

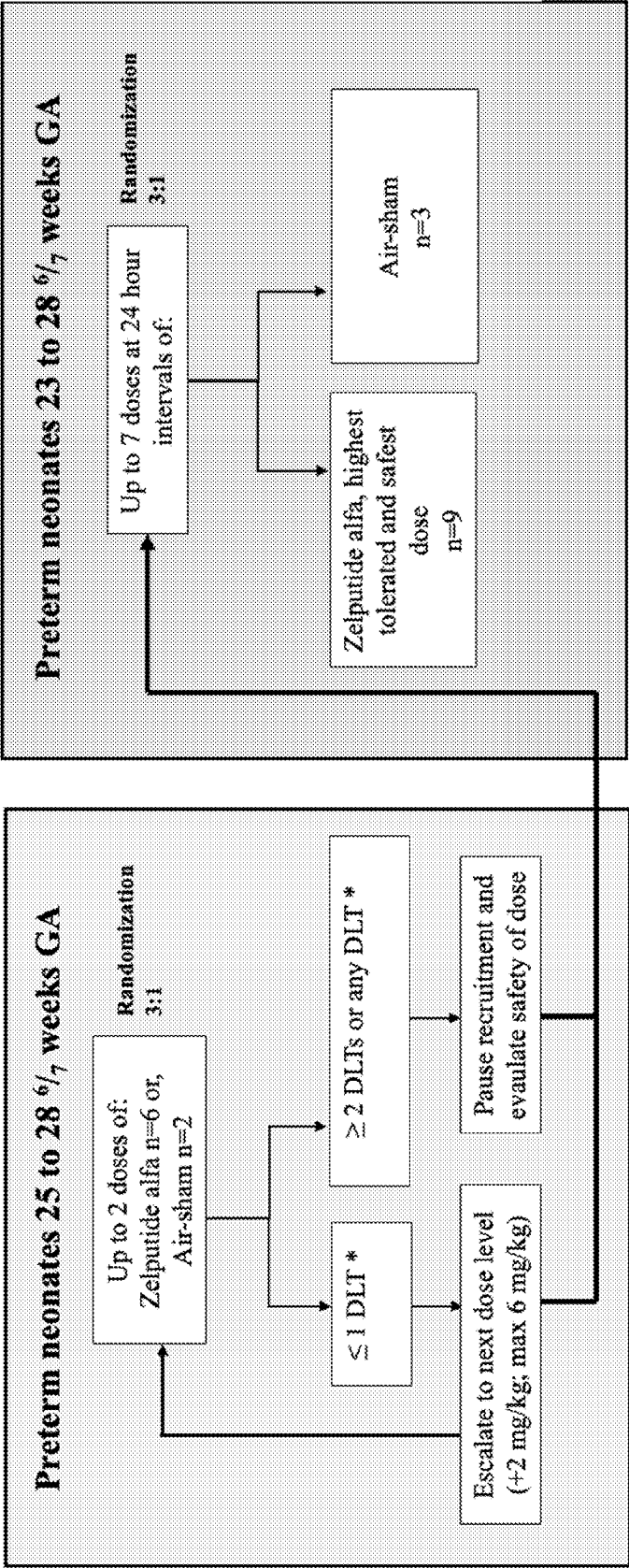


FIG. 1A

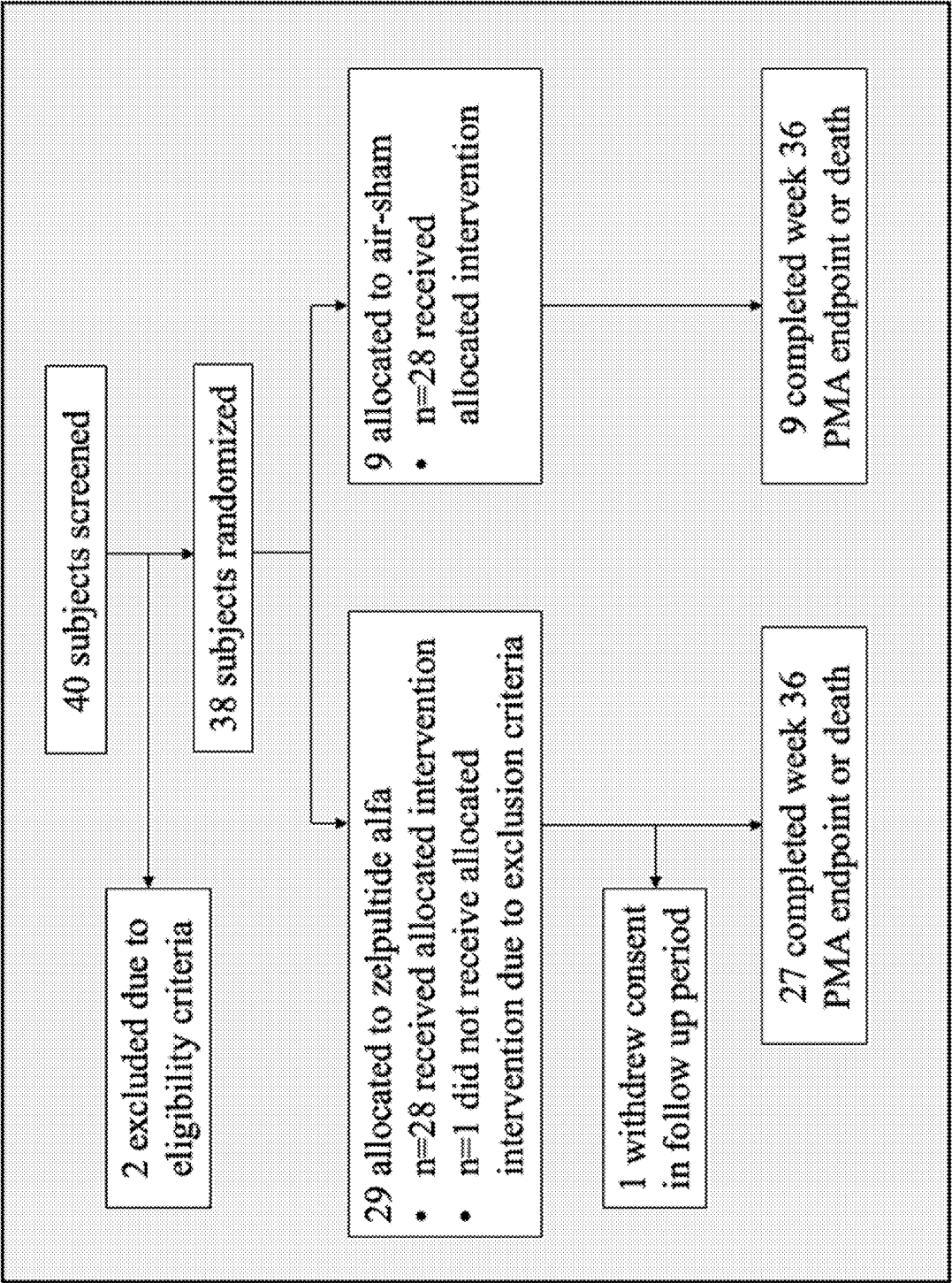


FIG. 1B

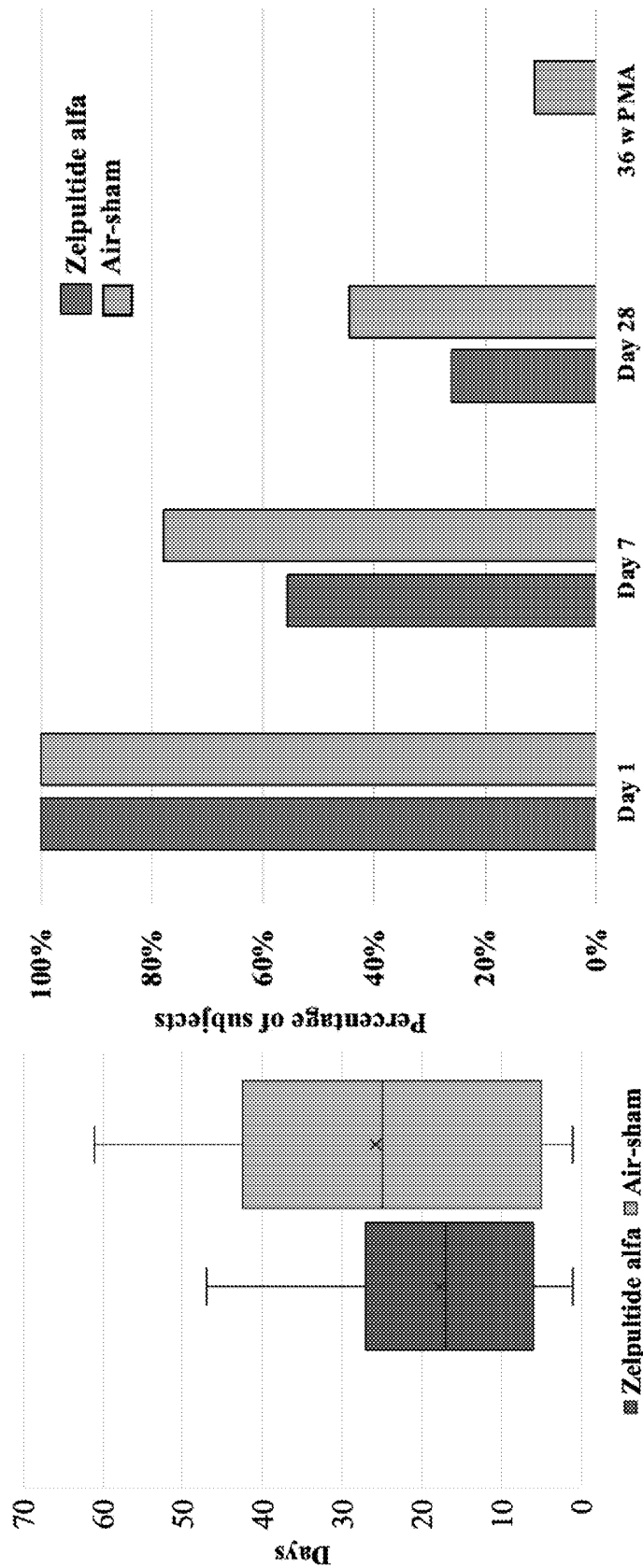


FIG. 2B

FIG. 2A

Table I. Baseline demographics and characteristics

	First phase of trial				Second phase of trial	Total
	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=9)	All zelpultide alfa (n=28)	Air-sham (n=9)
GA, weeks						
Mean (SD)	26.1 (0.43)	26.4 (0.92)	27.4 (1.3)	25.6 (1.83)	26.3 (1.41)	25.8 (1.6)
Median	26.0	26.0	27.8	25.9	26.1	25.6
Min, max	26, 27	26, 28	26, 29	23, 29	23, 29	24, 28
Birth weight, kg, mean (SD)	0.8 (0.18)	0.8 (0.23)	1.0 (0.27)	0.7 (0.27)	0.8 (0.25)	0.7 (0.25)
Sex, male, n (%)	4 (57.1)	4 (66.7)	4 (66.7)	7 (77.8)	19 (67.9)	6 (66.7)
Race, n (%)						
Caucasian	5 (71.4)	5 (83.3)	4 (66.7)	6 (66.7)	20 (71.4)	5 (55.6)
Black or African American	1 (14.3)	0	2 (33.3)	2 (22.2)	5 (17.9)	1 (11.1)
Asian	0	0	0	0	1 (3.6)	0
Other	1 (14.3)	1 (16.7)	0	0	2 (7.1)	2 (22.2)
Ethnicity, n (%)						
Hispanic/ Latino	2 (28.6)	1 (16.7)	0 (0)	3 (33.3)	6 (21.4)	6 (66.7)
Non-Hispanic/ Latino	4 (57.1)	5 (83.3)	6 (100.0)	6 (66.7)	21 (75.0)	3 (33.3)
Not reported	1 (14.3)	0	0	0	1 (3.6)	0
Baseline length/ height, cm, mean (SD)	32.9 (1.89)	33.1 (4.92)	34.6 (3.36)	31.9 (3.98)	32.9 (3.61)	31.3 (2.57)
Head circumference, cm mean (SD)	23.1 (1.86)	24.0 (2.92)	23.9 (2.13)	23.6 (2.84)	23.6 (2.39)	22.6 (1.52)
Congenital abnormalities,* n (%)	3 (42.9)	0	4 (66.7)	2 (22.2)	9 (32.1)	1 (11.1)
PDA, n (%)	3 (42.9)	0	2 (33.3)	0	5 (17.9)	1 (11.1)
Maternal use of antenatal steroids, n (%)	2 (28.6)	4 (66.7)	2 (33.3)	4 (44.4)	12 (42.9)	3 (33.3)

*Congenital disorders measured: hypospadias, adrenal insufficiency neonatal, adrenogenital syndrome, ankyloglossia congenital, atrial septal defect, congenital cytomegalovirus infection, exomphalos, homocystinuria, microcephaly, sickle cell trait, talipes.

FIG. 3

Table II. Summary of AEs and SAEs. The number of patients experiencing AEs and SAEs in each treatment arm from first treatment to week 36 PMA are presented with percentages in brackets

n (%)	First phase of trial			Second phase of trial	Total	
	Zelpulvide alfa, 2 mg/kg (n=7)	Zelpulvide alfa, 4 mg/kg (n=6)	Zelpulvide alfa, 6 mg/kg (n=6)	Zelpulvide alfa, 6 mg/kg (n=9)	All zelpulvide alfa (n=28)	Air-sham (n=9)
At least one AE	7 (100.0)	4 (66.7)	6 (100.0)	9 (100.0)	26 (92.9)	9 (100.0)
At least one SAE	4 (57.1)	2 (33.3)	1 (16.7)	6 (66.7)	13 (46.4)	4 (44.4)
At least one AE leading to discontinuation of study drug	1 (14.3)	0	1 (16.7)	2 (22.2)	4 (14.3)	0

FIG. 4

Table III.A. AEs reported in more than 10% of subjects in any treatment arm from first treatment to week 36 PMA. The number of patients experiencing AEs in each treatment arm are presented with percentages in brackets.

n (%)	First phase of trial			Second phase of trial		Total
	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=9)	All zelpultide alfa (n=28)	
Pulmonary edema	1 (14.3) * [0]	0	3 (50.0) * [0]	3 (33.3) * [0]	7 (25.0) * [0]	0
Pulmonary hemorrhage	1 (14.3)	1 (16.7)	0	1 (11.1)	3 (10.7)	1 (11.1)
Pulmonary interstitial emphysema syndrome	1 (14.3)	0	0	2 (22.2)	3 (10.7)	1 (11.1)
BPD	0	1 (16.7)	0	0	2 (7.1)	1 (11.1)
Respiratory failure	1 (14.3)	0	1 (16.7)	0	2 (7.1)	1 (11.1)
Pulmonary hypertension	0	0	1 (16.7)	0	1 (3.6)	1 (11.1)
Respiratory acidosis	0	0	0	1 (11.1)	1 (3.6)	1 (11.1)
Anemia	3 (42.9)	2 (33.3)	2 (33.3)	3 (33.3)	10 (35.7)	3 (33.3)
Anemia neonatal	1 (14.3)	0	0	1 (11.1)	2 (7.1)	3 (33.3)
Thrombocytopenia	1 (14.3)	0	0	1 (11.1)	2 (7.1)	1 (11.1)
Hyperglycemia	1 (14.3)	0	2 (33.3)	4 (44.4)	7 (25.0)	1 (11.1)
Electrolyte imbalance	1 (14.3)	0	2 (33.3)	2 (22.2)	5 (17.9)	0
Hypomagnesemia	0	1 (16.7)	0	2 (22.2)	3 (10.7)	0
Metabolic acidosis	1 (14.3)	0	0	2 (22.2)	3 (10.7)	0
Hypernatremia	0	1 (16.7)	0	0	1 (3.6)	1 (11.1)
Hyperchloremia	0	0	0	0	0	1 (11.1)
Sepsis	0	0	0	2 (22.2)	2 (7.1)	1 (11.1)
Conjunctivitis	1 (14.3)	0	0	0	1 (3.6)	1 (11.1)
Staphylococcal sepsis	0	1 (16.7)	0	0	1 (3.6)	1 (11.1)
Urinary tract infection	1 (14.3)	0	0	0	1 (3.6)	1 (11.1)
Bronchiolitis	0	0	0	0	0	1 (11.1)
Device related sepsis	0	0	0	0	0	1 (11.1)

*Further investigation of these events concluded that pulmonary edemas should not have been recorded as AEs as all events happened at the same site in which furosemide was given as standard of care. This should have been reported as concomitant medication instead of as AE. Therefore, the incidence of pulmonary edema has been corrected to [0] in all cases where pulmonary edema was reported.

FIG. 5A

Table III.B. Continued from Table III.A. AEs reported in more than 10% of subjects in any treatment arm from first treatment to week 36 PMA. The number of patients experiencing AEs in each treatment arm are presented with percentages in brackets.

	First phase of trial			Second phase of trial		Total
n (%)	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=9)	All zelpultide alfa (n=28)	Air-sham (n=9)
Eye infection	0	0	0	0	0	1 (11.1)
Meningitis staphylococcal	0	0	0	0	0	1 (11.1)
Nosocomial infection	0	0	0	0	0	1 (11.1)
Pneumonia bacterial	0	0	0	0	0	1 (11.1)
Pneumonia staphylococcal	0	0	0	0	0	1 (11.1)
Septic shock	0	0	0	0	0	1 (11.1)
Gastrointestinal disorders	4 (57.1)	2 (33.3)	0	5 (55.6)	11 (39.3)	4 (44.4)
Inguinal hernia	1 (14.3)	1 (16.7)	0	1 (11.1)	3 (10.7)	1 (11.1)
Intestinal perforation	1 (14.3)	0	0	2 (22.2)	3 (10.7)	1 (11.1)
Abdominal distension	1 (14.3)	0	0	2 (22.2)	3 (10.7)	0
Neonatal intestinal perforation	1 (14.3)	0	0	1 (11.1)	2 (7.1)	1 (11.1)
NEC	1 (14.3)	0	0	0	1 (3.6)	1 (11.1)
PDA	3 (42.9)	2 (33.3)	2 (33.3)	3 (33.3)	10 (35.7)	3 (33.3)
ROP	3 (42.9)	0	2 (33.3)	2 (22.2)	7 (25.0)	3 (33.3)
Hyperbilirubinemia	2 (28.6)	1 (16.7)	3 (50.0)	2 (22.2)	8 (28.6)	1 (11.1)
IVH	2 (28.6)	2 (33.3)	0	2 (22.2)	6 (21.4)	1 (11.1)
Hypotension	1 (14.3)	1 (16.7)	1 (16.7)	3 (33.3)	6 (21.4)	2 (22.2)
Decreased oxygen saturation	1 (14.3)	1 (16.7)	0	1 (11.1)	3 (10.7)	0
Renal failure	1 (14.3)	0	1 (16.7)	3 (33.3)	5 (17.9)	0
Acute kidney injury	0	0	0	0	0	1 (11.1)
Bradycardia	1 (14.3)	1 (16.7)	0	1 (11.1)	3 (10.7)	0
Adrenal insufficiency	0	0	2 (33.3)	3 (33.3)	5 (17.9)	0

*Further investigation of these events concluded that pulmonary edemas should not have been recorded as AEs as all events happened at the same site in which furosemide was given as standard of care. This should have been reported as concomitant medication instead of as AE. Therefore, the incidence of pulmonary edema has been corrected to [0] in all cases where pulmonary edema was reported.

FIG. 5B

Table IV. SAEs reported from first treatment to week 36 PMA in any treatment arm from first treatment to week 36 PMA. The number of patients experiencing SAEs in each treatment arm are presented with percentages in brackets.

n (%)	First phase of trial			Second phase of trial	Total	
	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)		All zelpultide alfa (n=28)	Air-sham (n=9)
Intestinal perforation	1 (14.3)	0	0	2 (22.2) *	3 (10.7)	0
Neonatal intestinal perforation	1 (14.3)	0	0	1 (11.1)	2 (7.1)	1 (11.1)
Pulmonary hemorrhage	1 (14.3)	0	0	1 (11.1)	2 (7.1)	0
IVH	0	0	0	2 (22.2) *	2 (7.1)	0
NEC	0	0	0	0	0	1 (11.1)
Small intestinal obstruction	1 (14.3)	0	0	0	1 (3.6)	0
Bronchiolitis	0	0	0	0	0	1 (11.1)
Enterobacter sepsis	0	0	0	1 (11.1) *	1 (3.6)	0
Meningitis staphylococcal	0	0	0	0	0	1 (11.1)
Pneumonia bacterial	0	0	0	0	0	1 (11.1)
Pneumonia staphylococcal	0	0	0	0	0	1 (11.1)
Sepsis	0	0	0	1 (11.1) *	1 (3.6)	0
Septic shock	0	0	0	0	0	1 (11.1)
Pulmonary arterial hypertension	0	1 (16.7)	0	0	1 (3.6)	0
Respiratory failure	0	0	1 (16.7) *	0	1 (3.6)	0
Status epilepticus	0	1 (16.7)	0	0	1 (3.6)	0
Ventricular tachycardia	0	0	0	1 (11.1)	1 (3.6)	0
PDA	1 (14.3) *	0	0	0	1 (3.6)	0
Hyperkalemia	0	0	0	1 (11.1)	1 (3.6)	0
Lactic acidosis	0	0	0	1 (11.1)	1 (3.6)	0

*Indicates SAEs that led to death; none of the six cases were related to the study drug.

FIG. 6

Table V. Key efficacy outcomes included the incidence of BPD or death at week 36 PMA in all zelpultide alfa and air-sham treatment groups. The definition and classification of BPD was based on Jensen et al. 2019.

n (%)	All zelpultide alfa	Air-sham
Subjects	28	9
BPD or death	15 (54%)	6 (67%)
Incidence of BPD	9 (32%)	6 (67%)
BPD grade 1	4 (14.3%)	1 (11.1%)
BPD grade 2	5 (17.9%)	4 (44.4%)
BPD grade 3	0 (0%)	1 (11%)
Death	6 (21.4%)	0 (0.0%)
BPD grade 2 or 3, or death	11 (39%)	5 (56%)

FIG. 7

Table VI. Additional outcomes and comorbidities that occurred in any treatment arm from first treatment to week 36 PMA. The number of patients experiencing outcomes and comorbidities in each treatment arm are presented with percentages in bracket, except days in hospital that are presented as mean (SD). For the mean number of days in hospital, there was a recalculation for number of days in hospital excluding subjects that died. Data from the 6 subjects that died by week 36 PMA was excluded from the analysis and resulted in 87.2 days (± 24.1 , $n=21$) for the all zelpulvide alfa group and 90.2 days (± 21.1 , $n=9$) for the air-sham group.

	First phase of trial			Second phase of trial	Total	
n (%)	Zelpulvide alfa, 2 mg/kg (n=7)	Zelpulvide alfa, 4 mg/kg (n=6)	Zelpulvide alfa, 6 mg/kg (n=6)	Zelpulvide alfa, 6 mg/kg (n=9)	All zelpulvide alfa (n=28)	Air-sham (n=9)
Steroid use	2 (28.6)	2 (33.3)	0	1 (11.1)	5 (17.9)	3 (33.3)
Days in hospital, mean (SD)	76.3 (36.3)	87.8 (8.9)	81.5 (45.7)	51.6 (39.1)	72.7 (36.7)	90.2 (21.1)
Pneumonia*	0	0	0	0	0	1 (11.1)
Blood infection†	1 (14.3)	3 (50.0)	0	0	4 (14.3)	2 (22.2)
Viral infection‡	0	1 (16.7)	0	0	1 (3.6)	0
ROP	3 (42.9)	3 (50.0)	2 (33.3)	3 (33.3)	11 (39.3)	4 (44.4)
PDA	3 (42.9)	2 (33.3)	2 (33.3)	3 (33.3)	10 (35.7)	3 (33.3)
Pulmonary hypertension	0	1 (16.7)	1 (16.7)	0	2 (7.1)	1 (11.1)
NEC	0	0	0	1 (11.1)	1 (3.6)	1 (11.1)
Grade 2 IVH	0	0	1 (16.7)	0 (0.0)	1 (3.6)	1 (11.1)

*Confirmed by X-ray. †Confirmed by a positive blood culture. ‡Confirmed by culture or polymerase chain reaction test.

FIG. 8

Table VII. Pharmacokinetics of zelpultide alfa (ng/mL) and air-sham showing change in SP-D blood levels from baseline at day 1 for each treatment arm.

n (%)	First phase of trial			Second phase of trial	Total
	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=9)	Air-sham
n	1	3	3	0	4
Mean (SD)	-2.87 (-)	150.14 (182.549)	312.74 (249.638)	-	13.96 (20.440)
Median	-2.87	78.63	380.70	-	10.03
Range (minimum, maximum)	-2.9, -2.9	14.2, 357.6	36.2, 521.4	-	-6.5, 42.2

FIG. 9

Table VIII.A. Part 1 of doses of treatment received by preterm neonates in the first phase of the Phase 1b trial.

	Zelpultide alfa, 2 mg/kg	Zelpultide alfa, 4 mg/kg	Zelpultide alfa, 6 mg/kg	All zelpultide alfa	Air-sham
Subjects	7	6	6	19	6
1 doses n (%)	2 (28.6)	2 (33.3)	1 (16.7)	5 (26.3)	1 (16.7)
2 doses, n (%)	5 (71.4)	4 (66.7)	5 (83.3)	14 (73.7)	5 (83.3)

FIG. 10A

Table VIII.B. Part 2 of doses of treatment received by preterm neonates in the second phase of the Phase 1b trial.

	Zelpultide alfa 6 mg/kg	Air-sham
Subjects	9	3
1 doses n (%)	1 (11.1)	-
2 doses, n (%)	-	1 (33.3)
3 doses, n (%)	1 (11.1)	-
4 doses, n (%)	1 (11.1)	-
5 doses, n (%)	4 (44.4)	-
6 doses, n (%)	-	-
7 doses, n (%)	2 (22.2)	2 (22.2)

FIG. 10B

Table IX. Incidence of BPD or death and days on mechanical ventilation for each treatment arm and the all zelpulotide alfa group from first treatment to week 36 PMA. The number of patients experiencing BPD or death in each treatment arm are presented with percentages in brackets.

	Zelpulotide alfa, 2 mg/kg (n=7)	Zelpulotide alfa, 4 mg/kg (n=6)	Zelpulotide alfa, 6 mg/kg (n=6)	Zelpulotide alfa, 6 mg/kg (n=9)	All zelpulotide alfa (n=28)	Air-sham (n=9)
BPD or death at 36 weeks PMA						
Yes	4 (57.1)*	3 (50.0)	2 (33.3)	6 (66.7)	15 (53.6)*	6 (66.7)
No	2 (28.6)*	3 (50.0)	4 (66.7)	3 (33.3)	12 (42.9)*	3 (33.3)
BPD at 36 weeks PMA						
Yes	3 (42.9)	3 (50.0)	1 (16.7)	2 (22.2)	9 (32.1)	6 (66.7)
No	2 (28.6)	3 (50.0)	4 (66.7)	3 (33.3)	12 (42.9)	3 (33.3)
Death at 36 weeks PMA						
Yes	1 (14.3)	0	1 (16.7)	4 (44.4)	6 (21.4)	0
No	6 (85.7)	6 (100.0)	5 (83.3)	5 (55.6)	22 (78.6)	9 (100.0)

*One subject was lost to follow up therefore percentages may not match the total n(%) in the column header.

FIG. 11

Table X. Grades of BPD or death for each treatment arm and all zelpultide alfa group from the first treatment to week 36 PMA. The number of patients with each grade of BPD or death in each treatment arm is presented with percentages in brackets.

n (%)	First phase of trial			Second phase of trial	Total	
	Zelpultide alfa 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)		All zelpultide alfa (n=28)	Air-sham (n=9)
Grade 0 BPD						
Yes	2 (28.6)*	3 (50.0)	4 (66.7)	3 (33.3)	12 (42.9)*	3 (33.3)
No	3 (42.9)	3 (50.0)	1 (16.7)	2 (22.2)	9 (32.1)	6 (66.7)
Grade 1 BPD						
Yes	1 (14.3)*	1 (16.7)	1 (16.7)	1 (11.1)	4 (14.3)*	1 (11.1)
No	4 (57.1)	5 (83.3)	4 (66.7)	4 (44.4)	17 (60.7)	8 (88.9)
Grade 2 BPD						
Yes	2 (28.6)*	2 (33.3)	0	1 (11.1)	5 (17.9)*	4 (44.4)
No	3 (42.9)	4 (66.7)	5 (83.3)	4 (44.4)	16 (57.1)	5 (55.6)
Grade 3 BPD						
Yes	0*	0	0	0	0*	1 (11.1)
No	5 (71.4)	6 (100.0)	5 (83.3)	5 (55.6)	21 (75.0)	8 (88.9)
Death						
Yes	1 (14.3)	0	1 (16.7)	4 (44.4)	6 (21.4)	0
No	6 (85.7)	6 (100.0)	5 (83.3)	5 (55.6)	22 (78.6)	9 (100.0)

*One subject was lost to follow up therefore percentages may not match the total n(%) in the column header.

FIG. 12

Table XI (FIG. 13). Mean days on mechanical ventilation for each treatment arm and the all zelpultide alfa group from first treatment to week 36 PMA. Data are shown for subjects who survived to week 36 PMA and were not lost to follow up.

n (%)	First phase of trial			Second phase of trial	Total	
	Zelpultide alfa, 2 mg/kg (n=7)	Zelpultide alfa, 4 mg/kg (n=6)	Zelpultide alfa, 6 mg/kg (n=6)			
Subjects	5	6	5	5	21	9
Mean (SD)	22.2 (17.46)	18.0 (15.54)	13.2 (18.99)	17.4 (6.50)	17.7 (14.56)	25.8 (21.61)
Median	25.0	12.5	6.0	19.0	17.0	25.0
Range (minimum, maximum)	1, 46	2, 39	2, 47	6, 22	1, 47	1, 61

FIG. 13