predictive of late death or survival with neurodevelopmental impairment.<sup>25</sup> We primarily used the French EIPAGE 2 definition because the BETADOSE trial was conducted in France, but similar results were observed when using 2 other slightly different

TABLE

**Maternal and neonatal baseline characteristics of neonates born before 32 weeks of gestation**

Characteristics	Half-dose group (N=472)	Full-dose group (N=482)
<b>Maternal</b>		
Maternal age, median (IQR), y	31.1 (27.5–35.1)	31.2 (27.5–34.8)
<b>Place of birth (n/N)</b>		
France	311/462 (67.3)	309/469 (65.9)
Europe	17/462 (3.7)	19/469 (4.1)
North Africa	52/462 (11.2)	43/469 (9.2)
Sub-Saharan Africa	74/462 (16.0)	78/469 (16.6)
Asia	4/462 (0.9)	9/469 (1.9)
Other	4/462 (0.9)	11/469 (2.3)
Body mass index, median (IQR), kg/m <sup>2</sup>	23.3 (20.6–28.5)	23.9 (20.9–28.3)
<18.5	36/451 (9.2)	28/474 (5.9)
18.5–24.9	239/451 (56.1)	243/474 (51.3)
25–29.9	99/451 (20.0)	115/474 (24.3)
≥30	77/451 (14.6)	88/474 (18.6)
Insulin-treated diabetes (n/N)	7/472 (1.5)	11/482 (2.3)
<b>Indication for trial entry</b>		
Preterm labor	115 (24.4)	95 (19.7)
Preterm premature rupture of membranes	150 (31.8)	150 (31.1)
Preeclampsia	83 (17.6)	97 (20.1)
Intrauterine growth restriction	87 (18.4)	102 (21.2)
Bleeding	28 (5.9)	32 (6.6)
Other	9 (1.9)	6 (1.2)
Gestational age at trial entry, median (IQR), wk	27.1 (25.7–29.0)	27.7 (25.6–29.6)
<28 wk 0 d	277 (58.7)	266 (55.2)
From 28 wk 0 d to 31 wk 6 d	195 (41.3)	216 (44.8)
Betamethasone rescue course	0 (0.0)	1 (0.2)
Antenatal magnesium sulfate for fetal neuroprotection (n/N)	341/466 (73.2)	346/479 (72.2)
Cesarean delivery	307 (65.0)	313 (64.9)
<b>Neonatal</b>		
Delay between first betamethasone administration and birth, median (IQR), d	7 (4–17)	7 (3–16)
Birth within 7 d after first administration	238 (50.4)	254 (52.7)
Gestational age at birth, median (IQR), wk	29.1 (27.3–30.7)	29.7 (27.6–30.9)
<28 wk 0 d	152 (32.2)	138 (28.6)
From 28 wk 0 d to 31 wk 6 d	320 (67.8)	344 (71.4)
Birthweight, mean ±SD, g	1125±377	1124±371
Birthweight <10th centile <sup>a</sup>	84 (17.8)	104 (21.6)
Male neonate	261 (55.3)	262 (54.4)

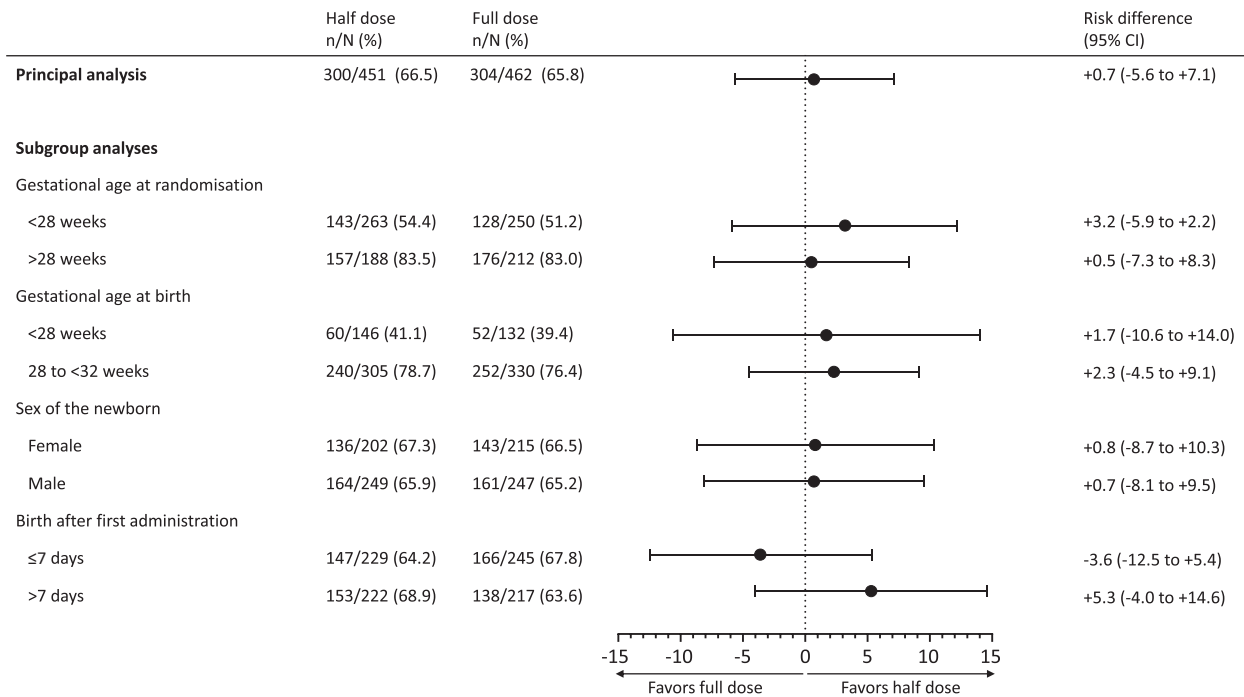
IQR, interquartile range; SD, standard deviation.

<sup>a</sup> According to the Fenton chart.

Baud. Betamethasone dose reduction and neonatal health. Am J Obstet Gynecol 2024.

FIGURE 2

## Survival without severe neonatal morbidity among infants born before 32 weeks of gestation and in prespecified subgroups



CI, confidence interval.

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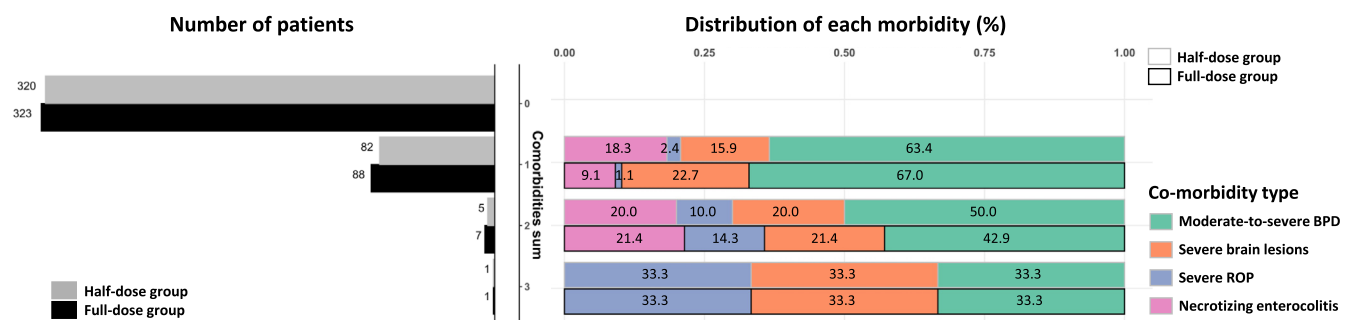
definitions. Bassler et al<sup>11</sup> included any episode of proven sepsis as a predictor of poor outcome, consistent with a recent population-based study reporting increased odds of severe bronchopulmonary dysplasia, cystic white matter damage, and severe retinopathy of

prematurity in very preterm infants with culture-positive late-onset sepsis.<sup>26</sup> When using the Victorian Infant Collaborative Study definition of severe neonatal morbidity, we found some subtle changes in the distribution of comorbidities reported in surviving

infants. Indeed, fewer severe brain lesions but more surgical procedures were observed after antenatal corticosteroid dose reduction. Besides congenital malformations, which was an exclusion criterion in the BETADOSE trial, patent ductus arteriosus closure and perforated

FIGURE 3

## Distribution of the number and types of severe cumulative morbidities among infants born before 32 weeks of gestation



BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

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necrotizing enterocolitis are the 2 leading causes of neonatal surgery. The increased occurrence of neonatal surgery in the half-dose group appears to be consistent with (1) a similar direction in the incidence of necrotizing enterocolitis observed with definitions A and B, and (2) overall with the slight increase in severe respiratory distress syndrome,<sup>10</sup> a risk factor for patent ductus arteriosus.<sup>27</sup> Conversely, one major concern regarding antenatal betamethasone dose reduction was a potential increased risk of severe intraventricular hemorrhage, which was not supported by our data. However, interpretation of these exploratory findings on comorbidity distribution should be cautious given the small sample size.

### Clinical and research implications

Our data suggest that reducing the dose of antenatal betamethasone given to women might be safe for neonates at hospital discharge, particularly when birth occurs before 32 weeks of gestation. Despite the post hoc nature of these data, they could be informative for obstetricians and neonatologists in discussion with parents about the optimal perinatal management of infants at risk of preterm delivery before 32 weeks of gestation, a population not specifically studied in the previous report of our trial. However, because the current analysis was based on a relatively short-term outcome, long-term neurodevelopmental outcomes of infants enrolled in the trial must be assessed before deciding whether this 50% dose reduction could be considered. Pending results of the 5-year follow-up of these children (BETA-NINO [BETAmethasone Dose Reduction: Non-Inferiority on the Neurocognitive Outcomes of Children Born Before 32 Weeks of Gestation] study, NCT04021485) are expected to identify potential domains of neurocognitive development sensitive to betamethasone exposure and clarify whether antenatal betamethasone dose reduction may interfere with neurocognitive and behavioral outcomes of infants born very preterm. These results should be released in 2026.

### Strengths and limitations

The main strengths of this study include the use of a database from a large randomized controlled trial, the consistency between the variables in the definitions of severe neonatal morbidity and the data collected in this trial, and the completeness of data, which exceeded 95%. The lack of difference in survival without severe morbidity at discharge was also consistently observed between half-dose and full-dose antenatal betamethasone groups, regardless of the outcomes considered, supporting the generalizability of the results. In this study, we used 3 different internationally recognized definitions based on major prematurity-induced morbidities. They were selected because they were (1) either population-based (A: EPIPAGE 2 and C: Victorian Infant Collaborative Study Group) or derived from a randomized controlled trial (B: TIPP trial), (2) found to predict long-term outcomes, (3) tested in distinct areas of the world (A: France; B: North America; C: Australia), and (4) comprised morbidities frequently observed in very preterm infants.

The main limitation of this study relates to the post hoc nature of the analyses and the relatively small sample size of infants born before 32 weeks of gestation, who are at highest risk of developing comorbidities. However, investigating only neonates born very preterm increases the clinical relevance of the definitions chosen for assessing severe prematurity-related morbidities. Considering the rate of survival without severe neonatal morbidity in the full-dose group and the number of neonates available for the analyses, our study was underpowered to detect reductions in the primary outcome <9% in the half-dose group. However, to demonstrate significant differences in the percentage range as reported herein between the 2 groups, considering similar rates of very preterm delivery and of survival without severe neonatal morbidity, an unreachable sample size of 120,000 women per group would need to be randomized. Risk differences in other subpopulations also may be underestimated because of small sample size, particularly for infants

exposed to antenatal steroids within 7 days before birth.

### Conclusion

This post hoc analysis of the BETADOSE trial further extends previously reported findings regarding the safety of antenatal betamethasone dose reduction in infants born very preterm, who constitute the main target population for antenatal steroids. It suggests that survival without severe neonatal morbidity at hospital discharge among infants born before 32 weeks of gestation did not differ between those exposed to half-dose and those exposed to full-dose of antenatal betamethasone. In addition, no association between treatment groups and the cumulative number of comorbidities was found. ■

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## Author and article information

From the Division of Neonatology and Pediatric Intensive Care, Children's University Hospital of Geneva, University of Geneva, Geneva, Switzerland (Dr Baud); Université Paris Cité, Inserm U1141, Paris, France (Dr Baud); Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France (Dr Sentilhes); Clinical Epidemiology Unit, CIC-EC 1426, Robert Debré Hospital, Assistance Publique—Hôpitaux de Paris, Paris, France (Drs Ursino and Alberti); Centre de Recherche des Cordeliers, Inserm U1138, Université Paris Cité, Sorbonne Université, Paris, France (Dr Ursino); HeKA, Inria Paris, Paris, France (Dr Ursino); Department of Obstetrics and Gynecology, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, University Claude Bernard Lyon 1, Lyon, France (Dr Doret-Dion); Université Paris Cité, Inserm U1123, ECEVE, Paris, France (Drs Alberti and Aupiais); Pediatric Emergency Department, Jean Verdier Hospital, Assistance Publique—Hôpitaux de Paris, Sorbonne Paris Nord University, Paris, France (Dr Aupiais); Department of Obstetrics and Gynecology, Robert Debré Hospital, Assistance Publique—Hôpitaux de Paris, Paris, France (Dr Schmitz); and Université Paris Cité, Centre for Research in Epidemiology and Statistics (CRESS), Inserm, INRAE, Paris, France (Dr Schmitz).

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### Clinical trial registration

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URL of the registration site: <https://classic.clinicaltrials.gov/ct2/show/record/NCT02897076>

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### Data sharing

Data sharing requests will be considered by the management group upon written request to the corresponding author. Deidentified participant data or other prespecified data will be available, subject to a written proposal and a signed data sharing agreement.

Corresponding author: Olivier Baud, PhD. [olivier.baud@hcuge.ch](mailto:olivier.baud@hcuge.ch)

## Supplemental Materials

### List of participating members of the BETADOSE study group

Thomas Schmitz, MD, Muriel Doret-Dion, MD, Loïc Sentilhes, MD, Olivier Parant, MD, Olivier Claris, MD, Laurent Renesme, MD, Julie Abbal, MD, Aude Girault, MD, Héroïse Torchin, PhD, Marie Houllier, MD, Nolwenn Lesache, MD, Alexandre J. Vivanti, MD, Daniele De Luca, MD, Norbert Winer, MD, Cyril Flamant, MD, Claire Thuillier, MD, Pascal Boileau, MD, Julie Blanc, MD, Véronique Brevaut, MD, Pierre-Emmanuel Bouet, MD, Géraldine Gascoin, MD, Gaël Beucher, MD, Valérie Datin-Dorriere, MD, Stéphane Bounan, MD, Pascal Bolot, MD, Christophe Poncelet, MD, Philippe Boize, MD, Charles Garabédian, MD, Florence Flamein, MD, Maela Le Lous, MD, Alain Beuchée, MD, Jean Gondry, MD, Pierre Tourneux, MD, Perrine Coste-Mazeau, MD, Antoine Bedu, MD, Denis Gallot, MD, Caren Coste, MD, Céline Chauleur, MD, Hugues Patural, MD, Gilles Kayem, MD, Delphine Mitanché, PhD, Héléne Heckenroth, MD, Farid Boubred, MD, Jeanne Sibiude, MD, Luc Desfrère, MD, Caroline Bohec, MD, Thierry Mansir, MD, Antoine Koch, MD, Pierre Kuhn, MD, Nadia Tillouche, MD, Fabrice Lapeyre, MD, Franck Perrotin, MD, Géraldine Favrais, MD, Edouard Lecarpentier, MD, Xaxier Durrmeyer, PhD, Véronique Equy, MD, Thierry Debillon, MD, Luc

Rigonnot, MD, Stéphanie Lefoulogoc, MD, Claudia Brie, MD, Anne-Sophie Pagès, MD, Romy Rayssiguier, MD, Gilles Cambonie, MD, Corinne Cudeville, MD, Dorianne Madeleneau, MD, Olivier Morel, MD, Jean-Michel Hascoet, MD, Vincent Letouzey, MD, Massimo Di Maio, MD, Laurent J. Salomon, MD, Alexandre Lapillonne, MD, Corinne Alberti, PhD, Moreno Ursino, PhD, Camille Aupiais, MD, and Olivier Baud, PhD.

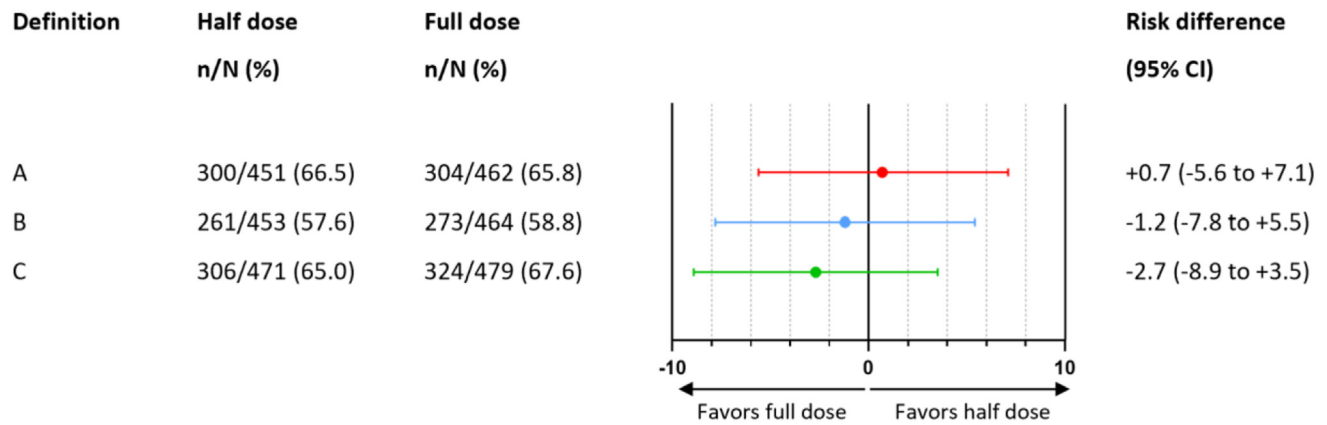
### List of participating members of the Groupe de Recherche en Obstétrique et Gynécologie

Thomas Schmitz, MD, PhD, Department of Obstetrics and Gynecology, Assistance Publique—Hôpitaux de Paris; Robert Debré, GROG president; Julie Blanc, MD, PhD, Assistance Publique—Hôpitaux de Marseille, Marseille; Céline Chauleur, MD, PhD, Department of Obstetrics and Gynecology, Saint Etienne; Catherine Deneux-Tharaux, MD, PhD, UMR1153 — Obstetric, Perinatal and Pediatric Epidemiology (EPOPé research team), Paris, Descartes University, Inserm, Paris; Philippe Deruelle, MD, PhD, Department of Obstetrics and Gynecology, Lille; Raoul Desbrière, MD, Department of Obstetrics and Gynecology, Saint Joseph Hospital, Marseille; Muriel Doret-Dion, MD, PhD, Department of Obstetrics and Gynecology, Lyon; Denis Gallot, MD, PhD, Department of Obstetrics and Gynecology,

Clermont-Ferrand; Charles Garabédian, MD, PhD, Department of Obstetrics and Gynecology, Lille; Aude Girault, MD, PhD, Department of Obstetrics and Gynecology, Assistance Publique—Hôpitaux de Paris, Cochin-Port Royal; François Goffinet, MD, PhD, Department of Obstetrics and Gynecology, Assistance Publique—Hôpitaux de Paris, Cochin-Port Royal; Gilles Kayem, MD, PhD, Department of Obstetrics and Gynecology, Assistance Publique—Hôpitaux de Paris, Paris; Camille Le Ray, MD, PhD, Department of Obstetrics and Gynecology Assistance Publique—Hôpitaux de Paris, Cochin-Port Royal; Olivier Morel, MD, PhD, Department of Obstetrics and Gynecology, Nancy; Franck Perrotin, MD, PhD, Department of Obstetrics and Gynecology, Tours; Patrick Rozenberg, MD, PhD, Department of Obstetrics and Gynecology, Poissy; Marie-Victoire Senat, MD, PhD, Department of Obstetrics and Gynecology, Assistance Publique—Hôpitaux de Paris, Bicêtre; Loïc Sentilhes, MD, PhD, Department of Obstetrics and Gynecology, Bordeaux; Damien Subtil, MD, PhD, Department of Obstetrics and Gynecology, Lille; Christophe Vayssière, MD, PhD, Department of Obstetrics and Gynecology, Toulouse; Norbert Winer, MD, PhD, Department of Obstetrics and Gynecology, Nantes. Participating members of the GROG had a role in the design of the study. They have not received any compensation for their role in the study.

## SUPPLEMENTAL FIGURE 1

## Survival without severe neonatal morbidity measured according to 3 definitions of severe neonatal morbidity (A, B, and C) among infants born before 32 weeks of gestation



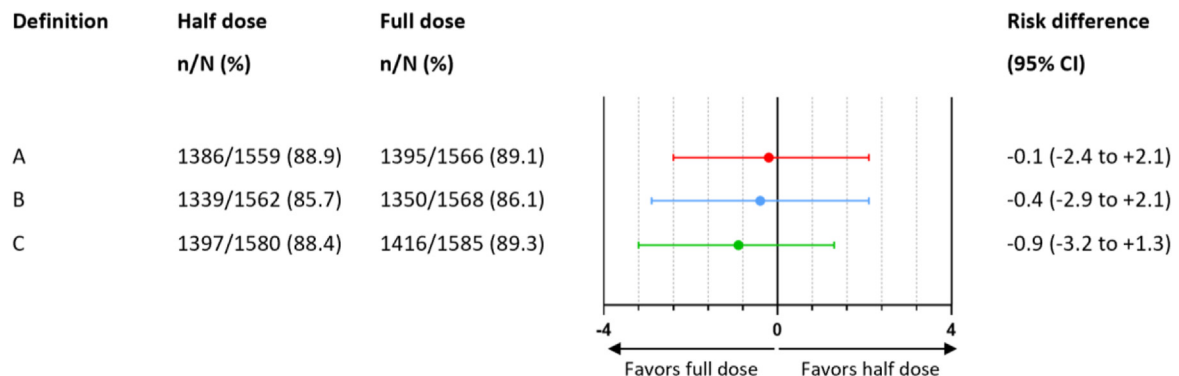
Definition A: grade 3 to 4 intraventricular hemorrhage, cystic periventricular leukomalacia, necrotizing enterocolitis stage  $\geq 2$ , retinopathy of prematurity requiring anti-vascular endothelial growth factor therapy or laser, and bronchopulmonary dysplasia.<sup>15</sup> Definition B: definition A+early- and late-onset proven infections.<sup>11</sup> Definition C: grade 3 to 4 intraventricular hemorrhage, cystic periventricular leukomalacia, use of postnatal corticosteroids, and surgery.<sup>12</sup>

CI, confidence interval.

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## SUPPLEMENTAL FIGURE 2

## Survival without severe neonatal morbidity measured according to 3 definitions of severe neonatal morbidity (A, B, and C) in the overall population enrolled in the BETADOSE trial

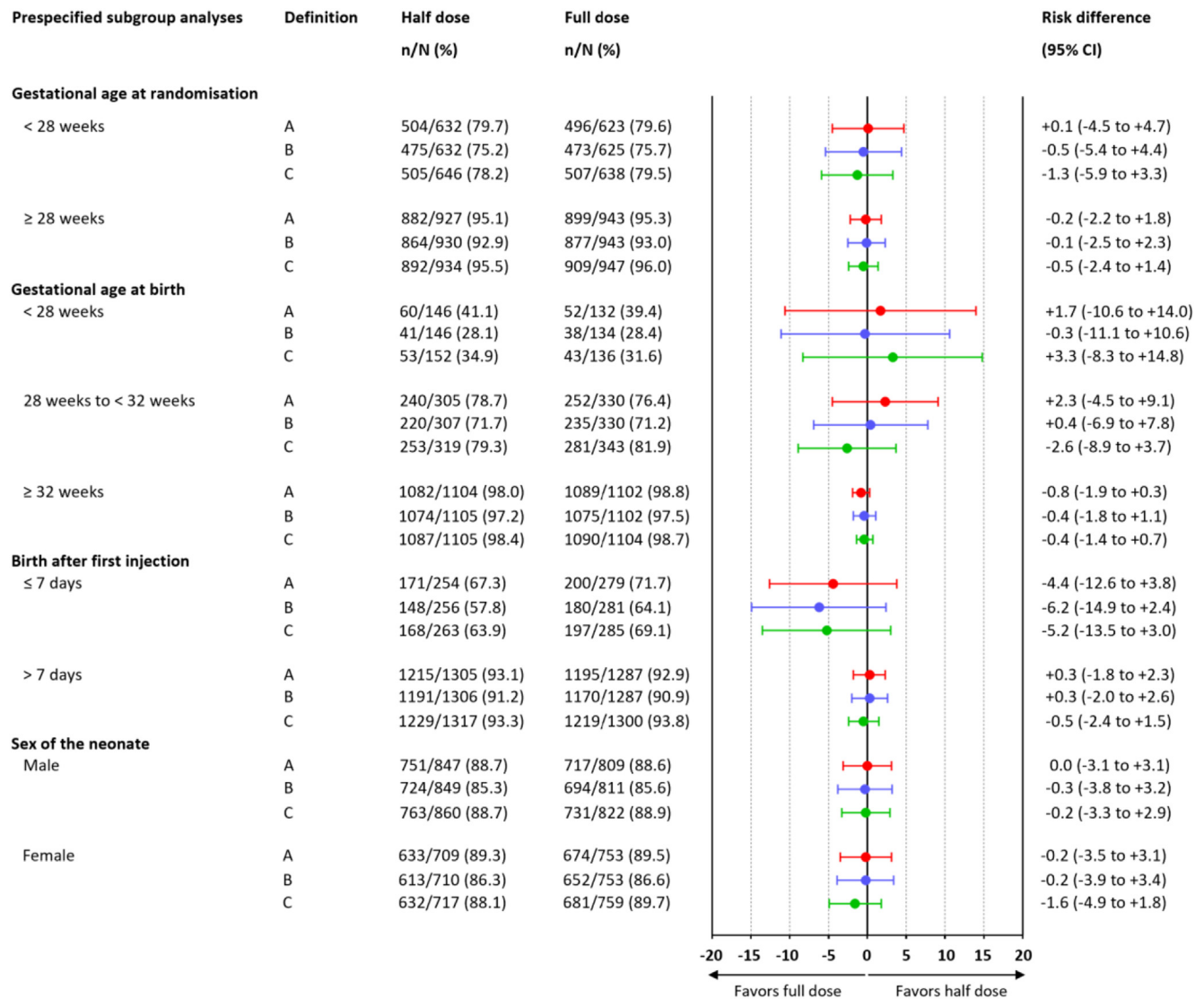


CI, confidence interval.

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## SUPPLEMENTAL FIGURE 3

## Survival without severe neonatal morbidity measured according to 3 definitions of severe neonatal morbidity (A, B, and C) in the overall population enrolled in the BETADOSE trial, among prespecified subgroups

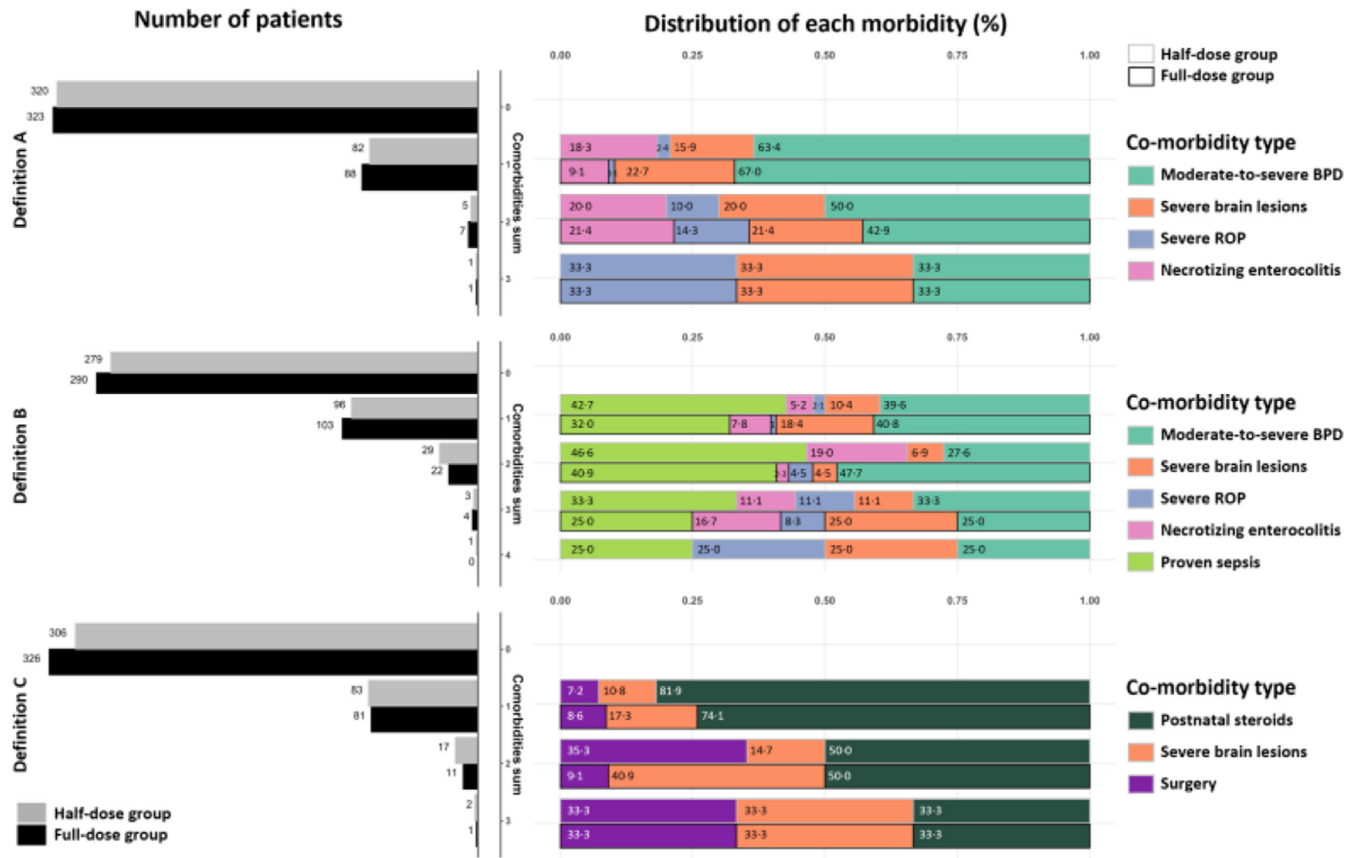


CI, confidence interval.

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**SUPPLEMENTAL FIGURE 4**

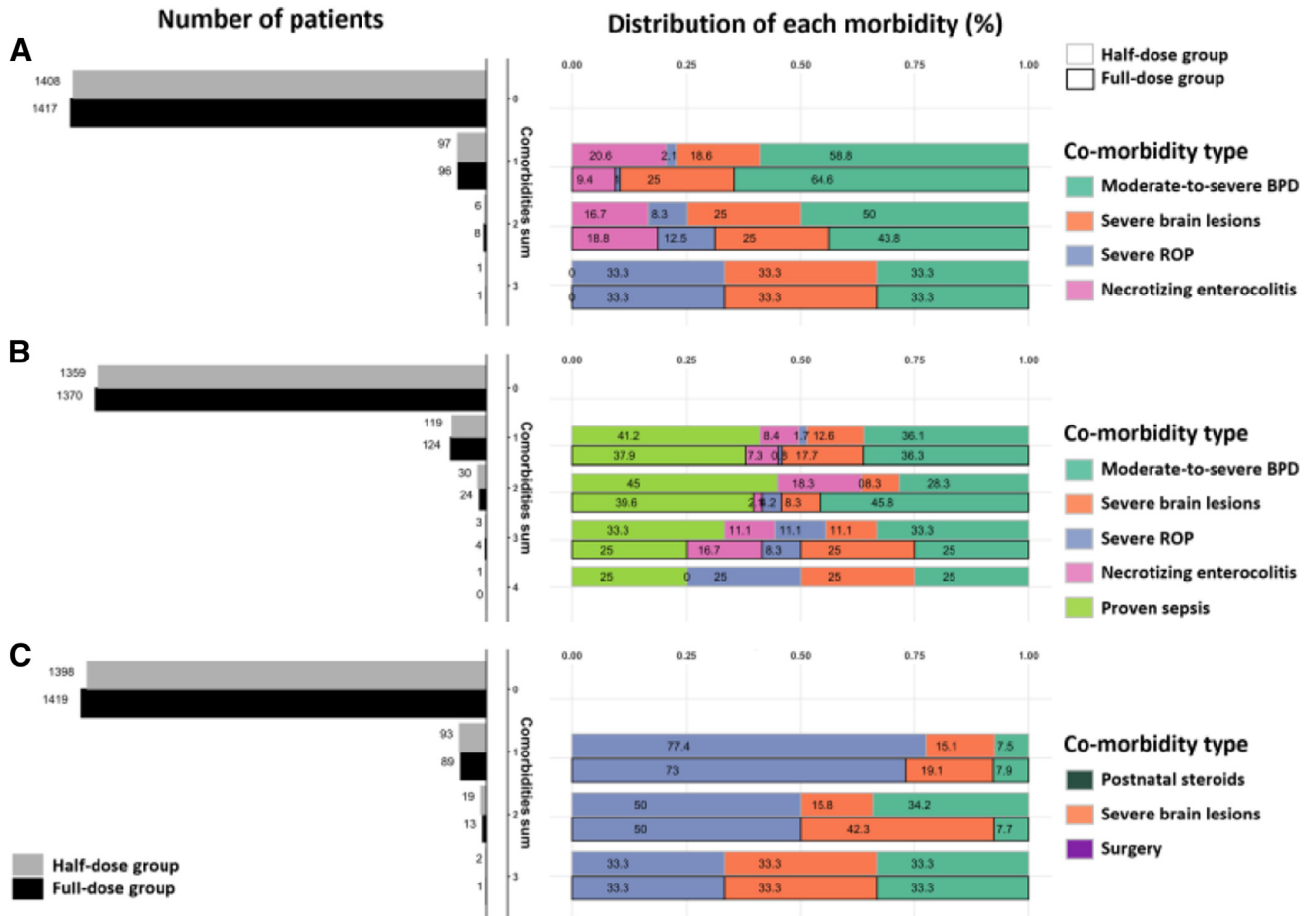
**Number and distribution of the cumulative morbidities according to 3 definitions of severe neonatal morbidity (A, B, and C) in the population of neonates born before 32 weeks of gestation**



BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.  
 Baud. Betamethasone dose reduction and neonatal health. Am J Obstet Gynecol 2024.

**SUPPLEMENTAL FIGURE 5**

**Number and distribution of the cumulative morbidities according to 3 definitions of severe neonatal morbidity (A, B, and C) in the overall population enrolled in the BETADOSE trial**



BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

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**SUPPLEMENTAL TABLE 1**

**Between-treatment difference in the number of the cumulative comorbidities reported in the overall population and in neonates born before 32 weeks of gestation, according to the definition of severe neonatal morbidity (A, B, C)**

Group	Parameter estimate <sup>a</sup>	Standard error	P value
Overall population			
A	-0.005	0.143	.975
B	0.019	0.121	.877
C	0.12	0.141	.395
Neonates born before 32 wk of gestation			
A	-0.082	0.167	.625
B	0.061	0.148	.68
C	0.172	0.163	.292

<sup>a</sup> Effect of the half dose relative to the full dose as the reference. The results are shown as the increase/decrease in the log-odds of falling into a higher category.

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**SUPPLEMENTAL TABLE 2**

**Between-treatment difference in comorbidity distribution for 1 and 2 cumulative comorbidities, in the overall population and in neonates born before 32 weeks of gestation, according to the definition of severe neonatal morbidity (A, B, C)**

Group	Cumulative number of comorbidities	P value
Overall population		
A	1	.1552
	2	1
B	1	.7404
	2	.144
C	1	.8743
	2	.005
Neonates born before 32 wk of gestation		
A	1	.2548
	2	1
B	1	.3412
	2	.0119
C	1	.4548
	2	.0318

Results were obtained using the chi-square test, with P value computed via Monte Carlo simulation (10,000 replications).

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## SUPPLEMENTAL TABLE 3

## Maternal and neonatal baseline characteristics of the overall population recruited in the BETADOSE trial

Characteristics	Half-dose group (N=1583)	Full-dose group (N=1589)
<b>Maternal</b>		
Maternal age, median (IQR), y	30.9 (26.8–35.0)	31.1 (27.0–35.4)
Place of birth (n/N)		
France	1071/1543 (69.5)	1097/1550 (70.8)
Europe	65/1543 (4.2)	61/1550 (3.9)
North Africa	161/1543 (10.4)	151/1550 (9.7)
Sub-Saharan Africa	207/1543 (13.4)	180/1550 (11.6)
Asia	23/1543 (1.5)	26/1550 (1.7)
Other	16/1543 (1.0)	35/1550 (2.3)
Body mass index, median (IQR), kg/m <sup>2</sup>	23.0 (20.3–27.3)	22.8 (20.4–27.0)
<18.5	142/1537 (9.2)	144/1556 (9.3)
18.5–24.9	863/1537 (56.1)	865/1556 (55.6)
25–29.9	307/1537 (20.0)	325/1556 (20.9)
≥30	225/1537 (14.6)	222/1556 (14.3)
Insulin-treated diabetes	23 (1.5)	30 (1.9)
Indication for trial entry		
Preterm labor	709 (44.8)	684 (43.0)
Preterm premature rupture of membranes	321 (20.3)	314 (19.8)
Preeclampsia	170 (10.7)	203 (12.8)
Intrauterine growth restriction	146 (9.2)	148 (9.3)
Bleeding	166 (10.5)	185 (11.6)
Other	71 (4.5)	55 (3.5)
Gestational age at trial entry, median (IQR), wk	28.6 (26.4–30.4)	28.7 (26.6–30.4)
<28 wk 0 d	647 (40.9)	640 (40.3)
From 28 wk 0 d to 31 wk 6 d	936 (59.1)	949 (59.7)
Betamethasone rescue course (n/N)	43/1580 (2.7)	46/1586 (2.9)
Antenatal magnesium sulfate for fetal neuroprotection (n/N)	392/1524 (25.7)	410/1537 (26.7)
Cesarean delivery (n/N)	660/1578 (41.8)	687/1586 (43.2)
<b>Neonatal</b>		
Delay between first betamethasone injection and birth, median (IQR), d	45 (15–69)	45 (14–68)
Birth within 7 d after first injection	263 (16.6)	288 (18.1)
Gestational age at birth, median (IQR), wk	35.7 (31.1–38.4)	35.4 (31.1–38.4)
<28 wk 0 d	152/1579 (9.6)	138/1587 (8.7)
From 28 wk 0 d to 31 wk 6 d	320/1579 (20.3)	344/1587 (21.7)
From 32 wk 0 d to 33 wk 6 d	178/1579 (11.3)	191/1587 (12.0)
From 34 wk 0 d to 36 wk 6 d	306/1579 (19.4)	268/1587 (16.9)
≥37 wk 0 d	623/1579 (39.5)	646/1587 (40.7)
Birthweight, mean±SD, g	2229±947	2208±931

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(continued)



## SUPPLEMENTAL TABLE 3

## Maternal and neonatal baseline characteristics of the overall population recruited in the BETADOSE trial (continued)

Characteristics	Half-dose group (N=1583)	Full-dose group (N=1589)
Birthweight <10th centile (n/N) <sup>a</sup>	275/1574 (17.5)	294/1582 (18.6)
Male neonate (n/N)	862/1580 (54.6)	826/1585 (52.1)

*IQR*, interquartile range; *SD*, standard deviation.

<sup>a</sup> According to the Fenton chart.

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