Une dose ou deux doses en antenatal ?

Dose reduction of antenatal betamethasone in women at risk of preterm delivery:

a randomized, multicenter, double blinded, placebo-controlled, non-inferiority trial (BETADOSE)

Thomas Schmitz, for the BETADOSE study group and the GROG

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

GROUPE DE RECHERCHE EN OBSTÉTRIQUE ET GYNÉCOLOGIE GROG

Inserm
Institut national de la santé et de la recherche médicale

The BETADOSE trial: rational

- One course of antenatal corticosteroids (ACS) reduces in preterm neonates the incidence of:
  - Respiratory distress syndrome (RDS),
  - Intraventricular hemorrhage (IVH),
  - Necrotizing enterocolitis (NEC) and
  - Neonatal death

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- ACS are recommended worldwide in women at risk of preterm delivery

- Indications and the number of fetuses exposed to ACS are rising

Gyamfi-Bannerman C, et al. N Engl J Med 2016
Saccone G, Berghella V. BMJ 2016

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- ACS are associated with long-term dose-related side effects

Wapner RJ, et al. N Engl J Med 2007
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A randomised non-inferiority trial testing
a 50% dose reduction of antenatal betamethasone

The BETADOSE trial: objectives

- **Primary aim**: to determine whether half dose regimen given to women at risk of very preterm delivery is not inferior to full antenatal betamethasone dose regimen to prevent severe RDS associated with preterm birth

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- **Secondary aims**: to compare other neonatal complications between half and full antenatal betamethasone dose regimens

The BETADOSE trial: eligibility criteria

- **Inclusion criteria**
  - Age ≥ 18 years
  - Singleton pregnancy
  - First betamethasone injection already performed
  - Gestational age < 32 weeks at first betamethasone injection
  - Signed informed consent has been obtained

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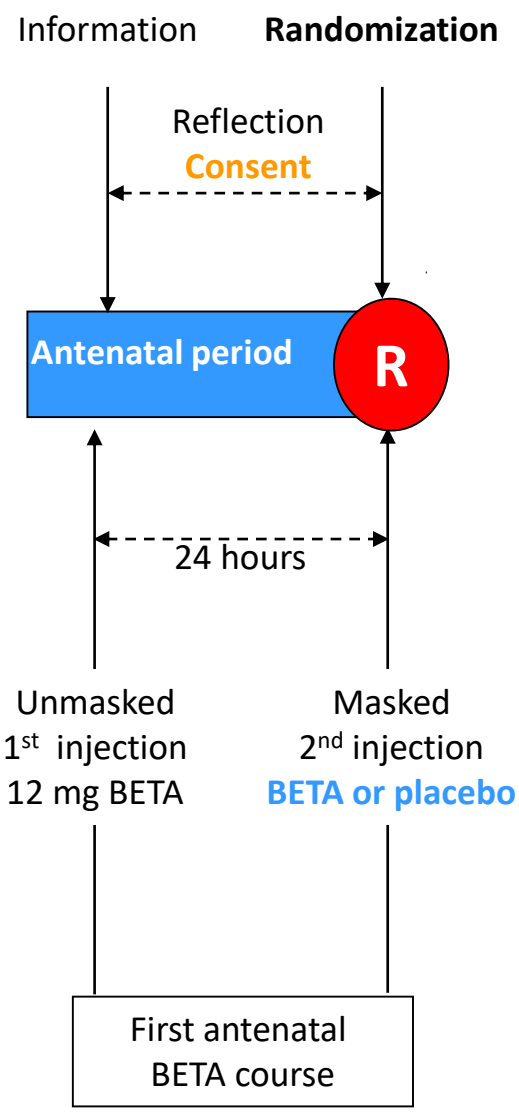
- **Exclusion criteria**
  - Already received a full course of betamethasone
  - First injection given by the intravascular route
  - In case of preterm labor:
    - Cervical dilatation ≥ 4 cm
    - Ultrasonographic cervical length ≥ 20 mm
  - Chromosomal aberrations and/or major fetal malformations
  - Poor understanding of the French language

The BETADOSE trial: intervention



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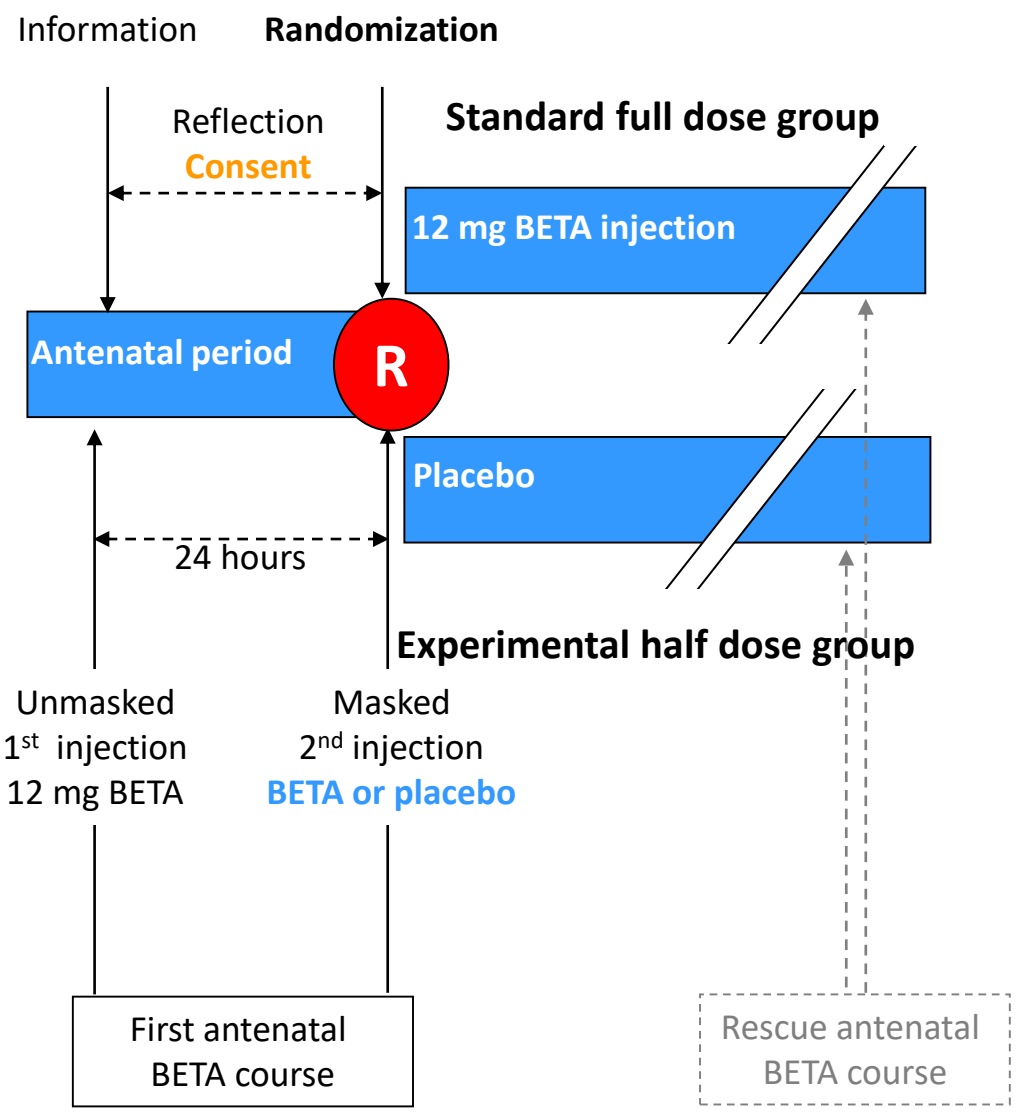

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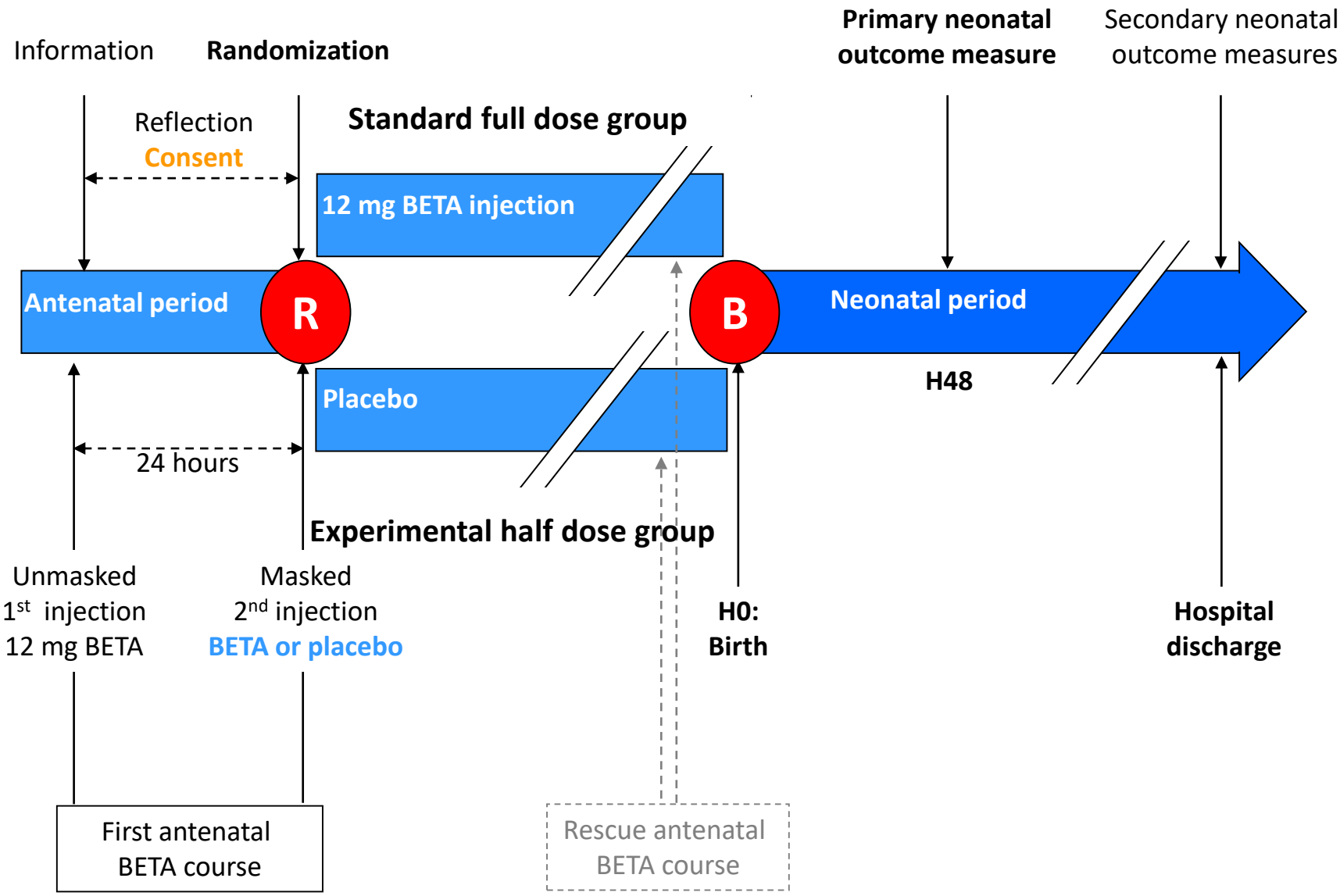

The BETADOSE trial: outcome measures

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  - Necrotizing enterocolitis (NEC) stage ≥2
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- **Secondary respiratory outcomes**

- **Other secondary prematurity-associated outcomes**

- **Secondary anthropometric outcomes**

The BETADOSE trial: sample size and statistical analyses

- We assumed a 20% rate of severe RDS in the full dose group because 60% of the children born <32 weeks received surfactant in the Epipage2 study and we anticipated a rate of delivery <32 weeks of 33% (0,33 X 60% = 20%)

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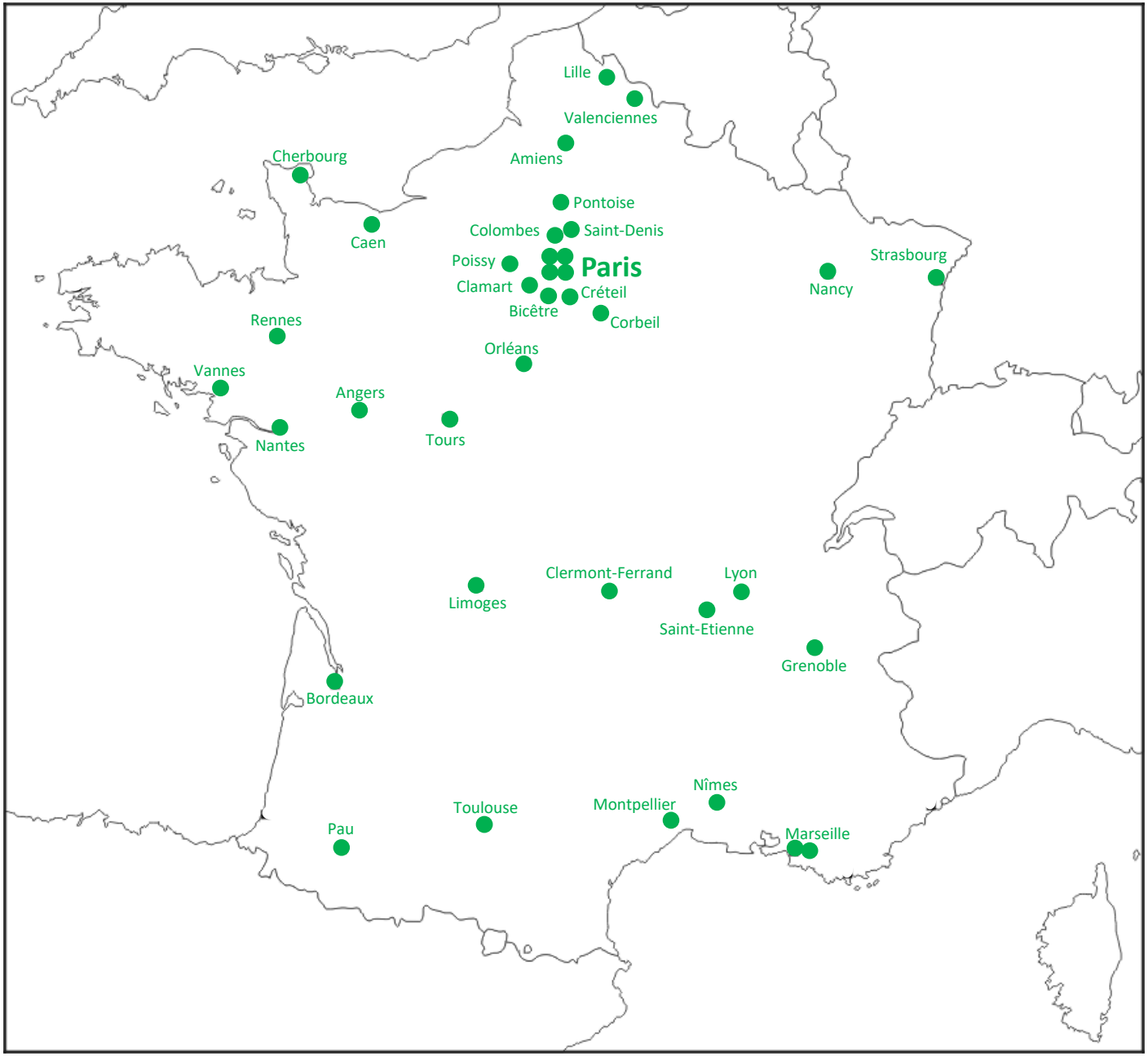
- Analyses in intention-to-treat and per protocol populations

- Subgroup analyses according to:
  - gestational age at randomization (before/after 28 weeks)
  - gestational age at delivery (<28, [28-32[, and >32 weeks)
  - Sex of the newborn

The BETADOSE trial: participating centers



The BETADOSE trial: Flow chart

January 3, 2017 to October 9, 2019
37 level-3 perinatal centers

3244 women were enrolled and underwent randomization

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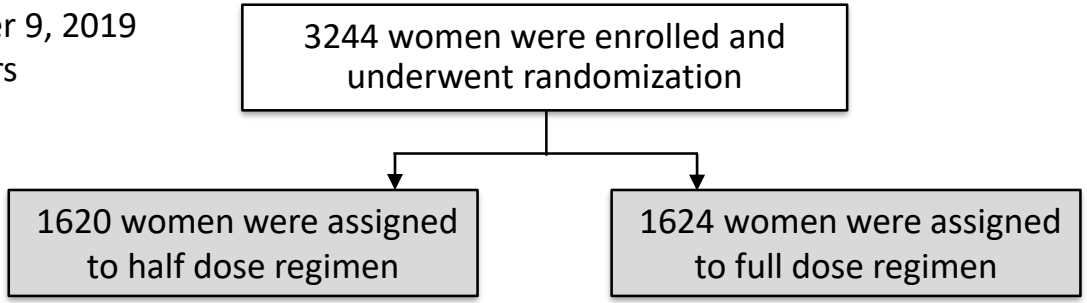

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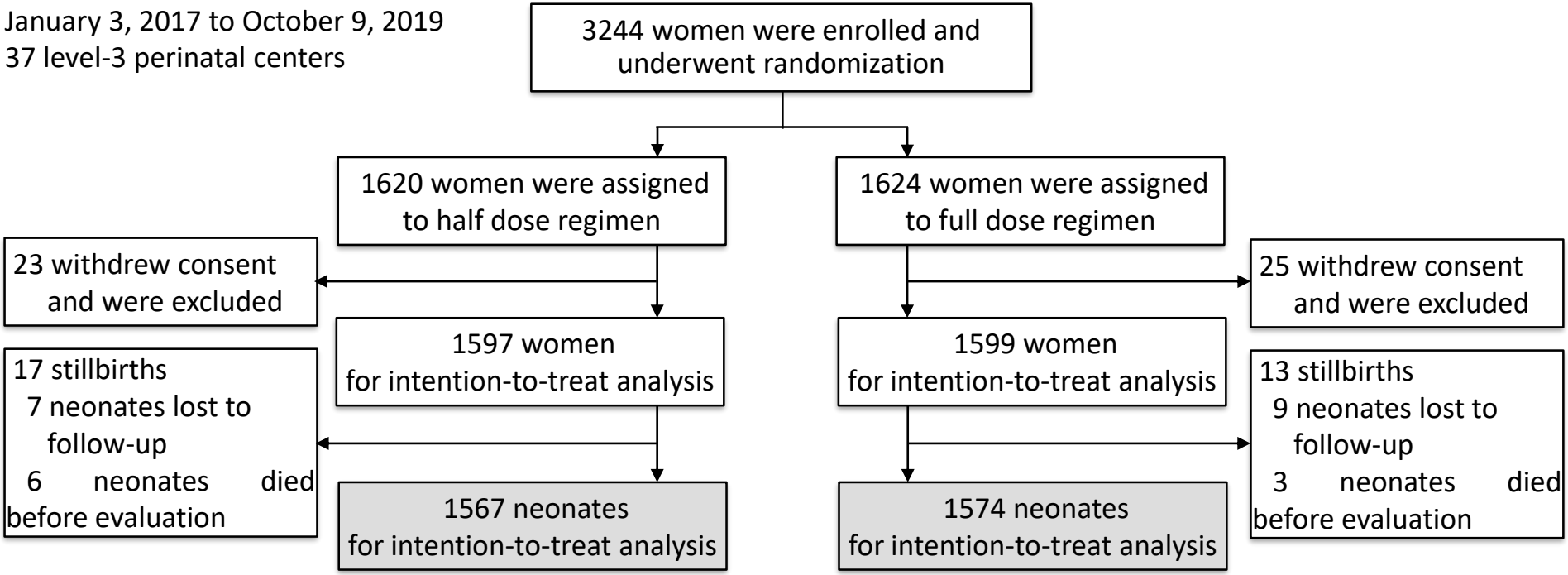

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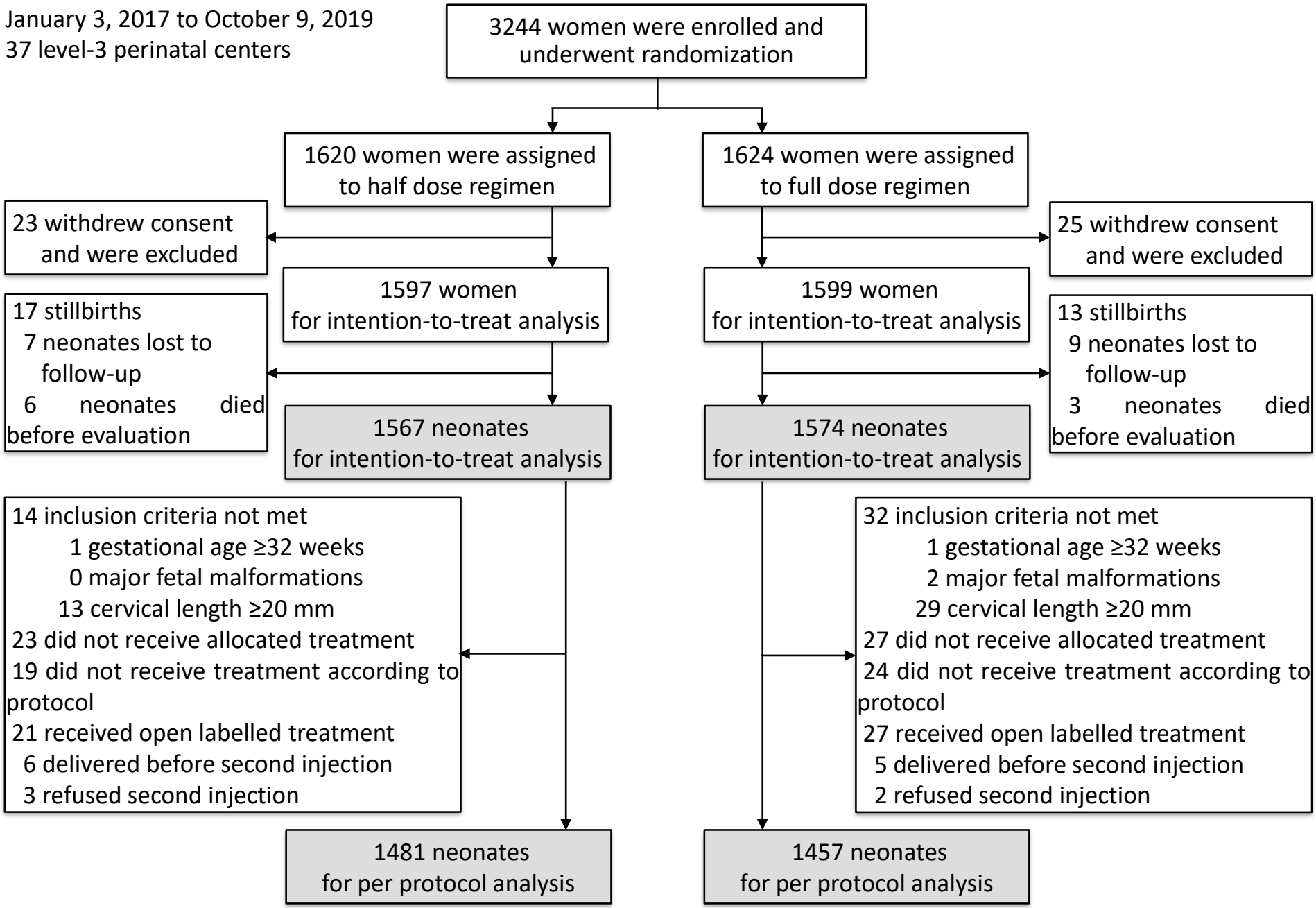

The BETADOSE trial: baseline characteristics

Maternal and pregnancy baseline characteristics	Half dose N=1598	Full dose N=1598
Maternal age (yr, med, Q1-Q3)	30.9 (26.8-35.0)	31.1 (27.0-35.3)
Body mass index ($Kg.m^{-2}$, med, Q1-Q3)	23.0 (20.3-27.3)	22.8 (20.4-27.0)
Previous preterm delivery < 37 wk	276 (17.6%)	272 (17.4%)

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Preterm labor	714 (44.7%)	691 (43.2%)
PPROM	322 (20.2%)	315 (19.7%)
Preeclampsia	173 (10.8%)	203 (12.7%)
IUGR	147 (9.2%)	148 (9.3%)
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Gestational age at trial entry		
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< 28 weeks	153 (9.6%)	139 (8.7%)
28 to <32 weeks	322 (20.3%)	345 (21.7%)
32 to <37 weeks	489 (30.8%)	461 (29.0%)
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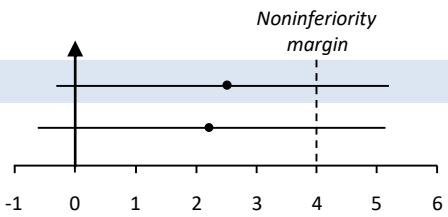
Betamethasone rescue course	44 (2.8%)	46 (2.9%)
Magnesium sulfate for fetal neuroprotection	392 (25.6%)	411 (26.7%)

The BETADOSE trial: primary outcome

A. Principal analysis	Half dose	Full dose	Risk Difference (95% CI)
	no / total no (%)		
Intention to treat population	319/1567 (20.0)	276/1574 (17.5)	2.4 (-0.3 to 5.2)
Per protocol population	301/1481 (20.3)	263/1487 (18.1)	2.2 (-0.6 to 5.1)



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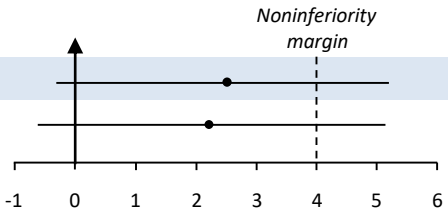
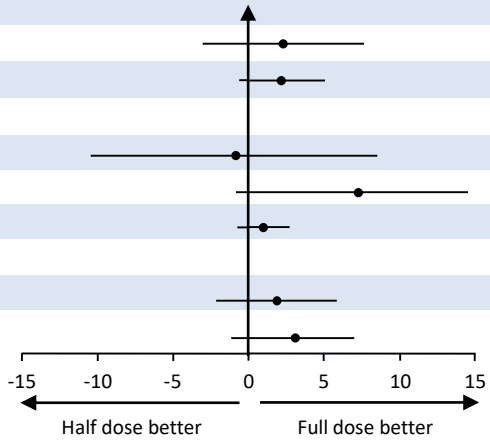


B. Subgroup analyses*	Half dose	Full dose	Risk Difference (95% CI)
	no / total no		
Gestational age at randomization			
<28 wk	212/637	194/626	2.3 (-3.0 to 7.6)
≥28 wk	101/930	82/948	2.2 (-0.6 to 5.0)
Gestational age at birth			
<28 wk	121/145	108/128	-0.9 (-10.4 to 8.5)
28 to <32 wk	144/317	131/341	7.0 (-0.8 to 14.8)
≥32 wk	48/1101	37/1103	1.0 (-0.7 to 2.7)
Sex of the newborn			
Male	180/855	158/822	1.8 (-2.1 to 5.8)
Female	133/710	118/748	3.0 (-1.1 to 7.0)



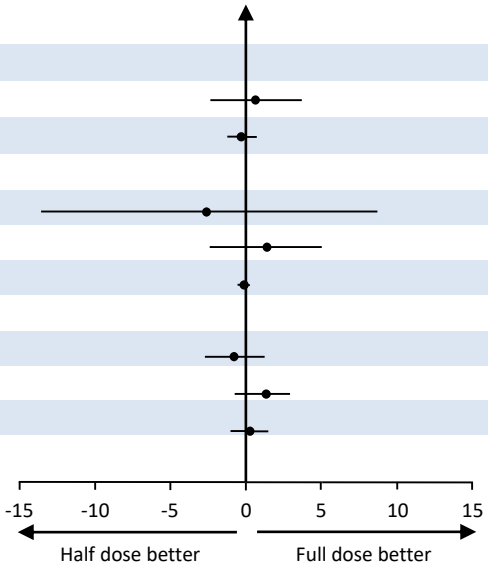
*Prespecified subgroup analysis were performed in the intention to treat population

The BETADOSE trial: secondary safety outcomes

Secondary safety neonatal outcomes	Half dose N=1567	Full dose N=1574	Risk difference (95% CI)
Neonatal death	53 (3.4%)	51 (3.2%)	0.1 (-1.2 to 1.5)
Intraventricular hemorrhage grade 3-4	18 (1.2%)	28 (1.8%)	-0.6 (-1.5 to 0.3)
Necroziting enterocolitis stage ≥2	31 (2.0%)	20 (1.3%)	0.7 (-0.2 to 1.7)
ROP treated by laser or anti-VEGF	6 (0.4%)	6 (0.4%)	0.0 (-0.4 to 0.4)
Neonatal survival without severe RDS, IVH 3-4, NEC ≥2 or ROP treated by laser or anti-VEGF	1231 (78.9%)	1271 (81.1%)	-2.3 (-5.1 to 0.6)

The BETADOSE trial: secondary safety outcomes

Subgroups	Half dose	Full dose	Risk Difference (95% CI)
A. Neonatal death	*no / total no*		
Gestational age at randomization			
<28 wk	47/636	42/626	0.7 (-2.3 to 3.7)
≥28 wk	6/929	9/947	-0.3 (-1.2 to 0.6)
Gestational age at birth			
<28 wk	35/145	34/128	-2.4 (-13.5 to 8.7)
28 to <32 wk	18/316	15/340	1.3 (-2.4 to 5.0)
≥32 wk	0/1101	2/1103	-0.2 (-0.5 to 0.2)
Sex of the newborn			
Male	30/854	35/821	-0.8 (-2.7 to 1.2)
Female	23/709	16/748	1.1 (-0.7 to 2.9)
All participants	**53/1565**	**51/1573**	**0.1 (-1.2 to 1.5)**



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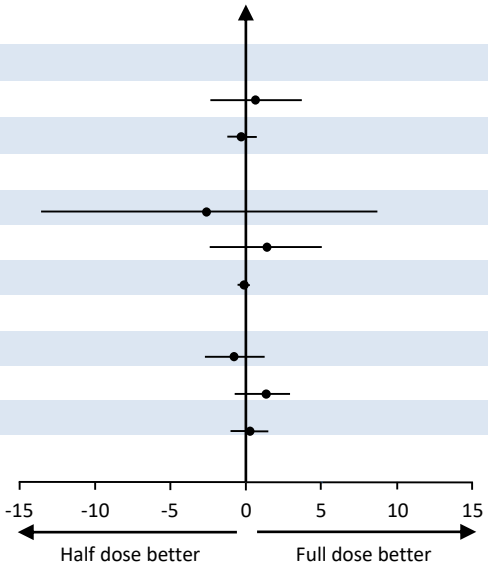
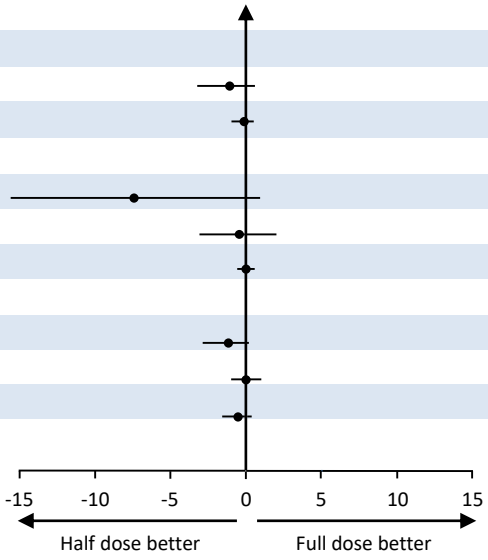
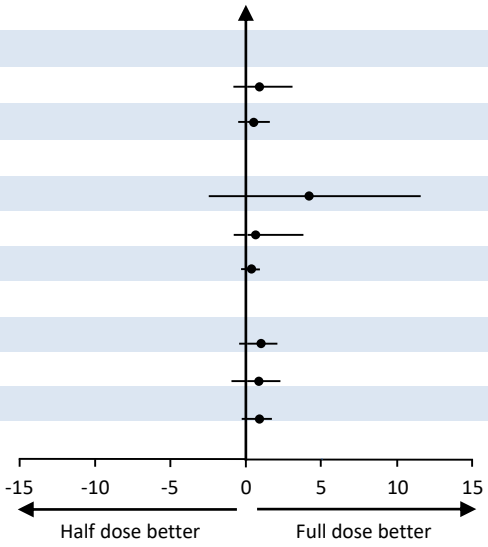


B. Grade 3-4 intraventricular hemorrhage			
Gestational age at randomization			
<28 wk	15/634	23/623	-1.3 (-3.4 to 0.7)
≥28 wk	3/927	5/945	-0.2 (-0.9 to 0.5)
Gestational age at birth			
<28 wk	10/142	18/125	-7.4 (-15.6 to 0.9)
28 to <32 wk	6/317	8/338	-0.5 (-3.0 to 2.0)
≥32 wk	2/1098	2/1103	0.0 (-0.4 to 0.4)
Sex of the newborn			
Male	12/851	22/818	-1.3 (-2.8 to 0.2)
Female	6/708	6/746	0.0 (-0.9 to 1.0)
All participants	**18/1561**	**28/1568**	**-0.6 (-1.5 to 0.3)**



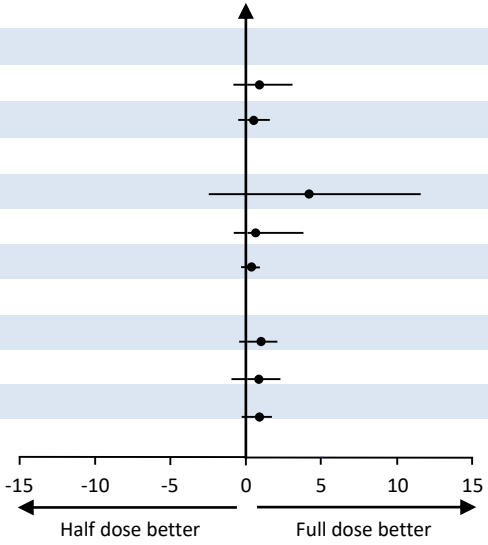
The BETADOSE trial: secondary safety outcomes

Subgroups	Half dose	Full dose	Risk Difference (95% CI)
C. Necrotizing enterocolitis stage ≥2	*no / total no*		
Gestational age at randomization			
<28 wk	20/632	13/623	1.1 (-0.8 to 3.0)
≥28 wk	11/929	7/944	0.4 (-0.5 to 1.4)
Gestational age at birth			
<28 wk	14/140	7/126	4.4 (-2.7 to 11.6)
28 to <32 wk	12/317	11/338	0.5 (-2.6 to 3.7)
≥32 wk	5/1100	2/1101	0.3 (-0.3 to 0.8)
Sex of the newborn			
Male	15/850	8/817	0.8 (-0.4 to 2.0)
Female	16/709	12/746	0.6 (-0.9 to 2.2)
All participants	**31/1561**	**20/1567**	**0.7 (-0.2 to 1.7)**

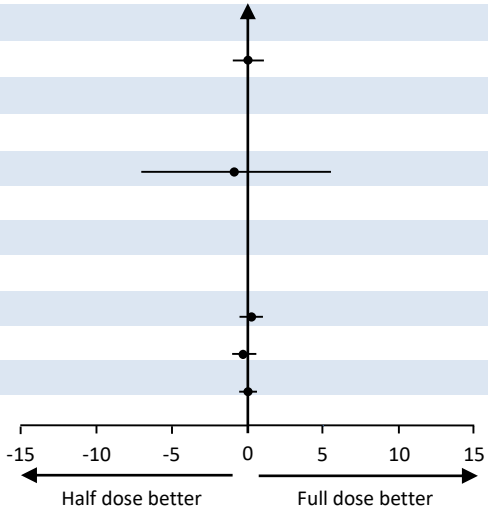


The BETADOSE trial: secondary safety outcomes

Subgroups	Half dose	Full dose	Risk Difference (95% CI)
C. Necrotizing enterocolitis stage ≥2	*no / total no*		
Gestational age at randomization			
<28 wk	20/632	13/623	1.1 (-0.8 to 3.0)
≥28 wk	11/929	7/944	0.4 (-0.5 to 1.4)
Gestational age at birth			
<28 wk	14/140	7/126	4.4 (-2.7 to 11.6)
28 to <32 wk	12/317	11/338	0.5 (-2.6 to 3.7)
≥32 wk	5/1100	2/1101	0.3 (-0.3 to 0.8)
Sex of the newborn			
Male	15/850	8/817	0.8 (-0.4 to 2.0)
Female	16/709	12/746	0.6 (-0.9 to 2.2)
All participants	**31/1561**	**20/1567**	**0.7 (-0.2 to 1.7)**



Subgroups	Half dose	Full dose	Risk Difference (95% CI)
D. Retinopathy of prematurity treated by anti-VEGF or laser	*no / total no*		
Gestational age at randomization			
<28 wk	6/621	6/604	0.0 (-1.2 to 1.1)
≥28 wk	0/930	0/948	-
Gestational age at birth			
<28 wk	6/134	6/115	-0.7 (-6.8 to 5.4)
28 to <32 wk	0/317	0/341	-
≥32 wk	0/1101	0/1103	-
Sex of the newborn			
Male	4/841	2/800	0.2 (-0.5 to 0.9)
Female	2/700	4/741	-0.3 (-1.1 to 0.5)
All participants	**6/1543**	**6/1545**	**0.0 (-0.4 to 0.4)**



The BETADOSE trial: other secondary outcomes

Other secondary outcomes	Half dose N=1567	Full dose N=1574	Risk difference (95% CI)
Respiratory outcomes			
RDS	699 (44.6%)	686 (43.7%)	1.0 (-2.6 to 4.5)
Transient tachypnea of the newborn	147 (9.5%)	156 (10.0%)	-0.5 (-2.6 to 1.7)
Mechanical ventilation in the first 48h	197 (13.1%)	166 (11.1%)	2.1 (-0.3 to 4.5)
CPAP in the first 48h	409 (27.2%)	411 (27.3%)	-0.2 (-3.4 to 3.1)
Bronchopulmonary dysplasia	66 (4.4%)	73 (4.9%)	-0.4 (-2.0 to 1.1)

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Other secondary prematurity-associated outcomes			
Admission to NICU	727 (46.4%)	718 (45.6%)	0.8 (-2.8 to 4.3)
Inotrope support	118 (7.5%)	99 (6.3%)	1.2 (-0.6 to 3.1)
Patent ductus arteriosus	181 (11.6%)	162 (10.3%)	1.3 (-0.9 to 3.5)
Cystic periventricular leukomalacia	20 (1.3%)	26 (1.7%)	-0.4 (-1.3 to 0.5)
Early onset sepsis	96 (6.1%)	93 (5.9%)	0.2 (-1.5 to 1.9)
Severe hypoglycemia	100 (6.4%)	97 (6.2%)	0.2 (-1.5 to 2.0)

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Secondary anthropometric outcomes at birth			Mean difference (95% CI)
Weight (g, mean ± SD)	2239 ± 941	2221 ± 926	18 (-47 to 84)
Length (cm, mean ± SD)	43.6 ± 5.9	43.3 ± 5.9	0.3 (-0.1 to 0.8)
Head circumference (cm, mean ± SD)	30.6 ± 4.0	30.4 ± 4.0	0.2 (-0.1 to 0.5)

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Secondary anthropometric outcomes at birth			Mean difference (95% CI)
Weight (z score, mean ± SD)	-0.37 ± 0.92	-0.43 ± 0.92	0.06 (-0.01 to 0.12)
Length (z score, mean ± SD)	-0.41 ± 1.05	-0.48 ± 1.07	0.07 (-0.01 to 0.15)
Head circumference (z score, mean ± SD)	-0.14 ± 1.14	-0.26 ± 1.18	0.12 (0.03 to 0.20)

The BETADOSE trial: other posthoc analyses

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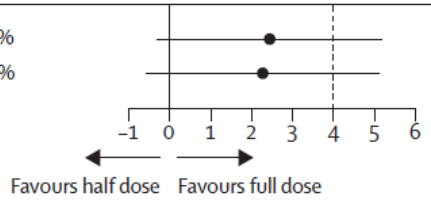
A Principal analysis

	Half dose		Full dose		Risk difference (95% CI)
	n/N	%	n/N	%	
Intention-to-treat population	313/1567	20·0%	276/1574	17·5%	2·4% (–0·3 to 5·2)
Per-protocol population	301/1481	20·3%	263/1457	18·1%	2·2% (–0·6 to 5·1)



B Subgroup analyses*

	Half dose		Full dose		Risk difference (95% CI)
	n/N	%	n/N	%	
Prespecified subgroup analyses					
Gestational age at randomisation					
<28 weeks	212/637	33·3%	194/626	31·0%	2·3% (–3·0 to 7·6)
≥28 weeks	101/930	10·9%	82/948	8·6%	2·2% (–0·6 to 5·0)
Gestational age at birth					
<28 weeks	121/145	83·4%	108/128	84·4%	–0·9% (–10·4 to 8·5)
28 weeks to <32 weeks	144/317	45·4%	131/341	38·4%	7·0% (–0·8 to 14·8)
≥32 weeks	48/1101	4·4%	37/1103	3·4%	1·0% (–0·7 to 2·7)
Sex of the neonate					
Male	180/855	21·1%	158/822	19·2%	1·8% (–2·1 to 5·8)
Female	133/710	18·7%	118/748	15·8%	3·0% (–1·1 to 7·0)
Post-hoc subgroup analysis					
Time interval between first injection and birth					
≤7 days	139/256	54·3%	122/282	43·3%	11·0% (2·3 to 19·8)
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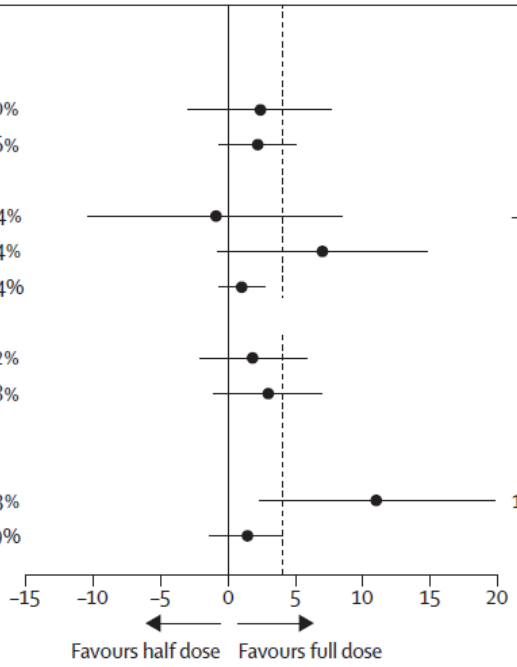

Figure 2: **Principal, prespecified, and post-hoc subgroup analyses for the primary outcome**
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The BETADOSE trial: other posthoc analyses

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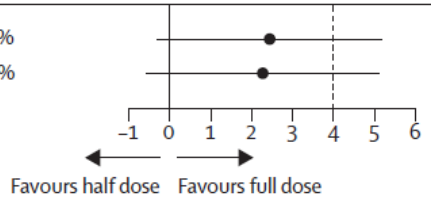

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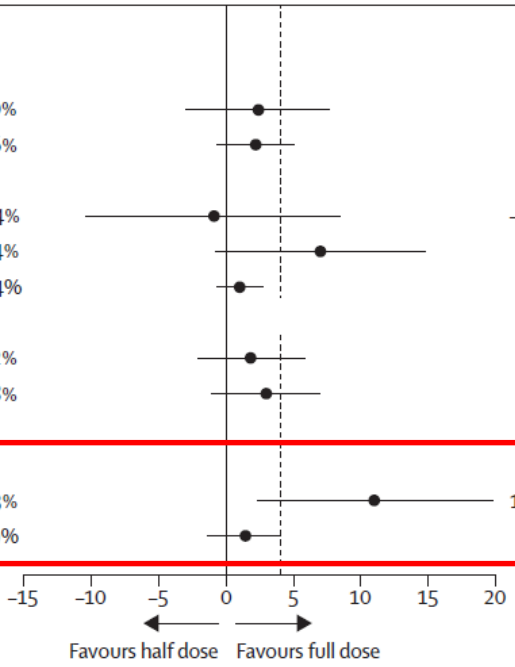

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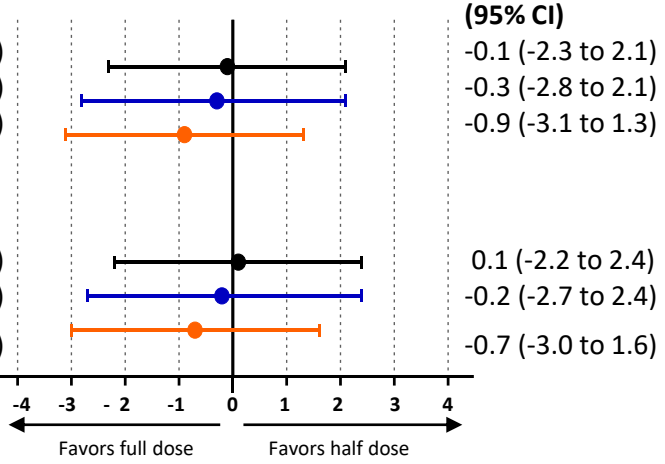
A. Principal analysis	Composite outcome*	Half dose n/N (%)	Full dose n/N (%)	Risk difference (95% CI)
Intention to treat population	A	1376/1533 (89.8)	1387/1543 (89.9)	-0.1 (-2.3 to 2.1)
	B	1329/1536 (86.5)	1343/1546 (86.9)	-0.3 (-2.8 to 2.1)
	C	1396/1563 (89.3)	1416/1570 (90.2)	-0.9 (-3.1 to 1.3)
Per protocol population	A	1289/1448 (89.6)	1278/1428 (89.5)	0.1 (-2.2 to 2.4)
	B	1252/1451 (86.3)	1237/1431 (86.4)	-0.2 (-2.7 to 2.4)
	C	1317/1477 (89.2)	1307/1454 (89.9)	-0.7 (-3.0 to 1.6)



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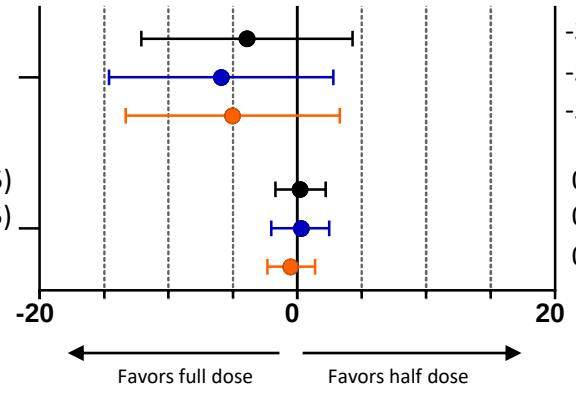
Birth after first injection		Half dose	Full dose	
≤ 7 days	A	171/247 (69.2)	199/272 (73.2)	-3.9 (-12.1 to 4.3)
	B	148/249 (59.4)	179/274 (65.3)	-5.9 (-14.6 to 2.8)
	C	168/256 (65.6)	197/279 (70.6)	-5.0 (-13.3 to 3.3)
> 7 days	A	1205/1286 (93.7)	1188/1271 (93.5)	0.2 (-1.7 to 2.2)
	B	1181/1287 (91.8)	1164/1272 (91.5)	0.3 (-2.0 to 2.5)
	C	891/927 (96.1)	909/946 (96.1)	0.0 (-1.8 to 1.8)



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- Neonatal morbidity did not differ between groups at hospital discharge
- Results of the 5-year follow-up study are needed to correctly address the benefits/risks ratio before deciding whether reducing ACS dose is possible