Supplemental Information

This material has been provided by the authors to give readers additional information about their work.

AERO-02 RESEARCH COLLABORATORS, LISTED BY SITE

The following is ordered by the total patients enrolled at each site, from high to low; all sites are in the United States.

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University of South Alabama Children's and Women's Hospital, Mobile AL: Fabien Eyal, MD.

Timpanogos Regional Hospital, Orem, UT: Dale Gerstmann, MD.

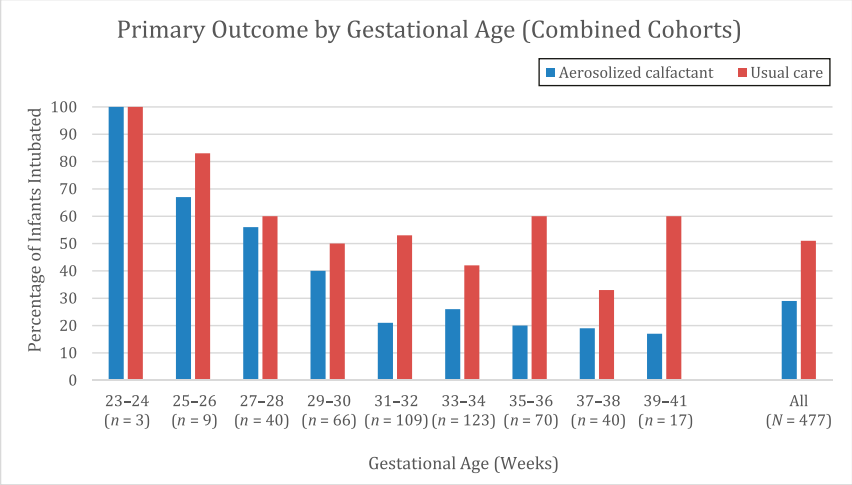
Piedmont Columbus Regional, Columbus, GA: David Levine, MD; Peter Resnick, MD; Jerry Chen, MD.

OSF Children's Hospital of Illinois, Peoria, IL: Praveen Kumar, MD; Nancy G. Shay, RRT-NPS; John Sanford, RRT-ACCS.

TRIAL REGISTRATION

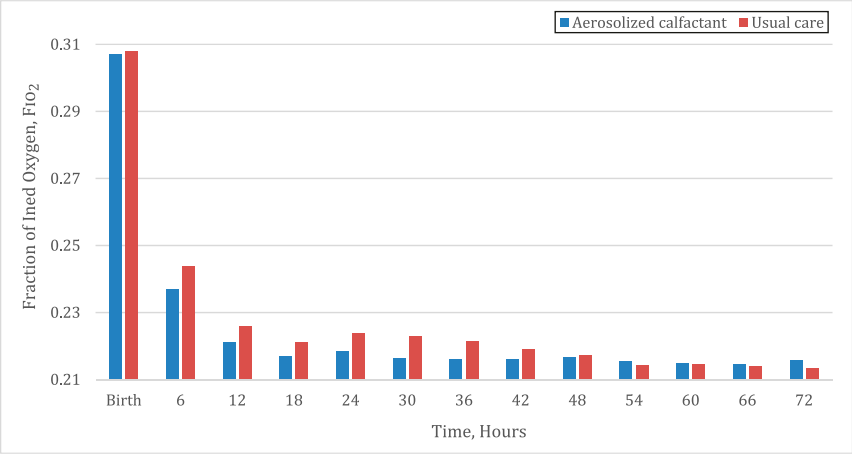
Trial registration can be found at www.clinicaltrials.gov.

The trial name is "Comparison of Aerosol Delivery of Infasurf to Usual Care in Spontaneously Breathing RDS Patients" (https://clinicaltrials.gov/ct2/show/NCT03058666?term=Aero-02&rank=1).



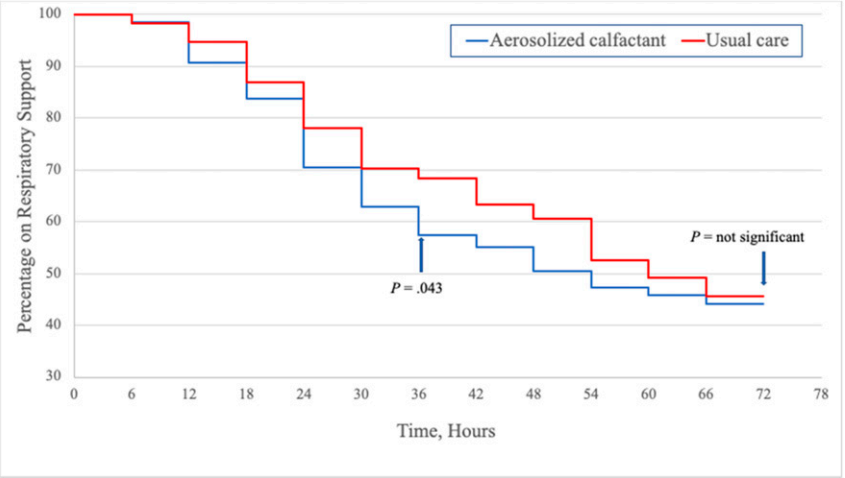
SUPPLEMENTAL FIGURE 4

Primary outcome (intubation for liquid surfactant) by gestational age. The percentage of infants intubated and treated with liquid surfactant instillation is shown for each study group (right hand) and broken down by 2-week gestational age blocks (left hand). The aerosolized calfactant group is shown in blue, and the usual care group is shown in red.



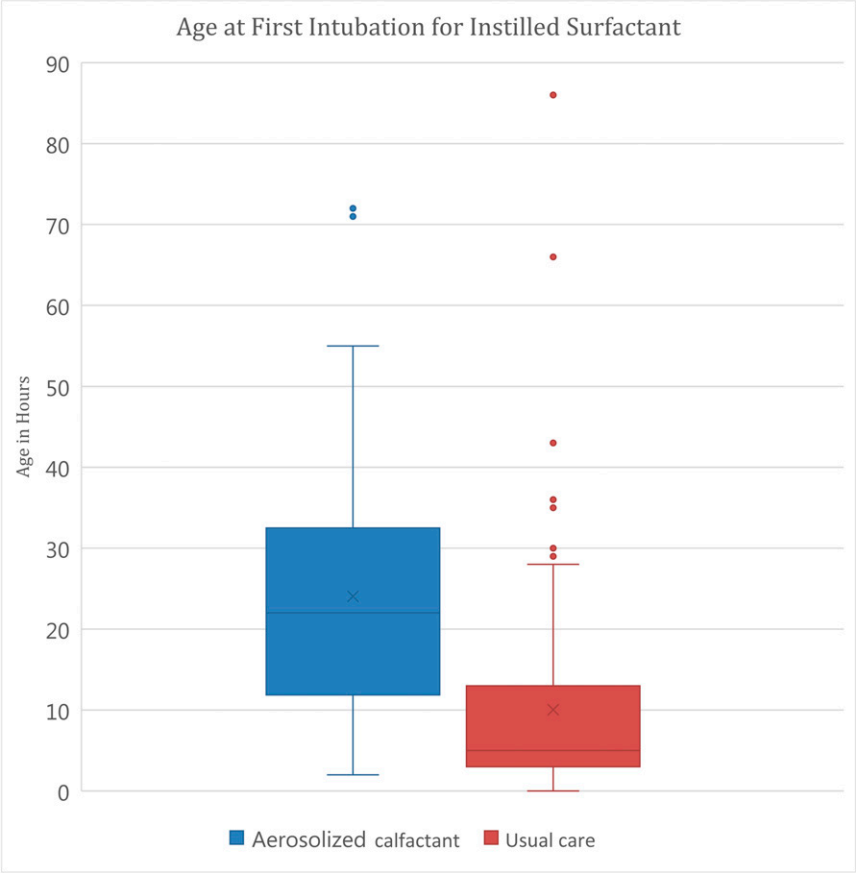
SUPPLEMENTAL FIGURE 5

Mean supplemental oxygen requirement during the first 72 hours of age in infants with "mild" RDS. Mild RDS was defined as those infants in the aerosolized calfactant group that only received 1 dose and did not require intubation for liquid surfactant and those infants in the usual care group that did not require intubation. The aerosolized calfactant group is shown in blue, and the usual care is group shown in red. There were no significant differences in mean FIO_2 requirement at any time point, by unpaired *t* test.



SUPPLEMENTAL FIGURE 6

Kaplan-Meier plot for weaning off respiratory support during the first 72 hours of age in infants with "mild" RDS. Mild RDS was defined as those infants in the aerosolized calfactant group that only received 1 dose and did not require intubation for liquid surfactant and those infants in the usual care group that did not require intubation. The figure shows the percentage of infants with mild RDS still requiring respiratory support for each study group. The aerosolized calfactant group is shown in blue, and the usual care group is shown in red. At time 0, all infants required noninvasive respiratory support, as per study protocol. By 72 hours, ∼55% of infants in each study group had weaned off all support. Infants in the aerosolized calfactant group tended to wean sooner so that, by 36 hours, the difference between groups was statistically significant ($P = .043$), consistent with a positive response to aerosolized calfactant. By 72 hours, a comparable percentage of infants in each group had weaned off support, consistent with the spontaneous improvement in RDS that occurs during the second and third day of age.



SUPPLEMENTAL FIGURE 7

Age at first intubation for instilled surfactant. In an intention-to-treat analysis, 59 infants in the aerosolized calfactant group and 113 infants in the usual care group were intubated for liquid surfactant instillation during the first 4 postnatal days. Each box-and-whisker plot of age shows IQR (shaded box), median (line within box), mean ("X" within box), range (line outside box), and outliers (filled circles). The median age was 22 hours (IQR: 12.25–32) for the aerosolized calfactant group and 5 hours (IQR: 3–12.5) for the usual care group. $P < .01$ by using the Mann–Whitney *U* test.

SUPPLEMENTAL FIGURE 8
Photographs of modified Solarys nebulizer. The modified Solarys device is shown in the top panel. The modified Solarys aerosol device on a manikin (with pacifier tip in mouth) with a separate nCPAP device in place is shown in the bottom panel.

SUPPLEMENTAL FIGURE 9
Chest radiographs from an infant with RDS before and after receiving an initial aerosolized calfactant treatment. A, 15 minutes before treatment. B, 45 minutes after treatment.

SUPPLEMENTAL TABLE 4 Cohort 2 Descriptive Data: Characteristics of Patients at Random Assignment

Characteristic	Aerosolized Calfactant (n = 11)	Usual Care (n = 9)
Male sex, No. (%)	8 (73)	5 (56)
Gestational age, wk, mean ± SD	29.9 ± 2.3	31.0 ± 3.1
Birth wt, g, mean ± SD	1370 ± 462	1570 ± 664
Singleton births, No. (%)	6 (55)	5 (56)
Vaginal delivery, No. (%)	3 (27)	3 (33)
Antenatal steroids for fetal lung maturation, No. (%)		
None	3 (27)	2 (22)
<12 h before delivery	1 (9)	1 (11)
>12 h before delivery	4 (36)	5 (56)
Unknown	3 (27)	1 (11)
Apgar score, median (IQR)		
1 min	7 (6)	8 (4)
5 min	8 (4)	9 (4)
Respiratory status at random assignment		
FIO_2, mean ± SD	0.48 ± 0.17	0.34 ± 0.05
nCPAP, No. (%)	5 (45)	7 (78)
Mechanical ventilation, No. (%)	6 (55)	2 (22)
Age at random assignment,[a] No. (%)		
<4 h	0 (0)	0 (0)
4–8 h	4 (40)	0 (0)
>8 h	6 (60)	3 (100)

[a] Data are missing for 6 infants in the usual care group and 1 infant in the aerosol calfactant group.

SUPPLEMENTAL TABLE 5 Respiratory Outcomes (Cohort 1 Only)

Respiratory Status	3 d of Life			7 d of Life or Discharge			28 d of Life or Discharge		
	Aerosolized Calfactant (n = 230), No. (%)	Usual Care (n = 227), No. (%)	P	Aerosolized Calfactant (n = 230), No. (%)	Usual Care (n = 227), No. (%)	P	Aerosolized Calfactant (n = 230), No. (%)	Usual Care (n = 227), No. (%)	P
Discharged or no support	82 (36)	84 (37)	.31	125 (54)	143 (63)	.25	184 (80)	188 (83)	.60
Low-flow nasal cannula with or without O_2	11 (5)	20 (9)		21 (9)	19 (6)		16 (7)	11 (5)	
Nasal positive airway pressure	114 (50)	106 (47)		73 (32)	57 (25)		27 (12)	26 (11)	
Mechanical ventilation	23 (10)	17 (7)		11 (5)	7 (3)		3 (1)	1 (0.4)	
Deceased	0 (0)	0 (0)		0 (0)	1 (0.4)		0 (0)	1 (0.4)	

Data are shown at age noted or at discharge if prior. P values via Fisher's exact test. —, not applicable.