Synthetic Surfactant CHF5633 Compared with Poractant Alfa in the Treatment of Neonatal Respiratory Distress Syndrome: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial

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Objective To compare efficacy and safety of a new synthetic surfactant, CHF5633, enriched with surfactant proteins, SP-B and SP-C peptide analogues, with porcine surfactant, poractant alfa, for the treatment of respiratory distress syndrome in infants born preterm.

Study design Neonates born preterm on respiratory support requiring fraction of inspired oxygen (FiO_2) ≥0.30 from $24^{0/7}$ to $26^{6/7}$ weeks and FiO_2 ≥0.35 from $27^{0/7}$ to $29^{6/7}$ weeks of gestation to maintain 88%-95% oxygen saturation were randomized to receive 200 mg/kg of CHF5633 or poractant alfa. If necessary, redosing was given at 100 mg/kg. Efficacy end points were oxygen requirement (FiO_2, respiratory severity score [FiO_2 × mean airway pressure]) in the first 24 hours, 7 and 28 days, discharge home, and/or 36 weeks of postmenstrual age; mortality and bronchopulmonary dysplasia at 28 days and 36 weeks of PMA. Adverse events and immunogenicity were monitored for safety.

Results Of the 123 randomized neonates, 113 were treated (56 and 57 in CHF5633 and poractant alfa groups, respectively). In both arms, FiO_2 and respiratory severity score decreased from baseline at all time points ($P < .001$) with no statistically significant differences between groups. Rescue surfactant use (19 [33.9%] vs 17 [29.8%]), bronchopulmonary dysplasia (31 [55.4%] and 32 [56.1%]), and mortality at day 28 (4 [7.1%] and 3 [5.3%]) were similar in the CHF5633 and poractant alfa groups, respectively. In 2 (3.4%) and 1 (1.7%) neonates, adverse drug reactions were reported in CHF5633 and poractant alfa groups, respectively. No immunogenicity was detected.

Conclusions Treatment with CHF5633 showed similar efficacy and safety as poractant alfa in neonates born preterm with moderate-to-severe respiratory distress syndrome. *(J Pediatr 2020;225:90-6)*.

Trial registration ClinicalTrials.gov: NCT02452476.

Surfactant deficiency resulting in respiratory distress syndrome (RDS) is the most common cause of respiratory failure in infants born preterm. Despite major improvements in perinatal care, RDS still represents one of the major causes of morbidity and mortality in infants born preterm.[1] Infants born before 29 completed weeks of gestation continue to need exogenous surfactant treatment and invasive or noninvasive mechanical ventilation. Although there is an increase in noninvasive ventilation use, the incidence of bronchopulmonary dysplasia (BPD) has not decreased significantly among infants born very preterm.[2] Synthetic as well as animal-derived surfactants from bovine or porcine origin have been evaluated in randomized controlled trials.[3] Animal-derived surfactants result in faster weaning of respiratory support, shorter duration of invasive ventilation, and decreased mortality when compared with the first or second

AE	Adverse event	OSI	Oxygen saturation index
ADR	Adverse drug reaction	PMA	Postmenstrual age
BPD	Bronchopulmonary dysplasia	RDS	Respiratory distress syndrome
BW	Birth weight	RR	Relative risk
CHF5633	Synthetic surfactant	RSS	Respiratory severity score
FiO_2	Fraction of inspired oxygen	SpO_2	Arterial oxygen saturation
MAP	Mean airway pressure		

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generations of synthetic surfactants.[4] Treatment with poractant alfa (Curosurf; Chiesi Farmaceutici S.p.A., Parma, Italy) is associated with better outcomes when compared with bovine surfactants, likely due to compositional difference, volume, and/or dose.[5] CHF5633 (Chiesi Farmaceutici S.p.A.) is the first fully synthetic surfactant containing phosphatidylcholine, phosphatidylglycerol, and enriched by peptide analogues of the 2 human surfactant proteins B (SP-B) and C (SP-C). It has been shown to be highly resistant to inactivation and effective in preclinical studies.[6-8] In the previous first-in-human clinical study on 40 neonates born preterm from $27^{0/7}$ to $33^{6/7}$ weeks of gestational age, CHF5633 was shown to be well tolerated with promising efficacy results.[9] This phase II, multicenter, double-blind, randomized, controlled clinical trial aimed to compare the efficacy and safety of CHF5633 with poractant alfa in neonates born extremely and very preterm with moderate-to-severe RDS.

Methods

This was a phase II, multicenter, double-blind, randomized, single dose, and active-controlled clinical trial. It was conducted in compliance with the International Council for Harmonization Good Clinical Research Practices (ICH E6). The ethics committee of each participating center and the Western institutional review board approved the study. An independent data safety monitoring board composed of 3 independent clinicians/neonatologists and 1 independent biostatistician was established to ensure the safety of the treated patients on an ongoing basis.

Patients

Inborn neonates with RDS requiring invasive or noninvasive ventilatory support were eligible within 24 hours from birth if requiring fraction of inspired oxygen (FiO_2) ≥0.30 or ≥0.35 from $24^{0/7}$ to $26^{6/7}$ or $27^{0/7}$ to $29^{6/7}$ weeks of gestation, respectively, to maintain arterial oxygen saturation (SpO_2) by pulse oximeter between 88% and 95%. Exclusion criteria included major congenital anomalies, received surfactant or inhaled nitric oxide before study entry, maternal illicit drugs or alcohol abuse in utero, mothers with prolonged rupture of the membranes (>21 days' duration), a strong suspicion of congenital pneumonia/infection, presence of air leaks, severe birth asphyxia, clinical seizures, or participation in another clinical trial. Written informed consent was signed by parents or legal guardians before any study related procedures. Patients were enrolled between December 2015 and February 2018 in 17 level III/IV neonatal intensive care units in the US.

Trial Procedures

CHF5633 or poractant alfa (200 mg/kg [2.5 mL/kg]) was administered intratracheally within 24 hours from birth. If indicated, up to 2 repeat doses of 100 mg/kg (1.25 mL/kg) were administered within approximately 12 hours after first/previous dosing with the same surfactant preparation of the first dose when patients met the following predefined criteria: lack of reduction in FiO_2 ≥0.10 to keep SpO_2 between 88% and 95% or intubated with FiO_2 ≥0.30 for babies $24^{0/7}$ to $26^{6/7}$ weeks and FiO_2 ≥0.35 for babies $27^{0/7}$ to $29^{6/7}$ weeks or nonintubated but with FiO_2 ≥0.35 for babies $24^{0/7}$ to $26^{6/7}$ weeks and FiO_2 ≥0.40 for babies $27^{0/7}$ to $29^{6/7}$ weeks.

Patients were centrally assigned to 1 of the 2 treatment arms through an IRT system (Interactive Response Technology, a combination of voice and web response system and also referred as IVRS/IWRS). A dynamic randomization method was used to balance the treatment groups by center and gestational age groups (ie, from $24^{0/7}$ to $26^{6/7}$ weeks and from $27^{0/7}$ to $29^{6/7}$ weeks).

In intubated patients, surfactant was given using medication administration catheter or side port without disconnecting the patient from the ventilator. In nonintubated patients, the INSURE (Intubation, SURfactant, Extubation) method was used.

Efficacy and safety assessments were performed at predefined times as follows: at surfactant administration, at 30 minutes; 1, 3, 6, 12, 18, and 24 hours and at the following days 2, 3, 5, 7, and 28 postdosing; at 36 weeks of postmenstrual age (PMA); and at the day of discharge. A stand-alone clinical assessment at 24 months' (±3 months) corrected age based on the Bayley Scales of Infant Development and a health status questionnaire (health problems, illnesses, injuries, well-being, diet, respiratory assessment) is ongoing and will be presented later. The immunogenicity assessment in serum was carried out before surfactant administration and approximately at 5 weeks after administration (with a window from 3 to 6 weeks). CXCL8, interleukin 1β, interleukin 6, tumor necrosis factor-alpha, and myeloperoxidase were collected from tracheal aspirates before study drug administration, at 24 ± 1 hours and on day 2 (48 ± 1 hours) from a subgroup of intubated babies whose clinical condition required invasive mechanical ventilation. The collection of tracheal aspirates was performed according to the most widely used method in neonates.[10] Blood samples for immunogenicity and tracheal aspirates for biomarkers of inflammation were analyzed at SGS Life Science Services Vieux C, Wavre, Belgium, and SGS Cephac Europe SAS, Saint-Benoît Cedex, France, respectively.

Data on SpO_2, ventilator settings (FiO_2, mean airway pressure [MAP], SpO_2/FiO_2 ratio, respiratory severity score [RSS: $FiO_2 \times MAP$], oxygen saturation index [OSI: $FiO_2 \times MAP \times 100/SpO_2$]), and duration of ventilation/oxygen therapy and concomitant medications were collected. Data on air leaks; pulmonary hemorrhage; sepsis, mortality at 28 days and at 36 weeks of PMA; BPD as mild, moderate, or severe using *Eunice Kennedy Shriver* National Institute of Child Health and Human Development criteria[11]; death or BPD; intraventricular hemorrhage using Papile criteria[12]; and necrotizing enterocolitis stage II or greater using Modified Bell staging criteria[13,14] were collected at appropriate time points. Hematologic and biochemical values were collected at 24 hours. Evidence for immunogenicity was evaluated in both groups by measuring antibodies to SP-B and SP-C analogues contained in CHF5633.

The following safety measures were collected and analyzed: incidence of major neonatal morbidities and complications

of prematurity, adverse events (AEs) and adverse drug reactions (ADRs), and vital signs. Blood tests were performed to assess the complete blood count and biochemistry, including blood urea nitrogen, creatinine and electrolytes (sodium, potassium, calcium, phosphorus), alanine aminotransferase, aspartate aminotransferase, glucose, and C-reactive protein.

The immunogenicity assay was based on an indirect and non-competitive enzyme immunoassay technique. The titer determination of anti-CHF-4902.03 and anti-CHF-5736.03 antibodies in the clinical serum samples were calculated using the cut-off obtained with the negative human serum. The samples were serially diluted, tested in each set of the analytical runs, and compared with the preimmune serum from nonimmunized animals (used as the negative control) and postimmune serum from the same species (as the positive control). The endpoint titer was determined by the last diluted specimen that provided positive results. To adjust for variation in collection of tracheal aspirates, cytokines were normalized to the total protein (an endogenous marker of dilution).

Statistical Analysis

Efficacy analyses were conducted on an intention-to-treat population (ie, randomized treated neonates with a post-baseline efficacy evaluation). Comparison between groups requiring redosing and percentage of neonates on room air within 24 hours was performed using the Fisher exact test; OR and related exact 95% CI also is provided. The Mann–Whitney *U* test was used for duration of ventilation and oxygen use. Death, BPD, and death or BPD were compared using the Cochran–Mantel–Haenszel test adjusted for the gestational age group, and relative risk (RR) and related 95% CI also was calculated. Post-hoc analyses were performed on data for severe BPD and death or severe BPD using the same analysis as noted previously. FiO_2, SpO_2, SpO_2/FiO_2 ratio, RSS, and OSI over the first 24 hours were analyzed using a linear mixed model for repeated measures with treatment, time point, treatment by time point interaction, study site, and gestational age group as fixed effects and predose values as covariates. Mean changes vs baseline for biomarkers of inflammation in the tracheal aspirates normalized by total protein were summarized by treatment by means of descriptive statistics.

Results

Patients' Disposition and Baseline Demographic Characteristics

From December 2015 through February 2018, a total of 297 infants were screened and 123 infants were randomized. Six patients were not treated with surfactant after randomization due to improved respiratory status, and 4 patients were excluded because the last FiO_2 prerandomization was <0.30. Of 113 included in the intention-to-treat population (Figure 1; available at www.jpeds.com), 56 received CHF5633 (mean birth weight [BW] 867 ± 267 g; mean gestational age 27 ± 1.8 weeks) and 57 infants (mean BW 904 ± 310 g; mean gestational age 27 ± 1.9 weeks) received poractant alfa (Table I). Overall, 46% and 56% of infants belonged to the gestational age strata between $24^{0/7}$ and $26^{6/7}$ weeks in the CHF5633 group and poractant alfa group, respectively. There were no significant differences between the 2 treatment groups with respect to the following baseline characteristics: BW, gestational age, antenatal steroid use, mode of delivery, 5-minute Apgar score, or age at first surfactant treatment (Table I). The mean FiO_2 at the baseline was slightly greater in the poractant alfa arm than in the CHF5633 arm (0.51 vs 0.45). However, the mean SpO_2/FiO_2 ratio was similar for both groups (2.16 and 2.07 in the CHF5633 and poractant alfa arms, respectively).

Efficacy

Overall, oxygen requirement and ventilatory support were significantly reduced from baseline in both treatment groups, with no significant differences between them as well as for other clinical outcomes or comorbidities (Table II). A decrease in the mean FiO_2 from the baseline was observed until day 7 in both treatment arms (Figure 2). The mean SpO_2/FiO_2 ratios at different post-baseline assessed time points until day 7 were comparable between the treatment arms and there were no significant differences between groups at any of the assessed time points (Figure 3). A significant decrease in the mean RSS compared with baseline was observed in both treatment arms at all assessed time points. Notably, the adjusted mean (95% CI) values at day 2 were similar (3.67 [3.09-4.25] and 3.71 [3.02-4.39] in CHF5633 and poractant alfa groups, respectively). Similar results were observed with regards to OSI (data not shown). The number of neonates receiving 2 or more doses of surfactant was similar (33.9% vs 29.8%) in CHF5633 vs poractant alfa group, respectively (OR [95% CI]: 1.21 [0.55-2.67], $P = .69$ between groups). Days

Table I. Demographics and baseline characteristics (ITT population)

Demographics and baseline characteristics	CHF5633 (N = 56)	Poractant alfa (N = 57)
Age at first dose, h	6.6 ± 6.72	5.5 ± 6.54
Gestational age, wk	27.01 ± 1.79	26.72 ± 1.90
$24^{0/7}$ to $26^{6/7}$ wk gestational age, n (%)	26 (46.4)	32 (56.1)
Male, n (%)	24 (42.9)	28 (49.1)
Apgar score at 5 min*	7 (5-8)	7 (5-7)
Birth weight, g	862.0 ± 247.2	903.6 ± 310.2
Antenatal steroids, n (%)	54 (96.4)	54 (94.7)
Cesarean delivery, n (%)	43 (76.8)	42 (73.7)
FiO_2	0.45 ± 0.12	0.51 ± 0.20
SpO_2 (%)	91.6 ± 2.6	92.5 ± 3.1†
SpO_2/FiO_2 ratio	2.16 ± 0.49	2.07 ± 0.60
RSS‡	4.23 ± 1.39	5.14 ± 2.07

ITT, intention-to-treat.
Unless otherwise specified, values are mean ± SD.
*Median (IQR).
†n = 55.
‡RSS (n = 34 in the CHF5633 group, n = 37 in the poractant alfa group).

Table II. Clinical outcomes and comorbidities (ITT population)

Clinical outcomes and comorbidities	CHF5633 (N = 56)	Poractant alfa (N = 57)	CHF5633 vs poractant alfa (95% CI)	*P* value
Surfactant ≥2 doses, n (%)*	19 (33.9)	17 (29.8)	1.21 (0.55-2.67)	.69
Invasive ventilation, d, mean (SD)†	22 ± 39	21 ± 30	NA	.81
Noninvasive ventilation, d, mean (SD)†	44 ± 24	40 ± 28	NA	.36
Days on oxygen, mean (SD)†	13 ± 12	17 ± 12	NA	.12
Death at 28 days of age, n (%)‡	4 (7.1)	3 (5.3)	1.46 (0.35-6.09)	.60
Death at 36 weeks' PMA, n (%)‡	4 (7.1)	6 (10.5)	0.74 (0.23-2.42)	.62
BPD, n (%)‡	31 (55.4)	32 (56.1)	1.03 (0.81-1.32)	.81
Severe BPD,§ n (%)‡	11 (19.6)	18 (31.6)	0.71 (0.39-1.28)	.25
Death or BPD, n (%)‡	35 (62.5)	38 (66.7)	1.00 (0.81-1.25)	.97
Death or Severe BPD, n (%)‡	15 (26.8)	24 (42.1)	0.71 (0.44-1.14)	.15
FiO_2 at 24 h, adj. mean (95% CI)¶	0.28 (0.25-0.33)	0.30 (0.26-0.32)	−0.01 (−0.06, 0.04)	.63
SpO_2/FiO_2 ratio at 24 h, adj. mean (95% CI)¶	3.72 (3.47-3.98)	3.64 (3.38-3.89)	0.09 (−0.25, 0.43)	.61

NA, not available.
*OR, Fisher test.
†Mann–Whitney *U* test.
‡RR, Cochran–Mantel–Haenszel adjusted for the gestational age group.
§*Eunice Kennedy Shriver* National Institute of Child Health and Human Development definition for severe BPD.
¶Linear mixed model for repeated measures.

on invasive and noninvasive ventilation and oxygen use were similar between the 2 groups. CHF5633 also was comparable with poractant alfa in terms of incidence of BPD, 31 (55.4%) vs 32 (56.1%) patients, and mortality/BPD, 35 (62.5%) vs 38 (66.7%) at 36 weeks of PMA as well as in terms of RDS-related mortality at 14 days of life, 1 (1.8%) in the CHF5633 arm and 2 (3.5%) in the poractant alfa arm. There was a trend toward less severe BPD in the CHF5633 group compared with poractant alfa group (19.6% vs 31.6%; RR [95% CI]: 0.71 [0.39-1.28], $P = .25$) as well as a lower death or severe BPD as a composite outcome in CHF5633 group (RR [95% CI] 0.71 [0.44-1.14], $P = .15$).

Safety

The immunogenicity assessment was performed in 60 patients in the CHF5633 group and 61 patients in the poractant alfa group. An anti-SP-B (CHF5736.03) antibody titer of less than 100 and an anti-SP-C (CHF4902.03) antibody titer of less than 12.5 meant negative results and confirmed no evidence of immunogenicity to either peptide in both treatment groups.

The biomarkers concentrations were measured in a limited number of patients (29-35 patients) who were still intubated at 48 hours and where the procedure to collect the tracheal aspirate could be performed. Some patients had at least 2 tracheal aspirates (less than 15 patients per group), one predose and one postdose, necessary to evaluate the treatment effect. No clear trends were observed for each cytokine, and thus, it was not possible to discriminate between the CHF5633 and poractant alfa groups in terms of reduction of inflammation (Table III).

Serious AEs were reported in a similar proportion of patients in both treatment groups: 20 (33.9%) patients with 36 events in the CHF5633 group and 20 (34.5%) patients

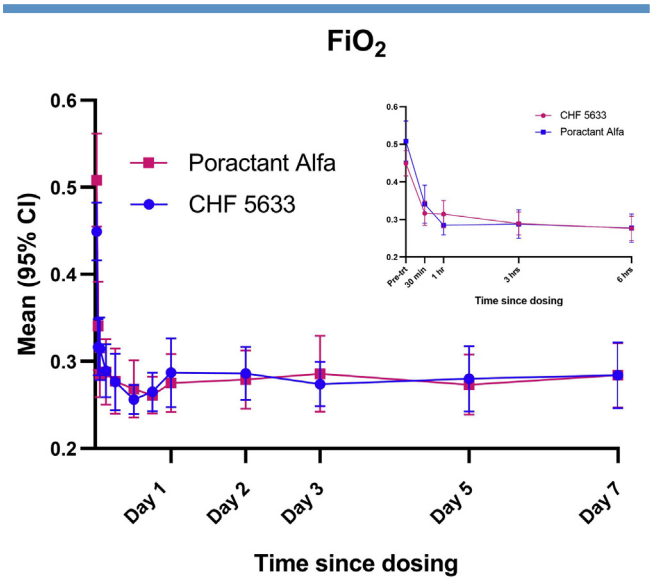

Figure 2. Changes in FiO_2 postsurfactant treatment (intention-to-treat [ITT] population).

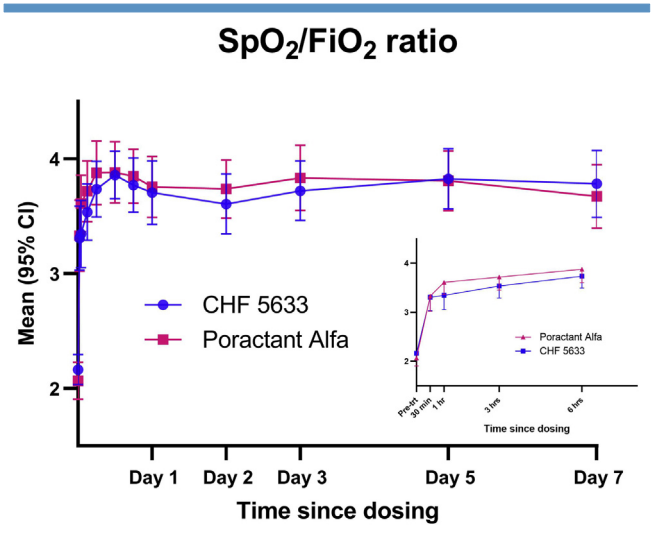

Figure 3. Changes in SpO_2/FiO_2 ratio postsurfactant treatment (ITT population).

with 31 events in the poractant alfa group. Two infants in the CHF5633 group and 1 in the poractant alfa group developed pulmonary hemorrhage, considered related to study drug (ADRs); in one case treated with CHF5633 besides the pulmonary hemorrhage, a pneumothorax occurred (ADR). A low and similar proportion of patients had AEs leading to death, with a slightly greater proportion of patients in the poractant alfa group (5 [8.6%]) than in the CHF5633 group (3 [5.1%]). The most frequently reported AE in both treatment groups was anemia (Table IV): 49 (83.1%) patients in the CHF5633 group and 47 (81%) patients in the poractant alfa group. Pneumothorax was reported in 2 vs 1 patient in the CHF5633 and poractant alfa group, respectively, and pulmonary hemorrhage in 1 patient in the CHF5633 group as serious ADRs. Intraventricular hemorrhage grade IV (1 vs 3) and sepsis (4 vs 2) were reported as not related serious AEs in CHF5633 vs poractant alfa treated patients, respectively. Protocol violations were reported in 3 patients (5.4%) in the CHF5633 group and 1 patient (1.8%) in poractant alfa group. Following protocol deviations were reported: volume of surfactant administered (1 patient in the CHF5633 group [2.1 mL per kg]); randomization before birth (1 patient in the poractant alfa group); redosing using

Table III. Biomarkers concentration (normalized for total proteins)

	CHF5633 (N = 56)		Poractant alfa (N = 57)	
Biomarkers per total protein, pg/mg	**Observed values**	**Change from baseline**	**Observed values**	**Change from baseline**
IL-1β				
Baseline				
n	34		32	
Mean (SD)	26.5 (65.2)		39.5 (140.4)	
Day 1				
n	15	14	15	12
Mean (SD)	15.8 (15.2)	−38.5 (93.1)	6.8 (10.3)	−39.9 (134.7)
Day 2				
n	13	13	11	9
Mean (SD)	64.00 (103.8)	3.7 (154.7)	23.2 (29.2)	−40.56 (159.2)
IL-6				
Baseline				
n	34		32	
Mean (SD)	255.4 (511.4)		405.8 (1703.5)	
Day 1				
n	15	14	14	13
Mean (SD)	187.49 (189.0)	−200.07 (761.4)	93.39 (88.7)	−792.2 (2657.4)
Day 2				
n	13	13	11	9
Mean (SD)	294.35 (471.9)	−129.37 (954.3)	106.8 (79)	−1089.8 (3222.01)
IL-8				
Baseline				
n	35		33	
Mean (SD)	1126.19 (2851.6)		1477.89 (4192.57)	
Day 1				
n	15	14	15	13
Mean (SD)	2509.47 (2214.9)	389.86 (5240.8)	1549.87 (1686.2)	−843.74 (4720.4)
Day 2				
n	13	13	11	9
Mean (SD)	3178.54 (3461.3)	821.16 (5978.9)	2651.45 (2086.3)	−243.7 (6425.9)
TNF-α				
Baseline				
n	34		31	
Mean (SD)	9.63 (28.5)		10.11 (42.8)	
Day 1				
n	14	13	14	12
Mean (SD)	4.1 (5.0)	−16.1 (42.9)	1.83 (1.9)	−20.0 (67.5)
Day 2				
n	11	11	11	9
Mean (SD)	27.03 (47.2)	2.9 (71.2)	2.84 (2.8)	−25.57 (78.9)
MPO				
Baseline				
n	31		29	
Mean (SD)	141 221 (215 349)		203 226 (561 936)	
Day 1				
n	13	11	13	10
Mean (SD)	403 662 (339 168)	267 338 (399 695)	204 769 (269 929)	52 664 (264 661)
Day 2				
n	11	10	11	8
Mean (SD)	535 364 (431 089)		674 227 (612 0678)	508 378 (381 999)

IL-1β, interleukin 1β; *IL-6*, interleukin 6; *IL-8*, interleukin 8; *MPO*, myeloperoxidase; *TNF-α*, tumor necrosis factor-α.

Table IV. AEs by treatment groups (safety population)

AEs	Values	CHF5633 (N = 59)	Poractant alfa (N = 58)
Neonatal anemia	n (%)	49 (83.1)	47 (81.0)
Neonatal hyperbilirubinemia	n (%)	40 (67.8)	32 (55.2)
Pneumothorax	n (%)	2 (3.30)	1 (1.7)
BPD	n (%)	34 (57.6)	34 (58.6)
Patent ductus arteriosus	n (%)	27 (45.8)	34 (58.6)
Metabolic acidosis	n (%)	18 (30.5)	23 (39.7)
Necrotizing enterocolitis, stage II or greater	n (%)	1 (1.7)	1 (1.7)
Intraventricular hemorrhage, grade II or greater	n (%)	9 (15.3)	13 (22.4)
Retinopathy of prematurity, stage III-IV	n (%)	3 (5.1)	2 (3.4)
Neonatal hyponatremia	n (%)	17 (28.8)	19 (32.8)
Neonatal hypotension	n (%)	19 (32.2)	17 (29.3)
Hyperglycemia	n (%)	20 (33.9)	13 (22.4)
Atrial septal defect*	n (%)	21 (35.6)	19 (32.8)

MeDRA, Medical Dictionary for Regulatory Activities.
*Most of the cases are reported as patent foramen ovale and coded as per MeDRA dictionary with its preferred term "atrial septal defect."

noninvestigational drug (1 patient in the CHF5633 group); 1 patient in CHF5633 group not meeting the inclusion criterion of FiO_2 ≥0.30.

Discussion

In this multicenter, double-blind, randomized, active-controlled, proof-of-concept study, treatment with synthetic surfactant CHF5633 containing surfactant protein analogues (SP-B and SP-C) was as effective and safe as treatment with porcine derived surfactant, poractant alfa in preterm neonates from $24^{0/7}$ to $29^{6/7}$ weeks of gestational age with moderate-to-severe RDS.

Several clinical trials have been conducted to compare other synthetic surfactants with animal-derived surfactants. Treatment with animal-derived surfactants has been shown to result in better clinical response than synthetic surfactants during the acute phase of RDS, as evidenced by rapid improvement in the need for supplemental oxygen and ventilatory support, fewer pneumothoraces, and fewer deaths.[4] Animal-derived surfactants do not resist inactivation well secondary to inflammatory mediators or plasma or blood components in the lung lining liquid in patients with pneumonia or pulmonary hemorrhage.[15] In vitro studies have shown that addition of surfactant-associated proteins to animal-derived surfactant extracts makes the surfactant preparation more resistant to the inhibitory effects of plasma proteins such as albumin, fibrinogen, and hemoglobin. CHF5633 has been developed to have the same surfactant concentration as poractant alfa preparation (80 mg/mL), enriched with SP-B and SP-C peptide analogues and with a low viscosity, making it ideal to be administered intratracheally (Table V). This fully synthetic surfactant preparation has been shown to resist inactivation better than synthetic surfactant with only a single peptide or animal-derived surfactant.[16,17]

In an in vivo preterm lamb model of RDS due to surfactant inactivation with albumin, treatment with CHF5633 resulted in improvements in ventilation and oxygenation as well as survival benefit.[6] The poractant alfa surfactant doses used in this study followed the recommendations approved by the Food and Drug Administration in the US, determined as 200 mg/kg for the first dose and 100 mg/kg for additional doses. This dosing scheme was shown to decrease the risk of mortality before discharge, death, or BPD; patent ductus arteriosus requiring treatment; and the need for more than 1 dose of surfactant in infants born preterm with RDS in randomized clinical trials compared with bovine derived surfactants.[18] In the first-in-human study using CHF5633, a lower dose of 100 mg/kg was initially tested and then escalated to 200 mg/kg and was reported to be safe and efficacious at both doses.[9] In the present study, CHF5633 and poractant alfa, at 200 mg/kg, showed similar efficacy in reducing oxygen requirement and ventilatory support over time with no statistically significant differences between the 2 groups; no significant differences were observed in terms of incidence of death, BPD, mortality/BPD as well as in terms of RDS mortality. The need for redosing was quite low and was similar between the 2 groups. Many patients were extubated after the first dose of surfactant, resulting in the collection of only a small number of tracheal aspirate samples, not allowing us to detect differences between CHF5633 and poractant alfa in anti-inflammatory properties, even in terms of changes from baseline levels of biomarkers normalized for total protein concentration. No immunogenicity effect in both treatment arms was detected, confirming what was observed in the first-in-human study. Sixty-three randomized patients per treatment group (126 in total), in this vulnerable preterm population, was deemed reasonable to describe the efficacy and safety profile of CHF5633 compared with poractant alfa. However, this sample size did not allow

Table V. Composition of CHF5633 vs poractant alfa

Composition of surfactant	CHF5633	Poractant alfa
Source	Fully synthetic	Minced porcine lung extract
Phospholipids	DPPC and POPG 1:1 ratio (mg/mL): 39.32 each	76 mg/mL
SP-B	SP-B peptide analogue: 0.16 mg/mL	Porcine SP-B: 0.45 mg/mL
SP-C	SP-C peptide analogue: 1.2 mg/mL	Porcine SP-C: 0.59 mg/mL
Final surfactant concentration, mg/mL	80	80
Volume for initial dose at 200 mg/kg	2.5 ml	2.5 ml
Volume for subsequent doses at 100 mg/kg	1.25 ml	1.25 ml

DPPC, dipalmitoyl phosphatidylcholine; *PL*, phospholipid; *POPG*, 1-palmitoyl-2oleoyl-glycero-3-phospho-1-glycerol; *SP*, surfactant protein.

adequate subgroup analyses for RSS, OSI, and biomarkers of inflammation.

In infants born preterm born between $24^{0/7}$ and $29^{6/7}$ weeks of gestational age with moderate-to-severe RDS, treatment with the new synthetic surfactant CHF5633 containing SP-B and SP-C peptide analogs was as effective and safe as treatment with poractant alfa. Our study findings provide a rationale for further studies in neonates born preterm with uncomplicated RDS as well as complicated RDS secondary to asphyxia, acidosis, or congenital infections, where surfactant inactivation is a major reason for suboptimal response to treatment with currently available surfactant preparations. ■

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Data statement

Data sharing statement available at www.jpeds.com.

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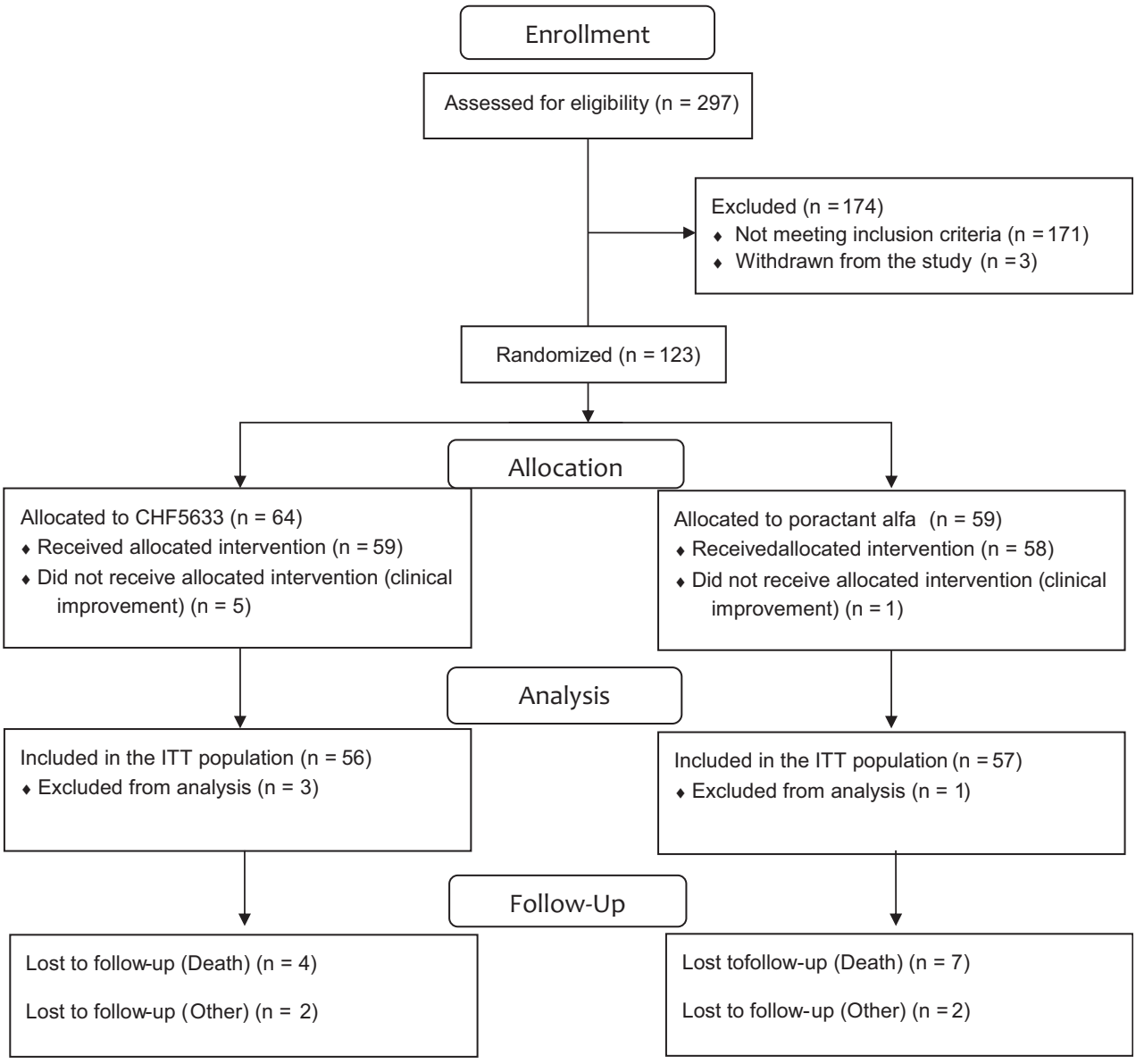

Figure 1. Enrollment, randomization, intervention, and analysis. *ITT*, intention-to-treat.