AEROFACT

APC-AF-CLN-004

A SOUTH AFRICAN, MULTICENTER, PHASE 2, NON-BLINDED, RANDOMIZED, CONTROLLED TRIAL TO DETERMINE IF AEROSOLIZED SURFACTANT PLUS CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) COMPARED TO CPAP ALONE CAN IMPROVE THE COURSE OF INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS) BY DECREASING THEIR NEED FOR INTRATRACHEAL BOLUS SURFACTANT IN THE FIRST 72 HOURS OF AGE

Indication studied:	Respiratory Distress Syndrome
Developmental phase of study:	Phase 2
First subject enrolled:	19 May 2023
Last subject completed:	01 June 2025
Release date of report:	23 June 2026

Company/Sponsor signatory:	Thomas O'Riordan, MD Chief Medical Officer Aerogen Pharma Limited

This study was performed in full compliance with the International Council for Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

2. SYNOPSIS

Name of Sponsor/Company: Aerogen Pharma Limited		*(For National Authority Use Only)*
Name of Finished Product: AeroFact (SF-RI 1 Surfactant for Inhalation Combined with a Dedicated Drug Delivery System)		
Name of Active Ingredient: Lyophilized SF-RI-1 dry powder surfactant (bovine-origin)		

Title of Study:

A South African, Multicenter, Phase 2, Non-Blinded, Randomized, Controlled Trial to Determine if Aerosolized Surfactant Plus Continuous Positive Airway Pressure (CPAP) Compared to CPAP Alone can Improve the Course of Infants with Respiratory Distress Syndrome (RDS) by Decreasing Their Need for Intratracheal Bolus Surfactant in the First 72 Hours of Age (NeoINSPIRe)

Study center(s):

This study was conducted at 4 study sites in South Africa.

Studied period:	**Phase of development:** Phase 2
Date first subject enrolled: 19 May 2023 Date last subject completed: 01 June 2025	

Objectives:

The primary objective of this study was to determine if aerosolized surfactant given to preterm infant subjects with RDS on nasal CPAP (nCPAP), compared with nCPAP alone, reduces the need for intratracheal bolus surfactant instillation in the first 72 hours of age.

The secondary objectives of the study were to compare the following measures between treatment groups:

- the need for repeat intratracheal bolus surfactant dosing
- the need for mechanical ventilation
- the duration of mechanical ventilation, CPAP, high-flow nasal cannula (HFNC) and supplementary oxygen
- the rate of adverse events and commonly reported select comorbidities of prematurity
- the incidence of bronchopulmonary dysplasia (BPD)
- the incidence of death at any time
- the incidence of death or BPD

Methodology:

This was a South African, multicenter, Phase 2, non-blinded, randomized controlled trial. Eligible subjects were randomized 1:1 to the Intervention group or Control group, according to a balanced block design, and stratified by site and birth weight (900 to 1199 g and 1200 to 1999 g). Subjects received up to 2 doses of AeroFact aerosolized surfactant (216 mg/kg/dose; prior to Protocol Amendment 3) or 4 doses of AeroFact aerosolized surfactant (108 mg/kg/dose) while on nCPAP in the

Intervention group or continued on nCPAP alone in the Control group. If twins were enrolled, each twin was randomized separately. High order multiples (three or more infants) were not enrolled.

According to the unit protocol at each study site, subjects with mild to moderate RDS were routinely treated with nCPAP and were only eligible to receive intratracheal bolus surfactant if they had a persistent fraction of inspired oxygen (F_iO_2) >0.40. Subjects in both the Intervention and Control groups with a persistent F_iO_2 >0.40 sustained for at least 15 minutes were regarded as meeting failure criteria and were eligible to receive intratracheal bolus surfactant. This was consistent with the unit protocols to administer intratracheal bolus surfactant and aligned with the current South African standard-of-care. However, bolus intratracheal surfactant instillation was not mandated and was administered at the discretion of the treating clinician, who was guided by the unit protocol. If a dose of intratracheal bolus surfactant was deemed necessary, it was administered by the neonatal intensive care unit (NICU) standard approach, either less invasive surfactant administration (LISA), intubation – surfactant – extubation (INSURE), or intubation for surfactant delivery with ongoing mechanical ventilation. At all study sites, beractant 100 mg/kg (Survanta) or poractant alfa 100mg/kg (Curosurf) via LISA was the standard-of-care for instilled bolus surfactant.

Number of subjects **(planned and analyzed):**

Approximately 232 subjects (116 per treatment arm) were planned for enrollment under Protocol Amendment 3 (Version 4.0). Approximately 100 subjects were planned for enrollment prior to Protocol Amendment 3 (Version 4.0). Therefore, the total planned sample size of the study was approximately 332 subjects.

The study was terminated early for futility based on a Data Safety and Monitoring Board (DSMB) review, as the probability of demonstrating efficacy was considered low. Prior to Protocol Amendment 3, a total of 83 subjects (42 AeroFact 216 mg/kg/dose and 41 Control) were randomized and included in the intent-to-treat (ITT) analysis. After Protocol Amendment 3, 60 subjects were randomized to 108 mg/kg/dose AeroFact (n=30) or Control (n=30) and all subjects were included in the ITT analysis. A total of 143 subjects were enrolled and randomized to this study.

Diagnosis and main criteria for inclusion:

This study enrolled inborn preterm infant subjects between 900 to 1999 g and 27 to 34 weeks gestation with a persistent F_iO_2 of 0.25 to 0.35 on nCPAP at 5-7 cm H_2O between 2 to 24 hours of age at the time of randomization. F_iO_2 requirement needed to be sustained for at least 15 minutes to maintain peripheral oxygen saturation of 90-95%.

Test product, dose and mode of administration, batch number:

AeroFact (SF-RI 1 Surfactant for Inhalation Combined with a Dedicated Drug Delivery System; also known as APC-0101). Doses administered in this study were 108 mg/kg/dose and 216 mg/kg/dose administered using a dedicated, breath-synchronized vibrating mesh nebulizer system designed to deliver aerosolized surfactant through CPAP support.

The following drug lot numbers were used during the study: P02428F and P03688B. Refer to Appendix 16.1.6 for lot numbers of device components.

Duration of treatment:

After Protocol Amendment 3, subjects randomized to active treatment received up to 4 doses of AeroFact aerosolized surfactant (108 mg/kg/dose) while on nCPAP. Prior to Protocol Amendment 3, subjects randomized to active treatment received up to 2 doses of AeroFact aerosolized surfactant (216 mg/kg/dose).

Reference therapy, dose and mode of administration, batch number:

nCPAP support alone with standard-of-care escalation, including intratracheal bolus surfactant per site practice.

Criteria for evaluation:

Efficacy: Efficacy was evaluated based on the proportion of subjects who required intratracheal bolus surfactant in the first 72 hours of age. Proportions of subjects in each treatment group who met prespecified treatment failure criteria; subjects receiving multiple doses of bolus surfactant; incidence of BPD or death at 36 weeks post-menstrual age (PMA); and number of hours/days on invasive mechanical ventilation, and/or HFNC, positive pressure, or supplemental oxygen were also evaluated.

Safety: Safety and tolerability were assessed through the monitoring of adverse events (AEs), serious adverse events (SAEs), nasal/oral aspiration and severe apnea, respiratory parameters, and need for respiratory support.

Statistical methods:

Continuous data summaries included number of observations, mean, standard deviation, median, and minimum and maximum values. Categorical data summaries included frequency counts and percentages by study group and overall. All data collected during this study were presented in subject data listings.

Analysis Populations

The following analysis populations were defined in this study:

- ITT population: The ITT population was defined as all randomized subjects in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. The ITT population was the primary population for the primary and secondary analyses.
- Per Protocol (PP) population: The PP population was defined as all randomized subjects who were not associated with a major protocol violation that affected subject safety or the integrity of the data. The PP analysis of primary and secondary endpoints was considered supportive.
- Safety Population: The Safety population included all subjects analyzed according to the treatment they actually received.

Efficacy Analysis

The primary efficacy endpoint of the study was the proportion of subjects requiring intratracheal bolus surfactant administration in the first 72 hours of age. This endpoint was summarized using counts and percentages and compared using contingency analysis (Fishers or a Chi-square test) between the post-Protocol Amendment 3 Intervention and Control groups. Logistic regression modelling was used to further compare the relative odds of requiring intratracheal bolus surfactant administration, adjusted for possible confounding variables, such as gestational age, sex, pre-natal steroid exposure, and F_iO_2 at randomization, if necessary. The ITT population was used for the primary analysis of this endpoint, with the PP population as supportive. The proportion of subjects requiring intratracheal bolus surfactant administration among subjects in each treatment group, including pre- and post-protocol amendment AeroFact and Control groups, Total AeroFact, and Total Control groups, were also summarized using descriptive statistics only. The primary analysis was performed using observed cases (no imputation). Subjects who were withdrawn were assessed until time of withdrawal.

The secondary efficacy endpoints were summarized for the ITT population, with the PP population as supportive. All secondary analyses included descriptive statistics for all treatment groups, including pre- and post-protocol amendment AeroFact and Control groups, Total AeroFact, and Total Control groups. Statistical comparisons were made between post-Protocol Amendment 3 Intervention and Control groups. Secondary comparisons were considered supportive and did not require adjustment for multiplicity of analyses.

Safety Analysis

All safety analyses were conducted using the Safety population. All data collected were summarized according to the variable type. No inferential statistics were performed.

Adverse events were classified by system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. Respiratory measurements and other collected safety data were summarized descriptively.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The primary endpoint of the study was not achieved. There was no evidence of efficacy of AeroFact as measured by a reduction in the need for instillation of liquid bolus surfactant in premature infants with RDS. A numerical trend towards increased use of liquid bolus surfactant in the AeroFact treated subjects was observed. Variability in primary outcome was noted across sites for both the Control and Intervention groups.

	AeroFact (216 mg/kg) (N=42)	**AeroFact (108 mg/kg) (N=30)**	**Total AeroFact (N=72)**	**Control 1 (nCPAP) (N=41)**	**Control 2 (nCPAP) (N=30)**	**Total Control (nCPAP) (N=71)**
Subjects who received bolus surfactant [a]						
n (%)	18 (42.9)	16 (53.3)	34 (47.2)	13 (31.7)	8 (26.7)	21 (29.6)
Odds ratio [b]	--	4.550	--	--	--	--
95% CI	--	1.335, 15.507	--	--	--	--

CI=confidence interval; nCPAP=nasal continuous positive airway pressure.

Notes: Control 1 includes control subjects enrolled prior to Protocol Amendment 3/Version 4.0 (corresponding AeroFact group of 216 mg/kg/dose). Control 2 includes control subjects enrolled after Protocol Amendment 3/Version 4.0 (corresponding AeroFact group of 108 mg/kg/dose).

a The primary endpoint was measured in the first 72 hours of age. Subjects who were withdrawn were assessed until the time of withdrawal. No imputation was used.

b Logistic regression modeling adjusted for gestational age, sex, prenatal steroid exposure comparing post-amendment AeroFact (108 mg/kg) and control (Control 2) groups.

Source: Table 14.2.1.1

No evidence of efficacy of AeroFact was observed in any of the prespecified secondary endpoints. Variability in the secondary endpoint of proportion of subjects meeting failure criteria was noted across sites for both the Control and Intervention groups.

The individual dose of AeroFact in the Intervention group was modified by Protocol Amendment 3 from 218 mg/kg/dose (maximum of 2 doses) to 108 mg/kg/dose (maximum of 4 doses), to reflect the outcome of a separate larger Phase 2b study of AeroFact (APC-AF-CLN-002). However, this dose change does not explain the lack of efficacy observed in this study.

SAFETY RESULTS:

The most frequently reported AEs in the AeroFact and Control groups were common complications of prematurity, including intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and sepsis. IVH and pneumothorax were reported in a higher proportion of subjects receiving AeroFact compared with Control. Most AEs across treatment groups were mild or moderate in severity.

A higher proportion of subjects in the AeroFact groups experienced SAEs compared with Control. The most frequently reported SAEs in the AeroFact treatment groups were sepsis, pneumothorax, and NEC. The most frequently reported SAE in the Control groups was sepsis.

- Four subjects (5.6%) in the AeroFact groups and 5 subjects (7.0%) in the Control groups experienced SAEs of sepsis.
- SAEs in the Respiratory, Thoracic and Mediastinal Disorders SOC were reported in a higher proportion of subjects in the AeroFact groups (6 subjects; 8.5%) compared with Control (2 subjects; 2.8%). Pneumothorax was reported in 4 subjects (5.6%) who received AeroFact compared with 1 Control subject (2.8%).
- NEC was reported in 4 subjects (5.6%) in the AeroFact groups and 1 subject (1.4%) in the Control groups.
- SAEs reported only in subjects who received AeroFact were IVH (2 subjects; 2.8%), seizure, pulmonary hemorrhage, and hypotension (1 subject each; 1.4%).
- One SAE reported only in Control subjects was a congenital anomaly (vitallo-intestinal duct remnant) (1 subject; 1.4%).

Three subjects died due to fatal AEs in the AeroFact groups (4.2%) (NEC, sepsis, hypotension) compared with 4 deaths in the Control groups (5.6%) (sepsis and congenital anomaly). One additional subject in the AeroFact 108 mg/kg/dose group died due to RDS.

While none of the SAEs or deaths reported in either of the AeroFact groups and Control groups were considered related to study drug or device by the investigator, the observed asymmetry in the incidence of pneumothorax and IVH in the AeroFact groups suggested that these AEs should be considered events of special interest in future studies. Pneumothorax and IVH are common events in preterm infants with RDS with multifactorial risk factors, and their incidence is increased with worsening respiratory failure.

CONCLUSION:

The study was terminated early due to futility based on a DSMB review, as the probability of demonstrating efficacy was considered low. The primary endpoint of the study was not achieved. No evidence of efficacy of AeroFact was observed in any of the prespecified secondary endpoints. Safety of AeroFact in this study was consistent with prior clinical study results.

Date of the report: 23 June 2026