PROTOCOL TITLE	A Partially-Blind, Randomized, Controlled, Parallel-Group Dose Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact™ (SF-RI 1 surfactant for inhalation combined with a dedicated drug delivery system) in Preterm Infants at Risk of Worsening Respiratory Distress Syndrome
PROTOCOL NUMBER	APC-AF-CLN-002
AMENDMENT NUMBER	Amendment 8
INVESTIGATIONAL PRODUCT	AeroFact™ (SF-RI 1 surfactant for inhalation combined with a dedicated drug delivery system)
Study IND	132548
INDICATION	Respiratory Distress Syndrome
PHASE	Phase 2b
SPONSOR	Aerogen Pharma 1660 S Amphlett Boulevard, Suite 360 San Mateo, CA 94402 United States
APPROVAL DATE	09 March 2022
GCP STATEMENT	This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
CONFIDENTIALITY STATEMENT	This document is confidential as it contains proprietary information of Aerogen Pharma. Any viewing or disclosure of such information that is not authorized in writing by the Aerogen Pharma is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

PROTOCOL APPROVAL PAGE

PROTOCOL TITLE	A Partially-Blind, Randomized, Controlled, Parallel-Group Dose Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact™ (SF-RI 1 surfactant for inhalation combined with a dedicated drug delivery system) in Preterm Infants at Risk of Worsening Respiratory Distress Syndrome
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INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE:	A Partially-Blind, Randomized, Controlled, Parallel-Group Dose Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact™ (SF-RI 1 surfactant for inhalation combined with a dedicated drug delivery system) in Preterm Infants at Risk of Worsening Respiratory Distress Syndrome
PROTOCOL NUMBER:	APC-AF-CLN-002
AMENDMENT NUMBER	Amendment 8-09 March 2022

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH-GCPs and all applicable local guidelines.

_____

Principal Investigator (printed/typed)

_____ _____

Principal Investigator Signature Date

1 CLINICAL PROTOCOL SYNOPSIS

Sponsor	Aerogen Pharma
Protocol Number	APC-AF-CLN-002
Title of Study	A Partially-Blind, Randomized, Controlled, Parallel-Group Dose Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact™ (SF-RI 1 surfactant for inhalation combined with a dedicated drug delivery system) in Preterm Infants at Risk of Worsening Respiratory Distress Syndrome
Study Centers	Multicenter
Phase of Development	Phase 2b
Objectives	**Part I** **Primary Objective** To determine an optimal dose of AeroFact™ administered to preterm infants on nCPAP or nIMV vs. nCPAP or nIMV alone in reducing the incidence of intubation/cannulation and bolus surfactant instillation in the first 7 days after birth. **Secondary Objectives** • To compare the time to the first intubation/cannulation across groups for infants requiring intubation due to surfactant deficiency • To compare need for repeat surfactant dosing between groups within 7 days • To evaluate the safety and tolerability of AeroFact administered by inhalation **Part II** **Additional Objectives** • To evaluate pulmonary outcomes and respiratory resource utilization at 3, 6, 9, and 12 months corrected age • To evaluate respiratory morbidity per quarter and compare pulmonary morbidity across groups • To evaluate early neurologic Gross Motor Function Score (modified GMFS) outcomes at 12 months corrected age
Study Design	This partially-blind, randomized, controlled, parallel-group, dose-ranging study is divided into 2 Parts. Part I includes birth through 40 weeks PMA or hospital discharge (treatment) and Part II discharge through 12 months corrected age (Follow Up). **Part I** Part I is to determine the optimal dose of AeroFact administered to preterm infants on nCPAP or nIMV (Active) vs. nCPAP or nIMV alone (Control) in reducing the incidence of intubation/cannulation and bolus surfactant instillation in the first 7 days after birth. 261 preterm infants who are at risk of worsening Respiratory Distress Syndrome (RDS) will be enrolled. The AeroFact dose and dosing strategy determined in this study will be used in

	a Phase 3 definitive trial. Preterm infants who require nCPAP (either by bubble CPAP or machine CPAP) or nIMV, and meet the inclusion and no exclusion criteria, will be enrolled into the study. In the delivery room, infants will be stabilized on nCPAP/nIMV per site clinical guidelines. Once the infant has been stabilized, determined as eligible, and parental consent obtained, the infant will be block randomized in a 1:1:1 partially-blind fashion to receive one of two doses of AeroFact or Control. The randomization will be stratified by site and two gestational age groups (26 0/7 to 28 6/7 and 29 0/7 to 31 6/7 weeks). Patients who meet all inclusion and no exclusion criteria and are randomized to receive an Active dose, will have the initial assigned treatment administered within the first twenty-four hours after birth. Patients who are assigned to the Control group will continue to receive nCPAP/nIMV. If twins or triplets are enrolled, only the first sibling will be randomized and subsequent siblings will receive the same treatment assignment. Active treatment dose allocation will be unblinded to pharmacy and respiratory dosing staff or designees. All other hospital personnel will be blinded. Randomization will be a two-step process. Step 1: a designated member of the study staff will obtain a randomization envelope for the appropriate gestational age group, which will randomize the infant to either the Active or Control group. Step 2: active envelopes will be forwarded to the unblinded pharmacist or designee, where the active envelope will be opened and allocation to the Low or High dose group (108 mg/kg or 216 mg/kg) will be determined. Active drug dose will be calculated and dispensed according to the pharmacy manual instructions. Active drug will be administered according to study protocol. For AeroFact dosing, oxygenation, ventilation parameters, and nasal congestion/aspiration will be monitored every 15 minutes for duration of dosing or a minimum of two hours by a blinded study/staff member. Dosing tolerance will be evaluated at 4 and 24 hours after the start of each AeroFact dose. Oxygenation, ventilation parameters, nasal congestion/aspiration and dosing tolerance will also be collected after each bolus surfactant instillation at similar timepoints. AeroFact tubing/nebulizer and vial will remain in place for a minimum of 2 hours. The AeroFact delivery system will be removed from the patient's bedside after dosing has been completed or a minimum of 2 hours. The patient may be transitioned back to their standard nCPAP interface. A new AeroFact drug delivery circuit must be used for each dose administered. Infants receiving active drug will continue on nCPAP/nIMV after dose completion. If oxygenation and ventilation requirements increase within 96 hours of birth, AeroFact administration may be repeated up to three times for a total of 4 doses over the first 96 hours after birth. Re-dosing of AeroFact (same randomized group) will be allowed if the RSS is 1.5 to 2.39 and at least two hours have elapsed since the start of the previous dose: • If FiO2 > 0.23, re-dosing will occur. • If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator. SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups. Infants randomized to the Control group will be clinically managed until the criteria for treatment escalation have been met. If at any time the criteria for treatment escalation are met in any of the three treatment arms, intubation and/or bolus instillation of surfactant may be administered at the discretion of the clinical team. Criteria for treatment escalation for AeroFact or Control groups include any of the

	following: • Respiratory Severity Score (RSS) ≥ 2.4 • Partial Pressure of Carbon Dioxide (PCO_2) > 65 mg Hg and/or pH < 7.20 • Base deficit > 10 mEq/L, on two blood gases 4 hours apart • nCPAP > 8 cm • Three severe apneas with bradycardia within six hours requiring escalation of support • Infant's work of breathing has increased warranting escalating therapy, but infant does not meet RSS or other criteria above. Study treatment will be discontinued if any of the following occur: 1. Pneumothorax *(requiring chest tube)* 2. Pulmonary hemorrhage *(frank bleeding from the lungs that is not related to irritation due to suctioning or infection)* 3. Infant shows evidence of pulmonary hypertension requiring iNO Each infant will be clinically assessed and evaluated per protocol during their stay in the NICU, to 40 weeks PMA or discharge, whichever comes first. **Part II** Patients who survive to 40 weeks PMA or discharge will be eligible for Part II. Part II will begin at discharge/40 weeks PMA and include telephone Questionnaires performed at 3, 6, 9 and 12 months corrected age . Evaluation of home environment, respiratory support, medical history, modified GMFS and respiratory resource utilization after discharge will be collected. (See Appendices for Questionnaires)
Number/Type of Subjects	Approximately 261 (87 per study arm) subjects will be block randomized in a 1:1:1 allocation. This number will be reassessed at the interim analysis.
Inclusion Criteria	Preterm infants are eligible for this study if they meet all of the following criteria: 1. Parental consent obtained prior to study procedures being performed (pre-natal consent is allowed) 2. 26 0/7 to 31 6/7 weeks of gestational age 3. Weight < 2000 grams 4. Weight appropriate for gestational age (AGA 3% to 97%) 5. Age ≤ twenty-four hours at the initiation of study treatment 6. RSS (MAP x FiO2) 1.4 – 2.0 on nCPAP or nIMV 7. Chest radiograph or lung ultrasound [13,14] consistent with a diagnosis of RDS
Exclusion Criteria	Preterm infants are **NOT** eligible for this study if they meet any of the following criteria: 1. Apgar score ≤ 5 at five minutes after birth 2. Need for chest compressions or administration of epinephrine or bicarbonate in the delivery room 3. Premature rupture of membranes (PROM) > 14 days, 4. *Criterion Removed* 5. Base deficit > 10 mEq/L on clinically indicated blood gas at time of randomization

	6. Need for intubation and/or mechanical ventilation prior to enrollment 7. HFNC and RAM Cannula or are not allowed to determine eligibility 8. Prior instillation of surfactant 9. Enrollment in another treatment study with competing outcomes 10. Active pneumothorax requiring chest tube 11. Significant congenital anomaly 12. Known or suspected chromosomal abnormality 13. Other etiologies of respiratory distress (e.g. meconium aspiration syndrome, hydrops fetalis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex) 14. Concomitant treatment with inhaled nitric oxide 15. Suspected PPHN with sustained pre/post SpO2 ductal differences > 10%
Study Treatment(s)	Infants will be block randomized in a 1:1:1 fashion to Active or Control. Stratification across all groups will be by site and gestational age (26 0/7 to 28 6/7 and 29 0/7 to 31 6/7 weeks). Patients randomized to Active drug will receive 1 of 2 nominal dose levels of AeroFact (108 mg/kg or 216 mg/kg). Up to three additional doses of AeroFact within 96 hours of birth will be allowed if RSS is 1.5 to 2.39 and at least two hours have elapsed since the start of the previous dose: • If FiO2 > 0.23, re-dosing will occur. • If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator. SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups. All infants randomized will be clinically managed until the criteria for treatment escalation have been met.
Concomitant Therapy	The use of Vitamin A or corticosteroids for BPD prophylaxis must be consistent, and appropriate for age, for all enrolled infants within each study site. The routine use of corticosteroids for blood pressure (BP) or adrenal support should be avoided during the first 96 hours after birth. HFNC and RAM Cannula are not permitted in the first 96 hours of life.
Duration of Treatment	The duration of study participation for each infant is as follows: **Part I:** • Treatment Period: 96 hours • Study Period: Through 40 weeks PMA or Discharge from NICU (whichever comes first) **Part II:** • Follow-Up Period: 12 months corrected age
Criteria for Evaluation	**Efficacy Assessments** **Part I:** <u>Primary Efficacy Endpoint</u> • Proportion of infants requiring intubation/cannulation and bolus surfactant instillation in the first 7 days of life.

	Secondary Efficacy Endpoints • Time to first intubation/cannulation and bolus surfactant instillation between study treatments for first 7 days of life • Compare the proportion of infants across groups receiving multiple doses of surfactant. • Number of days on mechanical ventilation from the day of birth to 40 weeks PMA or discharge. • Number of days on supplemental oxygen administration from the day of birth to 40 weeks PMA or discharge • Survival without bronchopulmonary dysplasia (BPD) at 36 and 40 week PMA. (If an infant is discharged from the NICU prior to 36 and/or 40 weeks, a study member will call the family to verify the respiratory support status.) **Safety and Tolerability Assessments** Safety and tolerability will be assessed through the monitoring of oxygenation, bradycardia, nasal congestion/aspiration, and other adverse events of interest (AEs) to 40 weeks PMA or discharge. Incidence of comorbidities of prematurity/AE's will be assessed. Tolerance of the AeroFact dosing administration and all doses of bolus surfactant will be assessed during and up to 24 hours following dosing. **Part II:** Additional Efficacy Endpoints • Assessment of pulmonary outcomes at 3, 6, 9 and 12 months corrected age • Length of NICU Stay (LOS) • Proportion of subjects with any respiratory resource utilization at 3, 6, 9 and 12 months corrected age • Respiratory morbidity per quarter till 12 months of corrected age • Assessment of modified GMFS (early neurologic) at 12 months of corrected age
Criteria for Individual Patient Discontinuation	Aerogen Pharma, the Investigator or parent (s) may discontinue pre-term infants from the study at any time for the following reasons: • Safety • Withdrawal of parental consent • At the discretion of the Investigator
Statistical Considerations	**Randomization, Stratification and Sample Size:** Two hundred and sixty-one (261) subjects (87 in each arm) will be randomized in a 1:1:1 ratio in order to assure that 246 subjects (82 in each arm) complete the study. The randomization will be stratified by site and gestational age. Infants requiring treatment escalation in the AeroFact dose groups is estimated to be 20% and in the control group is estimated to be 40%, with an odds ratio of 0.375. Under the above assumptions, 82 subjects in each treatment group will be required, to meet the Type I error rate of 0.05 and 80% statistical power. To accommodate the potential dropouts, a 5% dropout rate is included in this sample size calculation. **Analyses Populations:**

	Intent-to-Treat (ITT) population: The Intent-to-Treat (ITT) population is defined as all randomized subjects. The ITT population will be the primary population for the primary, secondary and additional efficacy analysis. **Per Protocol (PP) population**: The Per Protocol (PP) population is defined as all randomized subjects who were not associated with a major protocol violation. The PP analysis of primary, secondary and additional endpoints will be considered supportive. **Safety population:** The Safety population is defined as all randomized subjects . This population will be used for the analysis of safety parameters.
Interim Analysis	A blinded interim analysis is planned and will be conducted when approximately 60% of subjects have been randomized and completed first 7 days of life or early terminated, whichever occurs first. The main purpose of this interim analysis will be: • sample size re-assessment to evaluate the final sample size needed to proceed with the study based on the control responder rate at interim analysis, and;to evaluate the safety of AeroFact on the frequency of adverse events, nasal congestion/aspiration, dosing tolerance events, and serious adverse events
Efficacy Analyses	The primary analyses of the primary, secondary, and additional efficacy endpoints will be conducted on the ITT population. The PP population analyses of primary, secondary, and additional endpoints will be considered supportive. For the efficacy endpoints the data will be summarized and compared according to the variable type: • Continuous data summaries will include: o Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values. o Analysis of Covariance (ANCOVA) or Mixed Model Repeated Measures (MMRM) adjusted for stratification factors for inferential statistics. • Categorical data summaries will include: o Frequency counts and percentages o Logit model or Generalized Estimating Equation (GEE) method adjusted for stratification factors and clustering of multiple births within a mother for inferential statistics • Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and to depict the time to event data.
Safety Analyses	Safety will be evaluated on the Safety Population. The number and percent of infants experiencing TEAEs, serious adverse events, and TEAEs leading to study discontinuation will be summarized for each treatment group by Medical Dictionary for Regulatory Affairs (MedDRA) system organ class and/or preferred term. Additional summaries will include TEAE severity and relationship to study drug.
PK Sampling	Not applicable

Table 1 – Schedule of Assessments and Procedures – Part I and Part II

Part I								Part II
		Day 1	Day 2-4	Day 5 – Day 28	36 Weeks PMA	40 Wks PMA	Discharge	3, 6, 9, 12 Months Corrected Age
Informed Consent[1]	X							
Demographics		X						
Maternal/Infant Medical History		X						
Chest Radiograph or Lung Ultrasound		X						
Medication History		X						
Inclusion/Exclusion Criteria		X						
Randomization		X						
Clinical Blood Gas Assessments[2]		X	X					
Weight, Recumbent Length, Head Circumference[3]		X					X	X
Administer AeroFact or begin nCPAP/nIMV alone[4-5,]		X	X					
Oxygenation and Respiratory Parameters[6-7]		X	X	X	X[8]	X[8]		
Nasal Congestion Assessment[9]		X	X					
Dosing Tolerance[10]		X	X					
AE/Co-Morbidities Monitoring		X	X	X	X		X	
Concomitant Medications		X	X	X	X		X	
Feeding Status/Pulmonary Questionnaire/Audiology/Opthalmology Reports							X	
Room Air Challenge (RAC) [11]					X	X		
Follow-Up Telephone Questionnaire[12]								X

[1] Informed consent may be obtained prenatally

[2] Blood gases (pH, PCO_2, PO_2, HCO3-, base deficit) will be obtained prior to enrollment and intubation or in relationship to an SAE (if clinically obtained).

[3]Recumbent Length and Head Circumference at birth and discharge from NICU only

[4]AeroFact administered by nCPAP/nIMV or nCPAP/nIMV alone is to be initiated within 24 hours after birth. The anticipated duration of each AeroFact dosing is approximately approximately 2 hours.

[5] Re-dosing of AeroFact will be allowed if the RSS to maintain SpO_2 between 90 and 95% is 1.5 to 2.39 and at least two hrs. have elapsed since the start of the previous dose. If RSS is in range and FiO2 >0.23, re-dosing will occur. If RSS is in range and FiO2 is ≤0.23, re-dosing may occur at the discretion of the investigator. Up to 3 additional doses of AeroFact within 96 hrs. will be allowed.

[6] Oxygenation and respiratory parameters (FiO_2, SpO_2 [%], Positive-End Expiratory Pressure [PEEP]/CPAP [cm H_2O], Flow Rate [L/min], Mean Airway Pressure [Paw in cm H_2O], and Respiratory Support Status) will be obtained prior to dosing with AeroFact

delivery, every 15 minutes from the start of AeroFact dosing (T_0 to end of dose or a minimum of 2 hours). These parameters will be collected after the start of AeroFact administration or bolus instillation of surfactant for all groups.

[7] Days 1-7 oxygen and resp. parameters will be obtained q 8 hrs., followed by daily from Days 8-28 and daily from 35 to 37 Wks. PMA and 39 through 40 Wks. PMA, Monitoring of O_2/resp parameters will occur at the same frequency for all groups.

[8] Respiratory Support Status at 36 & 40 weeks PMA will be assessed by telephone if patient was discharged prior to that timepoint.

[9] Nasal congestion/nasal aspiration will be assessed prior to and during each AeroFact dose or bolus instillation of surfactant for all groups.

[10] Dosing tolerance completed at 4 and 24 hrs. after start of AeroFact administration or bolus instillation of surfactant for all groups.

[11] RAC will be performed if infant is on nasal cannula $\leq$ 2 L/min and oxygen or nasal cannula < 4 L/min in room air.

[12] Pulmonary outcomes will be assessed at 3, 6, 9 and 12 months corrected age and Neurologic Outcomes at 12 months corrected age. See Appendix II

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
AF	AeroFact
AGA	Appropriate for Gestational Age
APC	Aerogen Pharma Corporation
BiPAP	Bilevel Positive Airway Pressure
BP	Blood Pressure
BPD	Bronchopulmonary Dysplasia
CFR	Code of Federal Regulations
CLN	Clinical
CMV	Continuous Mandatory Ventilation
Corrected Age	Chronological Age - Weeks Premature
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
Cystic PVL	Cystic Periventricular Leukomalacia
DSMB	Data Safety Monitoring Board
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GMFS	Gross Motor Function Score (Modified)
HFJV	High Frequency Jet Ventilation
HFNC	High Flow Nasal Cannula
HFOV	High Frequency Oscillatory Ventilation
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ITT	Intention to Treat
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
IP	Investigational Product
kg	Kilogram
LOS	Length of Stay
MAP	Mean airway pressure

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	Minute
MOP	Manual of Procedures
NC	Nasal Cannula
nCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
nIMV	Nasal Intermittent Mandatory Ventilation
O_2	Oxygen
OTC	Over-the-Counter
PCO_2	Partial Pressure of Carbon Dioxide
PO_2	Partial Pressure of Oxygen
Paw	Mean Airway Pressure
PDA	Patent Ductus Arteriosus
PEEP	Positive-End Expiratory Pressure
PHT	Pulmonary Hypertension
PIE	Pulmonary Interstitial Emphysema
PIP	Peak Inspiratory Pressure
PMA	Postmenstrual Age
PPP	Per Protocol Population
PPHN	Persistent Pulmonary Hypertension in the Neonate
PROM	Premature Rupture of Membranes
RAC	Room Air Challenge
RDS	Respiratory Distress Syndrome
Respiration Sensor	aka Breath Sensor
ROP	Retinopathy of Prematurity
RR	Respiration Rate
RSS	Respiratory Severity Score = *CPAP or MAP (cm H_20) x $Fi0_2$*
SAE	Serious Adverse Event
SE	Standard Error
SOP	Standard Operating Procedures
SpO_2	Oxygen Saturation
TEAE	Treatment-Emergent Adverse Event
TLD	Target Lung Dose
T_0	Start of AeroFact dose
WHO	World Health Organization

2 BACKGROUND AND RATIONALE

2.1 Introduction

Aerogen Pharma is developing AeroFact, an investigational drug/device combination product consisting of lyophilized bovine-origin surfactant SF-RI 1 (sold in Europe since 1989 under the proprietary name AlveoFact®) administered following reconstitution to a 45 mg/ml suspension with semi-isotonic saline buffer using a proprietary breath-actuated vibrating mesh nebulizer with a nasal cannula interface.

Current surfactants used for prevention or treatment of Respiratory Distress Syndrome (RDS) in preterm infants are approved for delivery only as a liquid bolus instillation via an endotracheal tube (ETT) while intubated/cannulated. Intubation and cannulation with a tube into the trachea for surfactant administration are associated with adverse events (AEs) [1,2,3]. Access to surfactant therapy without invasive procedures that further exacerbate the condition is therefore a major unmet medical need in this vulnerable population. Reports suggest that AEs caused by intubation or cannulation can be avoided if there is a means of non-invasive delivery, i.e. aerosolized surfactant delivered through nasal continuous positive airway pressure (nCPAP) [5].

Current therapies for RDS in preterm infants are associated with the following challenges:

- Endotracheal intubation of preterm infants is an invasive procedure associated with airway tissue trauma, vagal stimulation, hypoxia, and bradycardia [1,2,3]. Additionally, insertion of small catheters into the infant trachea and positioning above the bifurcation can be traumatic. Both techniques require specialized skills, medical support, and training that must be kept current via frequent practice.
- Liquid bolus surfactant instillation via ETT is associated with airway obstruction (due to the large volume of liquid relative to preterm infant lung volumes) and transient physiological events such as hypoventilation, hyperventilation, changes in systemic blood pressure, alterations of cerebral blood flow, and other pulmonary and neurological effects.
- Respiratory support with nCPAP alone, albeit less traumatic compared to intubation/mechanical ventilation, results in delayed delivery of surfactant or absence of exogenous surfactant administration. This can lead to:
    - Atelectasis
    - Stress within the lungs associated with pneumothoraxes and bronchopulmonary dysplasia (BPD)
    - Increased fraction of inspired oxygen (FiO_2) requirements, which are associated with lung toxicity and ophthalmic vascular changes leading to Retinopathy of Prematurity (ROP)
    - Ventilation/perfusion mismatching resulting in intra-pulmonary and intra-cardiac shunts

In summary, as practice has evolved, many clinicians avoid subjecting preterm infants to risk of intubation/cannulation and instillation of liquid bolus surfactant until RDS has progressed to moderate or severe levels.

2.2 AeroFact

2.2.1 Nonclinical Experience

SF-RI 1 (the drug component of Aerofact) delivered as a bolus instillation has been assessed in a series of nonclinical studies in order to gain regulatory approval in several European countries and territories around the world. (Please refer to the Investigator's Brochure on non-clinical trials conducted with Alveofact). These nonclinical studies have been deemed acceptable to support the safety of SF-RI 1 for intratracheal bolus instillation in preterm neonates.

Several studies comparing IT instillation of surfactant to nebulized surfactant indicate potential advantages to inhaled aerosol therapy. Efficacy has been demonstrated by the Sponsor, using aerosolized SF-RI 1. In these studies, using a breath synchronized vibrating mesh nebulizer, similar to the clinical delivery platform, rabbits with surfactant depleted lungs from repeated saline washes, showed improvement in the oxygenation index and ventilation efficiency index after intratracheal delivery of aerosolized SF-RI 1. These data support the safe use of aerosolized SF-RI 1 in preventing progression of infant respiratory distress syndrome (RDS) when delivered either as a bolus instillation or as an aerosol.

Because SF-RI 1 administration with Aerofact is by a new route (nebulized aerosol passing through the neonate's nose to be delivered to the lungs), the potential toxicity of SF-RI 1 to the nasal cavity, and general lung tolerability, were evaluated by the Sponsor in support of the proposed clinical development program. Specifically, the toxicity and local tolerability of SF-RI 1 were assessed in two 14-day GLP studies, one in post-weanling Sprague Dawley rats and one in post-weanling New Zealand White rabbits. For these studies, nose only inhalation was used as this is the intended clinical route. Additionally, the drug was administered daily for 14 consecutive days, which exceeds the frequency of dosing in the clinical situation. The high dose in the 14-day animal studies was determined by using the maximum feasible concentration for SF-RI 1 in an attempt to obtain an acceptable margin over the anticipated clinical dose. In both studies standard parameters were assessed including, body weight, food consumption, clinical observations, clinical pathology (hematology, coagulation and clinical chemistry) and ophthalmology, as well as a complete necropsy and histopathology of over 50 tissues. No adverse effects were observed in any standard assessment of toxicity, including the electrocardiogram. Technical issues with the rabbit study resulted in lower-than-targeted aerosol exposure. Inflammation and increased alveolar macrophages were present in all treatment groups including the control. Therefore, a No-Observed-Adverse-Effect-Level (NOAEL) was not determined. In rats, based on the absence of any adverse findings in any of the measured parameters, the NOAEL from 14 days of nose-only inhalation of SF-RI 1 was considered to be the maximal feasible dose of 1,223 mg/kg/day.

2.2.2 Clinical Experience

More detailed summaries of AeroFact clinical experience can be found in the Investigator Brochure.

APC-AF-CLN-001, a Phase 2a study of AeroFact, was performed in three clinical centers in Australia. Only two of the centers enrolled subjects. The third site withdrew from the study prior to enrolling any subjects. The enrollment period was 21 November 2017 to 1 August 2018. The study was An Open-Label Study of the Safety and Tolerability of AeroFact™ (Aerosolized Alveofact®) in Preterm Infants on nCPAP at Risk of Worsening Respiratory Distress Syndrome.

The study was conducted in 2 parts, Part I, single dose and Part II, multiple dose. Each part was conducted in a separate group of preterm infants.

Infants who were 26 0/7 to 30 6/7 weeks gestational age at birth, required CPAP or nIMV after the delivery room, and satisfied the inclusion and exclusion criteria were enrolled within two hours into this study. For each enrolled infant, retrospective data was collected on 3 comparative infants of the same gestational age who were born within the two previous years.

AeroFact treatment failure criteria for intubation and bolus instillation of surfactant were one or more of the following:

1. RSS $\geq$ 2.4
2. PCO_2 > 65 mmHg and/or pH < 7.20
3. nCPAP > 8 cm
4. Three severe apneas with bradycardia within six hours requiring escalation of support

Infants were followed for their need for AeroFact and/or bolus dosing of surfactant. Tolerance of Aerofact dosing had the following data collected: changes in respiratory support over the first 28 days of life, BPD status at 36 weeks PMA and co-morbidities of prematurity/AEs monitored until the time of discharge.

2.2.2.1 APC-AF-CLN-001 Part I

Part I of the study was designed to determine the safety and tolerability of administering a single nominal dose of 216 mg/kg of aerosolized AeroFact (SF-RI 1) by nCPAP. Ten preterm infants who required nCPAP (machine CPAP) and satisfied the inclusion and exclusion criteria were enrolled into this part of the study.

After successful completion of Part I and a proceed recommendation by an Independent Data Safety Monitoring Board (DSMB), sites were permitted to begin enrollment into Part II of the study.

2.2.2.2 APC-AF-CLN-001 Part II

Part II of the study was designed to determine the safety and tolerability of administering up to four doses of aerosolized AeroFact (SF-RI 1) by nCPAP. Twenty (21) preterm infants were enrolled into this part of the study.

An initial nominal dose of 216 mg/kg of aerosolized SF-RI 1 was administered. Oxygenation and ventilation parameters were monitored as outlined in the protocol. Infants continued on nCPAP. Re-dosing of AeroFact (nominal dose of 216 mg/kg) occurred if the RSS to maintain SpO_2 between 90% and 95% (as measured by pulse oximetry) $\geq$ 2.0 and at least (1) 2 hours elapsed since the end of the first dose and (2) 4 hours elapsed since the end of either the second or third dose. Up to 3 additional doses of AeroFact within 96 hours were allowed.

2.2.3 Summary of Clinical Results

2.2.3.1 APC-AF-CLN-001-Safety Analysis Conclusions:

- The overall incidence of TEAEs was low among AeroFact patients; 3 patients (30%) had 1 or more TEAE(s) in Part I, and 5 patients (23.8%) had 1 or more TEAE(s) in Part II.
- There were no TEAEs which were assessed by the Investigator as related to the study drug, device, or procedure, and none led to premature discontinuation from the study drug or premature discontinuation from the study.
- The most common TEAEs reported were patent ductus arteriosus occurring for 1 patient (10%) in Part 1 and for 3 patients (9.5%) in Part II, and pneumothorax occurring for 1 patient (10%) in Part 1 and 1 patient (4.8%) in Part II.
- All TEAEs in Part I were mild and the majority of TEAEs in Part II were mild with a severe TEAE occurring in 1 patient (4.8%) (pulmonary hemorrhage identified after intubation).
- During Day 1 to study Day 4, following AeroFact dosing, there was 1 occurrence (10%) of moderate nasal congestion in Part I, and 5 occurrences (23.8%) of moderate nasal congestion and 1 occurrence (4.8%) of severe nasal congestion in Part II of the study. Nasal aspiration occurred in 2 patients (9.5%) in Part II on Day 1 in the study. Neither nasal congestion or nasal aspiration data were available from the historical control patients for comparison.
- One patient in Part I and 1 patient in Part II of the study had an SAE. Both patients had the SAE of culture-proven sepsis, which was not related to the study drug, the device, or the procedure, did not emerge during the treatment period, and resulted in death.
- Generally, the incidence of AEs associated with dosing tolerance in the first 24 hours was low; the incidence of AEs for AeroFact only vs. AeroFact plus bolus surfactant demonstrated comparability.
- The incidence of post-dose comorbidities of prematurity and AEs was low and consistent between the patients treated with AeroFact vs. historical controls.

2.2.3.2 APC-AF-CLN-001-Efficacy Analysis Conclusions:

- At 36 Weeks PMA, a larger proportion of patients receiving AeroFact in Part I and Part II of the study survived without BPD (88.9% and 78.9%, respectively) compared with Part I and Part II historical control patients (73.3% and 66.7%, respectively).
- The median (range) length of stay in the NICU for AeroFact patients in Part I and Part II was comparable to historical control patients.
- For AeroFact patients in Part I and Part II, the median time-to-failure using AeroFact criteria was consistently numerically greater than for historical control patients.
- For AeroFact patients in Part II, the median time-to-instilled surfactant was consistently numerically greater than for Part II historical control patients.
- No patients in the AeroFact group or in the historical control group required instilled surfactant after 72 hours of life.

- For patients receiving AeroFact treatment in Part II, the proportion of patients requiring rescue with instilled surfactant was lower than for the matched historical controls (25% vs 45%); this corresponded to a relative risk of 0.56, in favor of AeroFact treatment.

Study APC-AF-CLN-001 overall conclusions:

- Administration of AeroFact, up to 4 doses within 96 hours of life, was shown to be safe and well tolerated in patients ranging from 26 2/7 weeks to 30 4/7 weeks of gestational age and with weights between 640 to 1,664 grams.
- No AeroFact-treated patients in Part I or Part II of the study, or among the matched historical controls, received instilled surfactant beyond 72 hours of life.
- The need for rescue therapy by instilled bolus surfactant was lower in Part II of the study compared with matching historical controls; 5 AeroFact patients (25%) in Part II required rescue with surfactant bolus instillations vs. 27 patients (45%) who required instillations in the matching historical control group; this corresponded to a relative risk of 0.56, in favor of AeroFact treatment.

2.2.4 Summary of Pharmacokinetic Results

Pharmacokinetic studies are not applicable.

2.2.5 Summary of Known and Potential Risks of Aerosolized Surfactant Administration

Experimental use of inhaled surfactant is reported in the clinical literature and this use is expanding (Pillow and Minocchieri 2012, Minocchieri, Knoch et al. 2013, Minocchieri, Berry et al. 2018). Current publications indicate feasibility and safety of inhaled surfactant for managing preterm infants at risk for worsening RDS. SF-RI 1 was shown to have a significant effect on oxygenation, and none reported treatment-related AEs (Jorch, et al, 1997). As suggested, aerosolized surfactant is expected to augment current nCPAP therapy (Pillow and Minocchieri 2012, Soll, Edwards et al. 2013, Carlo 2014, Polin, Carlo et al. 2014) by delivering an effective surfactant dose, while minimizing the negative impacts of the current treatments for RDS.

The completed Phase 2a AeroFact™ study of inhaled SF-RI 1surfactant with nCPAP also showed no treatment-related AEs and appears safe and well tolerated.

2.2.6 Dosing Rationale for AeroFact

Marketed single doses of instilled Alveofact are 54 to 108 mg/kg. AeroFact dose selection was based on 50% delivery device efficiency from a nominal dose of 108 mg/kg and 216 mg/kg and additional approximetly 50% of the inhaled dose being delivered to lungs vs. the nasal passages. The maximal feasible dose determined in toxicology studies was 1,223 mg/kg/day.

This supports clinical dosing of up to a nominal dose of 864 mg/kg/day or 432 mg/kg/day (i.e. up to 4 doses in 96 hours after birth).

2.2.7 Risk Assessment

2.2.7.1 Risks to Subjects

The Sponsor has conducted risk analysis and the following clinical harms with overall high unmitigated risk have been identified:

- Hypoventilation, bradypnea, hypoxemia
- Progression of RDS (in the event of under-dosing)
- Skin irritation
- Pneumothorax, volutrauma

These clinical risks will be properly controlled and/or mitigated relative to the device design e.g. implementation of alarms, verification testing or labeling (instructions, warnings and cautions) prior to clinical trials on infants.

Furthermore, the drug delivery system will be tested for its safety following ISO and IEC standards for materials, biological and electrical safety, and electromagnetic compatibility.

The toxicology program in two species of newborn animals did not identify any risks with the dose or the route of administration.

The most common side effects reported when premature infants are given surfactant through the ETT or cannula are:

- decreases in oxygen saturation (SpO_2)
- plugging of breathing tube
- decreases in heart rate, reflux of surfactant into the breathing tube
- the need for extra mechanical breaths to be given from the breathing machine

These events are generally brief and not associated with serious complications or death.

Risks of aerosolized surfactant are unknown. However, due to the small aerosol size and gradual nature of the liquid aerosol administration, they are expected to be less than those associated with administration through an ETT/or cannula. The surfactant will be given by skilled caregivers in the NICU who can respond to all of these potential side effects should they occur.Risks of using the AeroFact drug delivery system are detailed in the Investigator's Brochure.

2.2.7.2 Benefits to Subjects

There is no guarantee that the infant will receive direct benefit from his/her participation in this study. Infants will have a 66% chance of receiving study drug. The benefits of being in this study may be the possibility that administering AeroFact may improve lung function and decrease the need for increases in respiratory support. Participation may provide information that may benefit other premature babies by helping to determine the safety and efficacy of aerosolized surfactant.

3 STUDY OBJECTIVES

3.1 Part I – Study Objective

3.1.1 Part I-Primary Objective

- To determine an optimal dose of AeroFact™ administered to preterm infants on nCPAP or nIMV vs. nCPAP or nIMV alone in reducing the incidence of intubation/cannulation and bolus surfactant instillation in the first 7 days after birth

3.1.2 Part I - Secondary Objectives

- To compare the time to the first intubation/cannulation across groups for infants requiring intubation due to surfactant deficiency
- To compare need for repeat surfactant dosing between groups within 7 days
- To evaluate the safety and tolerability of AeroFact administered by inhalation

3.2 Part II – Additional Objectives

- To evaluate pulmonary outcomes and respiratory resource utilization at 3, 6, 9, and 12 months corrected age.
- To evaluate respiratory morbidity per quarter and compare pulmonary morbidity across groups
- To evaluate early neurologic (modified GMFS) outcomes at 12 months corrected age

4 OVERALL STUDY DESIGN AND PLAN

The partially-blind, randomized, parallel-group, dose-ranging study is divided into 2 Parts. Part I includes birth through hospital discharge or 40 weeks PMA and Part II discharge through 12 months corrected age (Follow Up).

4.1 Part I

Part I is to determine the optimal dose of AeroFact compared to nCPAP or nIMV alone in reducing the incidence of intubation/cannulation and bolus surfactant instillation in the first 7 days after birth. 261 preterm infants who are at risk of worsening Respiratory Distress Syndrome (RDS), will be enrolled. The AeroFact dose and dosing strategy determined in this study will be used in a Phase 3 definitive trial. Preterm infants who require nCPAP (either by bubble CPAP or machine CPAP) or nIMV, and meet all inclusion and no exclusion criteria, will be enrolled into the study.

In the delivery room, infants will be stabilized on nCPAP/nIMV per site clinical guidelines. Once the infant has been stabilized, eligibility determined, and parental consent obtained, the infant will be block randomized in a 1:1:1 partially-blind fashion to receive one of two doses of AeroFact (Active) or Control. The randomization will be stratified by site and two gestational age groups (26 0/7 to 28 6/7 and 29 0/7 to 31 6/7 weeks). Patients who meet all inclusion, no exclusion criteria and are randomized to receive Active dose, will have the assigned treatment administered within first twenty-four hours after birth. Patients who are assigned to the Control group will continue to receive nCPAP/nIMV. If twins or triplets are enrolled, only the first sibling will be randomized

and subsequent siblings will receive the same treatment assignment. The Neonatal Intensive Care Unit (NICU) staff, the Principal Investigator (PI), the infant's family, and the sponsor will be blinded to AeroFact treatment allocation.

The study treatment allocation will be designated as either Active or Control. The Neonatal Intensive Care Unit (NICU) staff, the Principal Investigator (PI), the infant's family, and sponsor will be blinded to Active treatment dose allocation. Randomization will be a two-step process. Step 1: a designated member of the study staff will obtain a randomization envelope for the appropriate gestational age group, which will randomize the infant to either the Active or Control group. Step 2: active envelopes will be forwarded to the unblinded pharmacist or designee, where the active envelope will be opened and the Low or High dose group (108 mg/kg or 216 mg/kg) will be determined. Active drug dose will be calculated and dispensed according to the pharmacy manual instructions.

Active drug will be reconstituted according to the AeroFact package insert instructions or the pharmacy/respiratory therapy manual. Active study drug doses distributed by the pharmacy or designee will be labelled with patient ID. Parameters required to set up the AeroFact delivery system to administer the proper study treatment regimen (patient weight and mg/kg) will be programmed into the controller by the unblinded member of the study staff. For active drug doses, an unblinded study member will set up the AeroFact delivery system. The AeroFact system will be primed and set to deliver the appropriate dose. If the infant is randomized to Control, the infant will continue to receive nCPAP/nIMV.

While preparing the set-up for the AeroFact system, a privacy screen will be placed around the delivery system to ensure the blind is maintained. Once the system is set up, the privacy screen will be moved aside to allow access to the infant and controller. Prior to aerosol administration, infant will be transitioned from their standard CPAP/nIMV to the AeroFact interface. Administration of AeroFact will be managed by the unblinded staff member. When adjustment of the AeroFact system is required (drug vial change, alarms, etc.), a privacy screen should be utilized to mask the treatment allocation.

Oxygenation, ventilation parameters, and nasal congestion/aspiration will be monitored every 15 minutes for the duration of dosing or a minimum of two hours after the start of dosing by a blinded study or staff member. Dosing tolerance will be evaluated at 4 and 24 hours after the start of each AeroFact dose. AeroFact aerosol delivery will be stopped at the time of dose completion, but AeroFact tubing/nebulizer and vial will remain in place for a minimum of 2 hours. The AeroFact delivery system will be removed from the patient's bedside after dosing is completed or 2 hours have elapsed (whichever is longer) and patient may be transitioned back to their standard nCPAP circuit. A new drug delivery circuit must be used for each subsequent dose administered.

Infants receiving active drug will continue on nCPAP/nIMV after dose completion. If oxygenation and ventilation requirements increase within 96 hours after birth, AeroFact administration may be repeated up to three times for a total of 4 doses over the first 96 hours after birth. Re-dosing of AeroFact (same randomized group) will be allowed if the RSS to maintain SpO_2 between 90 and 95% is 1.5 to 2.39 and at least two hours have elapsed since the start of the previous dose:

- If FiO2 > 0.23, re-dosing will occur.
- If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator.

SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups. All infants randomized will be clinically managed until the criteria for treatment escalation have been met. If at any time the criteria for treatment escalation are met in any of the three treatment arms, intubation and/or bolus instillation of surfactant may be administered per site's standard of care. Oxygenation, ventilation parameters, nasal congestion/aspiration and dosing tolerance will be collected for each bolus instillation of surfactant.

Criteria for treatment escalation for AeroFact or nCPAP/nIMV only therapy includes any of the following:

1. Respiratory Symptom Severity (RSS) ≥ 2.4
2. Partial Pressure of Carbon Dioxide (PCO_2) > 65 mg Hg and/or pH < 7.20
3. Base deficit > 10 mEq/L, on two blood gases 4 hours apart
4. nCPAP > 8 cm
5. Three severe apneas with bradycardia within six hours requiring escalation of support
6. Infant's work of breathing has increased warranting escalating therapy, but infant does not meet RSS or other criteria above.

Data on all enrolled infants will be assessed through 40 weeks PMA or discharge from the NICU. Information to include: maternal/infant delivery, resuscitation history, oxygenation/ventilation parameters, concomitant medications of interest, and safety. Oxygenation and ventilation mode/parameters routinely monitored q 8 hours through Day 7, daily days 8 through 28, and daily at weeks 35 to 37 and 39 to 40 PMA/discharge. If an infant is discharged from the NICU prior to 36 and/or 40 weeks, a study member will call the family to verify the respiratory support status.

Co-morbidities of prematurity (e.g.: pneumothorax, IVH, PDA, NEC, sepsis, etc.) and adverse events (treatment-related or otherwise) will be collected to 40 weeks PMA/Discharge.

4.2 Part II – Follow-Up

Part II will begin at discharge and be based on telephone questionnaires performed at 3, 6, 9 and 12 months corrected age. Evaluation of home environment, asthma, respiratory support, medical and family history, and respiratory resource utilization after discharge will be collected. A modified GMFS is included in the questionnaire collected at 12 months.

Part II Follow Up Questions	**3 months**	**6 months**	**9 month**	**12 months**
Respiratory symptoms	X	X	X	X
Dr visit/ER/hospital visit	X	X	X	X
Oxygen/ventilator use	X	X	X	X
Respiratory Medications	X	X	X	X
Home living situation	X	X	X	X
Type and route of feedings		X		X
Care outside home		X		X
Smoking in home		X		X
Family/social history				X
Medical history, vision hearing				X
Medications for chronic conditions				X
Allergies				X
Motor milestones				X
Growth parameters				X
Modified Gross Motor Function Score				X

4.3 Screening

The purpose of Screening is to ensure that each infant meets all the specified inclusion and none of the exclusion criteria. Screening is conducted for Part I only. Any subject enrolled who participated in Part I will continue into Part II.

4.4 Treatment

4.4.1 Part I

In the two active arms of this study, nominal doses of 108 mg/kg or 216 mg/kg aerosolized SF-RI 1 will be administered by a dedicated drug delivery system to infants who are receiving nCPAP/nIMV. A maximum of four doses over 96 hours will be permitted. Re-dosing will be allowed if the RSS to maintain SpO_2 between 90% and 95% is 1.5 to 2.39 and at least 2 hours have elapsed since the start of the previous dose:

- If FiO2 > 0.23, re-dosing will occur.
- If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator.

In the control arm, infants will receive nCPAP/nIMV alone as determined by their clinical team until criteria for escalation of treatment occurs. SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups.

4.4.2 Part II

No treatment is given during Part II of this study.

5 SELECTION AND WITHDRAWAL OF PATIENTS

Two hundred and sixty-one (261) preterm infants will be enrolled at approximately 45 sites. Preterm infants who do not meet all the inclusion criteria or who meet any of the exclusion criteria will not be eligible for study participation.

5.1 Inclusion Criteria

Preterm infants are eligible for this study if they meet all of the following criteria:

1. Parental consent obtained prior to study procedures being performed (pre-natal consent is allowed)
2. 26 0/7 to 31 6/7 weeks of gestational age
3. Weight < 2000 grams
4. Weight appropriate for gestational age (AGA 3% to 97%)
5. Age ≤ twenty-four hours at the initiation of study treatment (active or nCPAP/nIMV alone)
6. Current RSS (MAP x FiO2) 1.4 - 2.0 (nCPAP or nIMV)
7. Chest radiograph or lung ultrasound [~~13~~14] consistent with a diagnosis of RDS

5.2 Exclusion Criteria

Preterm infants are NOT eligible for this study if they meet any of the following criteria:

1. Apgar score ≤ 5 at five minutes after birth
2. Need for chest compressions or administration of epinephrine or bicarbonate in the delivery room
3. Premature rupture of membranes (PROM) > 14 days

4. *Criterion Removed*
5. Base deficit > 10 mEq/L on clinically indicated blood gas at time of randomization
6. Need for intubation and/or mechanical ventilation prior to enrollment
7. HFNC and RAM Cannula are not allowed to determine eligibility
8. Prior instillation of surfactant
9. Enrollment in another treatment study with competing outcomes
10. Active pneumothorax requiring chest tube
11. Significant congenital anomaly
12. Known or supected chromosomal abnormality
13. Other etiologies of respiratory distress (e.g. meconium aspiration syndrome, hydrops fetalis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex)
14. Concomitant treatment with inhaled nitric oxide
15. Suspected PPHN with sustained pre/Post SpO2 ductal differences > 10%

5.3 Re-Screening of Patients

Infants may not be enrolled more than once.

5.4 Removal of Patients from Therapy or from the Study

Study treatment will be discontinued if any of the following occur:

- pneumothorax *(requiring chest tube)* or
- pulmonary hemorrhage *(frank bleeding from the lungs that is not related to irritation due to suctioning or infection).*
- Infant shows evidence of pulmonary hypertension requiring treatment with iNO.

Aerogen Pharma, the Investigator, or the parents of the preterm infant may discontinue study drug dosing or withdraw the infant early from the study at any time for safety or administrative reasons. Infants may be withdrawn from dosing per parent request, protocol violation, worsening clinical condition, investigator decision, study terminated by sponsor, or other. Infants who discontinue study drug dosing will remain in the study for outcomes measurements, unless consent has been withdrawn.

6 STUDY TREATMENT

6.1 Identity of Investigational Product

The drug in AeroFact is SF-RI 1 which is a lyophilized bovine-origin surfactant, marketed under the name Alveofact in Germany and 25 other European and non-European countries. It is manufactured by Lyomark Pharma GmbH and has been analyzed and released according to the approved specifications. The AeroFact drug delivery system consists of reusable and single-patient components and is manufactured by Aerogen Limited in Ireland.

The clinical label will identify both the study medication and drug delivery system components by protocol number, name, lot number, Sponsor, storage conditions, and indicate that it is limited to investigational use only.

6.2 Storage Conditions

Both the vials of lyophilized SF-RI 1 and pre-filled sterile syringe containing 0.45% saline should not be stored above 30ºC (86ºF) and should not be allowed to freeze. If unavoidable, transient excursions up to 40ºC are permissible as long as reconstitution has not occurred. Once the drug product has been reconstituted with the 0.45% saline, the resulting suspension can be stored up to 4 hours at 2-8°C or room temperature. In such cases, the vial should be inverted gently 5 times before use. Study medication will be stored in a secure, controlled-access location at the study sites. The storage conditions of the re-usable controller and the single-patient, single use disposable, drug delivery circuit and respiration sensor are: Temperature -20 to +60°C. In addition, the reusable controller and stand with basket should be stored in an area so that they may be charged when not in use.

6.3 Treatments Administered

6.3.1 Part I

Enrolled infants randomized to one of the two active drug treatments will receive nominal doses of 108 mg/kg or 216 mg/kg aerosolized SF-RI 1 by a dedicated drug delivery system while on nCPAP/nIMV. A maximum of four doses over 96 hours will be permitted. Re-dosing will be allowed if the RSS to maintain SpO_2 between 90% and 95% is 1.5 to 2.39 and at least 2 hours have elapsed since the start of the previous dose:

- If FiO2 > 0.23, re-dosing will occur.
- If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator.

Infants enrolled into the control arm will receive either nCPAP or nIMV alone. SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups.

6.3.2 Part II – Follow-Up

There is no active treatment in Part II of this study. Parents will be asked to complete a telephone questionnaire at 3, 6, 9, and 12 months corrected age. This questionnaire will assess the home environment, respiratory support, medical history, modified GMFS and respiratory resource utilization at each time period.

See Section 4.2 or Appendicesfor Questionnaires.

6.4 Study Medication Supply, Preparation, and Administration

6.4.1 Study Medication Supply

The pharmaceutical dosage form of AeroFact is lyophilized SF-RI 1 dry powder in a type 1 glass vial (nominal volume 5 mL). The labelled vial size is 108 mg. The closure is a gray butyl rubber, fluoropolymer-coated, 13 mm stopper with an aluminum/propylene, blue, 13 mm flip-off seal. The current manufacturing facility is BAG Health Care (BAG) GmbH, Amtsgerichtstrasse 1-5, 35423 Lich, Germany.

The pre-filled syringe is hydrolytic glass type 1, 3.0 mL. It is aseptically filled to 2.4 mL with 0.45% (semi-isotonic) saline buffer for reconstituting the 108 mg vials. There are two variants. The first, manufactured by IDT Biologika, Dessau-Rosslau, Germany, is a luer-slip format with a chlorobutyl rubber (4432/50) gray plunger stopper and a synthetic gray polyisoprene tip cap (7028/55). The second, manufactured by S.C. Rompharm Company S.R.L, Ilfov County, Romania, is a luer-lock format with a gray bromobutyl rubber (FM 257/2) plunger stopper, and a synthetic gray isoprene-bromobutyl blend tip cap (7025/65).

6.4.2 Study Medication Preparation

There are two ways to prepare the SF-RI 1 suspension, either with a vial-adapter or with a cannula. Please refer to the package insert, or the AeroFact Pharmacy/Respiratory Therapy Manual for reconstitution of the drug product.

6.4.3 Study Medication Administration

The study drug in the AeroFact, SF-RI 1, will be administered by a dedicated drug delivery system while infants are on nCPAP/nIMV. Please refer to the Directions for Use (DFU) or the AeroFact Pharmacy/Respiratory Therapy Manuals for details on aerosol administration.

6.5 Drug Delivery System

6.5.1 Identity of Device

AeroFact™ is a drug /device combination product consisting of three basic components: (i) drug (SF-RI 1 bovine-origin surfactant); (ii) reusable device controller; and (iii) disposable single-patient, single-use drug delivery circuit and breath sensor. This is a stand-alone drug delivery system that integrates with a variety of nCPAP and nIMV devices and is not designed to be connected to the hospital network or the Internet. The AeroFact™ drug delivery system is designed to administer aerosolized surfactant to the lungs of spontaneously breathing premature infants receiving nCPAP or nIMV.

6.5.2 Aerosol Delivery System Components

The AeroFact drug delivery system (Figure 1) consists of reusable and single-patient elements:

6.5.2.1 Reusable Components

The controller is a multi-patient, reusable component with flat panel touch-screen display, electronics, and software. The controller has three core functions:

- To detect inspiration via a single-patient-use respiration sensor
- To advance suspension to the nebulizer via an integrated feed mechanism
- To generate aerosol during inspiration at the nCPAP interface

These functions occur in synchrony with the infant's inspiratory cycle. The flat panel touch-screen utilizes a graphical user interface (GUI) to allow the user to set and monitor delivery parameters, alarms, and system diagnostics. Visual and audible alarms are integrated into the controller. The

Pod communicates the signal from the disposable single patient use respiration sensor to the controller and breath synchronizes aerosol generation.

6.5.2.2 Single-patient disposable items:

Drug Reservoir (drug vial) is the reservoir, from which the drug product (lyophilized SF-RI 1) is reconstituted into a suspension and dispensed.

Drug delivery circuit is a disposable, single-patient circuit consisting of:

- Drug Feed Tubing which includes drug contacting components as follows: (i) luer connector (to VVAD) and (ii) tubing conveying drug suspension from the luer to the AF nebulizer.
- Vented Vial Access Device (VVAD) facilitates access to the drug reservoir and is provided to the user in an individual package.
- AF Nebulizer/nCPAP Interface uses a custom photo defined aperture plate (PDAP) vibrating mesh, which is unique in its ability to provide small droplet sizes and higher output rates. This is due to its innovative architecture, which provides up to 20-fold more apertures with smaller diameters than the conventional mesh. This meets the stringent requirements for efficient surfactant delivery to infants and represents enabling technology for the AeroFact platform. The AF nebulizer/nCPAP interface is designed to dispense aerosol proximal to the infant's airway and connect to conventional nCPAP systems.

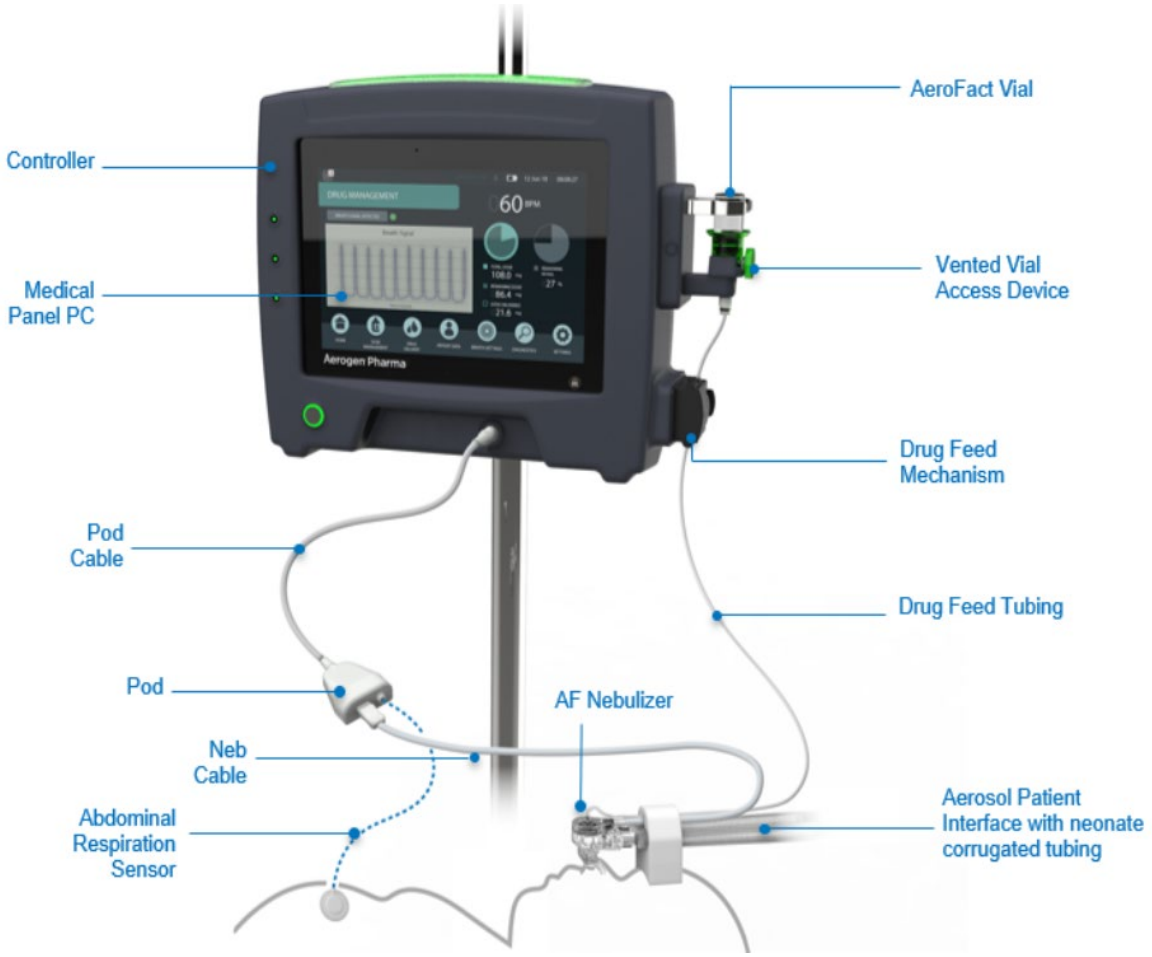
Respiration Sensor is a separate sensor that is placed on the infant's abdomen which synchronizes drug delivery with the infant's breathing.

Ancillary non-investigational clinical supplies include the following:

- Nasal Prongs connect to the end of the drug delivery circuit and are provided in a variety of sizes to accommodate different size infants
- Knit cap/bonnet (F&P™ not shown) to secure the nasal prongs and nebulizer to the infant
- Cavilon™ no sting barrier film to protect the integrity of the skin prior to applying the breath sensor
- Kind™ Removal silicone tape to be placed over the breath sensor which secures it to the abdomen without comprising the integrity of the skin
- Study Medication Lock box
- Bedsheet clip

Refer to the AeroFact Drug Delivery System Directions for Use.

Figure1-AeroFact Drug Delivery System



6.5.3 Device Supply

Prior to AeroFact dosing, the drug delivery system will be brought to the bedside. The serial numbers for the controller/Pod and disposable drug delivery circuit will be recorded in the study records. A controller and Pod will be used by more than one patient and will be cleaned between each patient (see DFU). A new drug delivery circuit is required for each dose of AeroFact given and will never be re-used.

Used and unused disposable devices will be inventoried and returned to the Sponsor or Sponsor's designee. Drug Delivery Systems and their components will be returned to the Sponsor or Sponsor's designee at the conclusion of Part I.

6.5.4 Device Replacement

One device (controller, drug delivery circuit and associated components) is expected to perform throughout the duration of dose. If the controller or the drug delivery circuit are not functioning optimally for any reason, instructions for trouble-shooting provided in the device instruction manual should be followed by the trained unblinded staff. If one or more devices need to be

replaced, the reason should be documented in the patient's medical record and appropriate study records. Additional devices are provided for this purpose. The unique serial numbers of the new controller and drug delivery circuit will be recorded in the patient's medical record and study records.

Controllers and drug delivery circuits should be replaced at any time if there is a confirmed or suspected malfunction.

- Device substitution, whether controller or circuit, should be recorded on the appropriate page of the study records.
- Notation must be made if the investigator suspects the device is not performing optimally for any reason.

If the Device fails, there is no way to restart a partial dose.

- For any partial dose delivered, note the amount of dose remaining on the controller drug delivery screen (if available) and record on Unblinded dosing record. Otherwise estimate the amount delivered and record on Unblinded dosing record. This will count as a one of the 4 delivered doses. Patient will be eligible for repeat dosing 2 hours after the start of the previous dose.
- Only a maximum of four doses of AeroFact will be delivered.

For device performance problems or complaints, the Sponsor or the Sponsor's designee should be contacted within 48 hours. Complaints should be submitted to: Complaints@aerogenpharma.com. Failed devices and drug delivery circuits will be inventoried and returned to the Sponsor or the Sponsor's designee.

6.6 Blinding

Clinical and research staff will remain blinded to dose level being administered with the exception of pharmacy staff or designee and respiratory therapy staff or designee. AeroFact drug delivery circuit will remain in line for the duration of dosing or a minimum of 2 hours, regardless of dose volume being administered.

6.7 Concomitant Medication/Therapies of Interest

Concomitant medications of interest will be collected for all enrolled infants. Concomitant medications of interest include: corticosteroids, methylxanthines, continuous infusion vasopressors, vitamin A, bolus surfactant and medications for the prophylaxis or treatment of PDA administered to the patient during the course of the study (starting on Day 1) will be recorded on the Concomitant Medications CRF. Blood products and surgeries will also be recorded. The Investigator will record any AE on the AE CRF for which a concomitant medication/therapy was administered during Part I only.

6.7.1 Discouraged Concomitant Therapy

The use of Vitamin A or corticosteroids for BPD prophylaxis must be consistent, and appropriate for age, for all enrolled infants within each study site.

The routine use of hydrocortisone as first-line therapy for BP/adrenal support should be avoided during the first 96 hours of life. Clinical guidelines for use of glucocorticoids can be found in the Manual of Procedures (MOP).

Potential candidates for initiation of glucocorticoids for hypotension will include inadequate response to vasopressor therapy (dopamine ≥ 20 mcg/kg/min ± dobutamine or epinephrine) with *either:*

- Persistent hypotension despite fluid resuscitation, or
- Inability to wean medications for > 48h

and

- No contraindications to glucocorticoid therapy

6.8 Investigational Product (IP) Supplies and Accountability

Investigational Product (IP) supplies will not be sent to the Investigator(s) until the following documentation has been received by the Sponsor:

- Written proof of approval of the protocol and its informed consent forms (ICFs) by the Independent Review Board (IRB) for the institution where the study is to be conducted.
- An Investigator-signed and dated FDA Form 1572.
- A signed and dated curriculum vitae (CV) of the Principal Investigator including a copy of the Principal Investigator's current medical license (required in the US).

The Sponsor may send components of the IP in advance of the completion of the regulatory documents if those components are for training purposes only. In these cases, the Sponsor should send documentation to the site instructing them that the IP components are for training purposes only and screening and enrolment may not begin until an SIV is completed and a favourable IRB approval has been granted The Investigator and study staff will be responsible for the accountability of all investigational product study supplies (dispensing, inventory, and record keeping) following Aerogen Pharma instructions, adhering to Good Clinical Practice (GCP) guidelines and local and/or regional requirements.

Under no circumstances will the Investigator allow the study investigational products or ancillary components to be used other than as directed by this protocol. Study investigational product will not be administered to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all study investigational product; dispensing of study investigational product to the patient; collection of unused study investigational product; and subsequent return of unused study investigational product to Aerogen Pharma (or designee) must be maintained. This includes but may not be limited to: (a) documentation of receipt of study investigational product, (b) study investigational product dispensing/return reconciliation log, (c) study investigational product accountability log, (d) all shipping service receipts, and (e) documentation of returned study investigational product to the Sponsor. All forms will be provided by Aerogen Pharma. Any comparable forms that the investigational site wishes to use must be approved by Aerogen Pharma.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Aerogen Pharma, a representative of the FDA, or a representative of a non-US health authority. All unused study investigational product, including empty containers are to be returned to Aerogen Pharma at the conclusion of the study, unless provision is made by Aerogen Pharma for destruction of supplies and containers at the investigational site. Upon completion of study investigational product accountability and reconciliation procedures by investigational site personnel and documentation procedures by Aerogen Pharma personnel, study investigational product that is to be returned to Aerogen Pharma, if necessary, must be boxed and sealed and shipped back to Aerogen Pharma following all local regulatory requirements.

7 EFFICACY ENDPOINTS

7.1 Primary Efficacy Endpoint – Part I

- Proportion of infants requiring intubation/cannulation and bolus surfactant instillation in the first 7 days after birth

7.2 Secondary Efficacy Endpoints – Part I

- Time to first intubation/cannulation and bolus surfactant instillation between study treatments for first 7 days of life
- Compare the proportion of infants across groups receiving multiple doses of surfactant.
- Number of days on mechanical ventilation from the day of birth to 40 weeks PMA or discharge.
- Number of days on supplemental oxygen administration from the day of birth to 40 weeks PMA or discharge
- Survival without bronchopulmonary dysplasia (BPD) at 36 and 40 weeks PMA

7.3 Additional Efficacy Endpoints – Part II

- Assessment of pulmonary outcomes at 3, 6, 9 and 12 months corrected age
- Length of NICU Stay (LOS)
- Proportion of subjects with any respiratory resource utilization at 3, 6, 9 and 12 months corrected age
- Respiratory morbidity per quarter till 12 months corrected age
- Assessment of modified GMFS at 12 months corrected age

8 SAFETY ASSESSMENTS

Safety and tolerability will be assessed through the monitoring of oxygenation, bradycardia, nasal congestion/aspiration, and other adverse events (AEs) of interest to 40 weeks PMA or discharge. Tolerance of the AeroFact dosing administration and all doses of bolus surfactant will be assessed during and following dosing. Safety assessment frequency is shown in the Schedule of Assessments and Procedures.

8.1 General Safety Procedures

8.1.1 Ventilator/Respiratory Measurements

Serial measurements of respiratory support will be collected from the time of birth through 28 days of life, 35 to 37 Weeks PMA, 39 through 40 Weeks PMA and at the time of discharge from the NICU for all groups. If infants are discharged from the NICU prior to 36 and or 40 weeks, the study staff will collect applicable 36/40 week PMA information by telephone. Measurements include: Mode of support (CPAP, Continuous Mandatory Ventilation [CMV], High Frequency Oscillatory Ventilation [HFOV]/High Frequency Jet Ventilation [HFJV], NIMV/Bilevel Positive Airway Pressure [BiPAP], high flow nasal cannula (HFNC) or nasal cannula (NC) > 2 liters per min (L/min), NC ≤ 2 L/min, or room air (RA), CPAP/PEEP, mean airway pressure (Paw), flow rate, FiO_2, SpO_2, and respiratory support status. A room air challenge (RAC) will be performed on those infants on nasal cannula support at 36 and 40 Weeks PMA. Duration of assisted ventilation and supplemental oxygen will also be collected. See Manual of Operations (MOP) for detailed instructions regarding the process for performing a RAC.

8.1.2 Weight Measurements

Weight (grams) will be obtained at the time of birth, discharge from NICU and 12 month corrected age assessment (Part II- by parent/guardian report). Head circumference and recumbent length will be collected at birth and discharge from the NICU.

8.1.3 Nasal Congestion

Prior to and during the AeroFact dosing period and bolus instillation of surfactant, the patency of the nasal prongs and blockage of nostrils with surfactant and/or secretions will be closely monitored and the severity of nasal congestion will be assessed every 15 minutes for the duration of dosing or a minimum of 2 hours. Document any suctioning done (none/oral/nasal/ETT) following AeroFact or bolus instillation of surfactant.

8.1.4 Surfactant Dosing Tolerance

Tolerance of surfactant dosing by AeroFact or bolus instillation will be assessed at 4 hours and 24 hours after the start of administration.

8.1.5 Clinical Blood Gas Measurements

Blood gas measurements drawn for clinical care only will be recorded if collected prior to dosing, and/or as verification for meeting escalation criteria or in relationship to an SAE.

Supplemental oxygen and respiratory support will be adjusted to maintain SpO_2 between 90% and 95% during the first 96 hours after birth.

8.2 Adverse Events/Co-Morbidities of Prematurity

Occurrence of any AEs of interest (Co-morbidities of prematurity) will be collected and recorded until discharge or 40 weeks PMA. Only SAEs that result in an outcome of death will be recorded during Part II. Death is not an SAE but the outcome of the SAE.

8.2.1 Definitions

8.2.1.1 Co-Morbidities of Prematurity (AEs of interest) include:

- Culture Proven Sepsis
- Cystic Periventricular Leukomalacia (PVL)
- Hearing Loss
- Hydrocephalus requiring shunt
- Intraventricular Hemorrhage (IVH) Grades 1, 2, 3, or 4 (Worst Grade)
- Isolated Gastrointestinal Perforation without NEC
- Necrotizing Enterocolitis (NEC) requiring treatment
- Patent Ductus Arteriosus (PDA) requiring ligation
- PDA requiring treatment with indomethacin, ibuprofen, or acetaminophen
- Pneumothorax requiring chest tube
- Pulmonary Hypertension
- Pulmonary Interstitial Emphysema (PIE)
- Retinopathy of Prematurity (ROP) Stages 1, 2, 3, 4, or 5 (Worst Grade)
- Severe hypotension
- Severe pulmonary hemorrhage
- Tracheal Stenosis
- Tracheomalacia
- Vocal Cord Paralysis

BPD is not recorded as an AE but is recorded as an outcome at 36 and 40 weeks PMA.

8.2.1.2 Adverse events

Adverse events (AE) for this study include the co-morbidities of prematurity listed above or any untoward medical occurrence deemed significant by the Principal Investigator. An AE does not necessarily have to have a causal relationship with this treatment. An AE may also occur which may be related to the medical device that is being tested. The Investigator will be asked to determine the causal relationship of each AE to the investigational device. This includes any event that is the result of incomplete user manual information or of incorrect use of the medical device.

8.2.1.3 Pre-existing Co-morbidities of Prematurity

A pre-existing condition or symptom/co-morbidity of prematurity prior to dosing is one that is present at the start of the study and is reported as part of the patient's medical history. A pre-existing condition or symptom should be reported as an AE only if its frequency, intensity or character worsens during study treatment.

All co-morbidities/AEs that occur from randomization through the discharge or 40 weeks PMA must be appropriately documented in the patient's medical chart and on the CRFs. When known, investigators should report syndromes rather than list symptoms associated with the syndrome.

AEs occurring in Part I should be followed until:

- resolution/stable sequelae; or
- the Investigator determines that it is no longer clinically significant; or
- the study patient is discharged.

If no follow-up is provided, the Investigator must provide a written justification.

8.2.2 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

- Grade 1 (Mild): usually transient; requires no special treatment
- Grade 2 (Moderate): usually ameliorated by simple therapeutic measures
- Grade 3 (Severe): may require systemic drug therapy or other medical treatment

8.2.3 Relationship to Study Medication/Study Device/Study Procedure

The Investigator must assess the relationship of each reported AE. The Investigator must assess the relationship of the AE to the study medication using the following scale:

- **Unrelated:** The AE is definitely not or unlikely to be associated with study medication/study device/study procedure and is judged due to causes other than the study medication/study device/study procedure.
- **Related:** The AE is possibly or probably related with study medication/study device/study procedure.

8.2.4 AE/Co-Morbidities of Prematurity Action Taken

Any action taken in response to AE/co-morbidities of prematurity will be recorded as follows:

- Study Medication
    - Dose not changed
    - Drug interrupted
    - Dosing stopped
- Study Device/Procedure
    - None
    - Remove/Replace Controller
    - Remove/Replace Circuit

8.2.5 AE/Co-Morbidities of Prematurity Outcomes

The following terms and definitions are used in assessing the final outcome of an AE/Co-Morbidities of Prematurity:

- **Recovered/Resolved** - The participant has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the participant signed the informed consent.
- **Recovering/Resolving** - The condition is improving, and the participant is expected to recover from the event.
- **Recovered/Resolved with sequelae** - The participant has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/Not resolved** - The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **Fatal** - This term is only applicable if the participant died from a condition related to the reported AE. An AE with fatal outcome must be reported as an SAE.

8.2.6 Serious Adverse Events (SAEs), Treatment Emergent Adverse Events (TEAE), and Suspected Unexpected Serious Adverse Reactions (SUSARs)

8.2.6.1 SAEs

The Investigator is required to determine if each AE is a Serious Adverse Event (SAE). A SAE is any AE occurring after randomization through discharge from NICU or 40 weeks PMA and results in any of the following outcomes:

- Death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

The Investigator is required to determine the causal relationship of each SAE to the investigational device based on the outcomes listed above in the definition of a SAE.

Important medical events that may not result in death, be life-threatening, or require prolongation of hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In the event of death, the cause of death should be recorded as the SAE (death is an outcome, not the AE itself).

8.2.6.2 TEAEs

Treatment-emergent adverse events (TEAEs) will be summarized up to 7 days after birth and are defined as one of the following occurring from the first dose of AeroFact for the active group or from the first bolus instillation of surfactant in the control group:

- AEs that emerge during treatment, having been absent at pretreatment (Baseline), or
- Reemerge during treatment, having been present at Baseline but stopped prior to treatment, or
- Worsen in severity during treatment relative to the pretreatment state, when the AE is continuous.

8.2.6.3 SUSARs

A Suspected Unexpected Serious Adverse Reaction is an AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

8.2.7 Reporting for SAEs

Part I

Regardless of causality, an SAE must be followed clinically until resolution or stabilization.

All SAEs after randomization through discharge from the NICU or 40 weeks PMA must be reported to the Sponsor or the Sponsor's representative within 24 hours of the investigational site's knowledge of the occurrence. The investigational site will either telephone the report to the Sponsor or the Sponsor's representative or transmit by email a Serious Adverse Event Report (SAER) to the Sponsor or the Sponsor's representative. If the initial report is made via telephone, a completed SAER must be emailed within 24 hours of the site's knowledge of the event. Investigational sites will be provided with SAER forms.

The SAER should be emailed within 24 hours with as much information as available at the time. At a minimum the initial report should include: patient number, event, treatment group (active or control), investigator assessment of causality, and event proximity to study drug dosing should be reported, if known. Supplemental information may be transmitted using a follow-up report and should not delay the initial report.

Part II

Only SAE's resulting in death will be recorded. Information on death will be collected and reported to Sponsor within 1 week of site notification.

9 PHARMACOKINETIC ASSESSMENTS

Not applicable.

10 SCHEDULE OF ASSESSMENTS AND PROCEDURES

The assessments and procedures for Part I and Part II of this study are described in detail below and presented in the Schedule of Assessments and Procedures located behind the Synopsis.

10.1 Part I

10.1.1 Consenting

Potential study patient(s) will be recruited by the study staff from hospitalized preterm infants 26 0/7 to 31 6/7 weeks of gestational age and who are at risk for worsening RDS. Prior to performing any study procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to the infant's parent(s) or legally authorized representative. An opportunity to ask questions will be provided to the parent(s) or legally authorized representative. Once all questions and concerns have been addressed by the study staff, a written informed consent will be obtained. A signed copy of the informed consent will be provided to the parent(s) or legally authorized representatives of the infant. Prenatal consent is allowed.

10.1.2 Screening (Assessment for Eligibility)

Preterm infants will be assessed for eligibility on Day 1. The following items will be assessed:

- Chest radiograph or lung ultrasound
- Gestational age and demographics (including date of birth, gender, race, and ethnicity)
- Medical history for mother and infant (including current medications)
- Birth weight, Recumbent Length, and Head Circumference
- Apgar Scores
- Respiratory support parameters (FiO_2, SpO_2, PEEP/CPAP pressure and flow rate, Paw, and Respiratory Support Status) (initial stabilization in delivery room, first stabilization in NICU, and one hour post nCPAP start)
- Qualifying RSS based on FiO2 and CPAP calculated from parameters above
- Inclusion and exclusion criteria

The following items will be obtained prior to dosing:

- If a blood gas has been obtained for clinical purposes only, record PO_2, PCO_2, pH, bicarbonate prior to randomization/dosing, and/or as verification for meeting intubation criteria or in relationship to an SAE.
- Assess and document nasal congestion just prior to AeroFact dosing
- Evaluate identified Co-Morbidities of Prematurity prior to AeroFact dosing

If the baby has been assessed as eligible to participate in study and informed consent has been obtained, the baby may be enrolled into the study.

10.1.3 Study Enrollment

10.1.3.1 Randomization

- Infant will be randomized to one of three study arms Active-Low Dose (108 mg/kg), Active High Dose-216 mg/kg or Control-nCPAP/nIMV alone. If twins or triplets are enrolled, only the first sibling will be randomized and subsequent siblings will receive the same treatment assignment.
- Randomization is a two-step process:
  - Step 1: a designated member of the study staff will obtain a randomization envelope for the appropriate gestational age group, which will randomize the infant to either the Active or Control group. The study staff will be made aware if the infant was randomized to the control group. The randomization envelope will be stored in a secure location within the infant's study file.
  - Step 2: active envelopes will be forwarded to the unblinded pharmacist or designee, where the active envelope will be opened and the Low or High dose group (108 mg/kg or 216 mg/kg) will be determined. Active drug dose will be calculated and dispensed according to the pharmacy manual instructions. Active drug will be administered according to study protocol.

10.1.3.2 Drug Dispensing & Preparation

- Pharmacy or designee will calculate AeroFact dose (depending on group assignment) and dispense the appropriate number of trays of AeroFact to the study drug lockbox provided
- Study medication will be labeled according to the study pharmacy manual
- Study drug will not be reconstituted in the pharmacy but prepared by the unblinded respiratory therapist or designee on a just in time basis, according to package insert.
- Medication, drug calculations, additional study labels, and reconstitution instructions will be delivered to the NICU in the study drug lockbox

10.1.3.3 AeroFact Delivery System Set-up (Unblinded Staff Member Only)

- Re-usable and single patient use device components will be brought to the infant's bedside.
- See Directions for Use (DFU) Manual or the Manual of Procedures (MOP) for step by step instructions of device set-up.

10.1.4 Study Conduct

10.1.4.1 AeroFact Dosing

Patients who meet inclusion and no exclusion criteria will receive initial assigned treatment administered via nCPAP or nIMV within first twenty-four hours after birth. Up to three additional doses of AeroFact within 96 hours of birth will be allowed. Re-dosing of AeroFact will be allowed if the RSS to maintain SpO_2 between 90 and 95% is 1.5 to 2.39 and at least two hours have elapsed since the start of the previous dose:

- If FiO2 > 0.23, re-dosing will occur.
- If FiO2 ≤ 0.23, re-dosing is at the discretion of the investigator.

All infants randomized will be clinically managed until the criteria for treatment escalation have been met. SpO2 between 90-95% must be used to meet study eligibility through 96 hours for all study groups (Active/Control). Site-specific SpO2 clinical guidelines may be used after 96 hours. Each site must use these guidelines uniformly across treatment groups.
Infants will be evaluated for tolerance of AeroFact administration:

- Assess nasal congestion (none,mild, moderate, or severe) and document aspiration (nasal, oral, ETT or none) every 15 minutes during the administration of AeroFact or a minimum of 2 hours.
- Monitor oxygenation and respiratory support parameters (FiO_2, SpO_2, PEEP/CPAP pressure and flow rate, Paw, and Respiratory Support Status) every 15 minutes from the start of AeroFact dosing (T_0) until dose has been completed or a minimum of 2 hours post start of dosing.
- Dosing Tolerance Adverse Events of interest will be assessed at 4 and 24 hours after the start of each AeroFact dose.

10.1.5 Neonatal Intensive Care Unit (NICU)

Data collection will occur at the same frequency regardless of treatment assignment.

10.1.5.1 Birth to Day 28

All study infants will undergo the following procedures and evaluations:

- Monitor clinical blood gases as clinically warranted
- Infants will have oxygenation and ventilation parameters routinely monitored q 8 hours through Day 7, daily days 8 through day 28. Parameters to include: FiO_2, SpO_2, PEEP/CPAP pressure and flow rate, Paw, and Respiratory Support Status
- Assess nasal congestion (none, mild, moderate, or severe) and document aspiration (nasal, oral, ETT or none) every 15 minutes during the administration of AeroFact and/or bolus surfactant or a minimum of 2 hours.
- Evaluate dosing tolerance of AeroFact administration and/or bolus surfactant instillation
- Record AEs of interest /Co-Morbidities of Prematurity
- Record concomitant medications of interest

10.1.5.2 36 Weeks PMA

Study infants will undergo the following procedures and evaluations:

- Monitor oxygenation and respiratory support parameters (FiO_2, SpO_2, PEEP/CPAP pressure and flow rate, Paw, and Respiratory Support Status) +/- one week around 36 Weeks PMA date (Daily the week before and the week after 36 week PMA date)
- Record concomitant medications of interest
- BPD outcomes will be assessed at 36 Weeks PMA. A RAC will be performed if infant is eligible
- Record AEs of interest/Co-Morbidities of Prematurity

If an infant is discharged from the NICU prior to 36 weeks, a study member will call the family to verify respiratory support status at 36 weeks.

10.1.5.3 End of Study at 40 weeks PMA

Study infants will undergo the following procedures and evaluations:

- Monitor oxygenation and respiratory support parameters (FiO_2, SpO_2, PEEP/CPAP pressure and flow rate, Paw, and Respiratory Support Status) +/- one week around 40 Weeks PMA date (Daily the week before and the week after 40 week PMA date)
- Record concomitant medications of interest
- Record AEs/Co-Morbidities of Prematurity
- BPD outcomes will be assessed at 40 Weeks PMA. A RAC will be performed if infant is eligible

If an infant is discharged from the NICU prior to 40 weeks, a study member will call the family to verify respiratory support status at 40 weeks.

10.1.5.4 Discharge from the NICU

Study infants will undergo the following procedures and evaluations:

- Date of discharge
- Discharge disposition
- Discharge weight (grams), Recumbent Length and Head Circumference
- SpO2
- Respiratory status
- BPD medications
- Feedings
- Audiology evaluation
- Assessment of Ophthalmology/ROP screening
- Records surgeries performed
- Record transfusions performed
- Assessment of ventilation days
- Last day on oxygen
- Last day on respiratory support
- Record concomitant medications of interest
- Discharge/End of Part I Pulmonary Questionnaire

10.2 Part II – Follow-Up

10.2.1 Follow-Up Questionnaires

Follow-Up Questionnaires will be completed by telephone with parents at 3, 6, 9, and 12 months corrected age to assess current respiratory support, the home environment, interim medical history and respiratory medical resource utilization and neurological outcomes (12 months corrected only).

11 DATA QUALITY ASSURANCE

11.1 Data Collection

Investigator(s) will enter the information required by the protocol onto the CRFs in accordance with the CRF Completion Guidelines that are provided with the CRFs. CRAs will visit each investigational site as frequently as documented in the monitoring plan to review the blinded CRFs for completeness and accuracy against the source documents. CRAs will highlight any discrepancies found in the documentation of study conduct and ensure that appropriate site personnel address the discrepancies. Only data that is blinded will be reviewed. If necessary, an unblinded CRA may visit site to review unblinded data and perform drug accountability during the course of the study. An unblinded CRA will perform drug accountability and return used and unused investigational product prior to close-out.

11.2 Clinical Data Management

Data from CRFs and other external data will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. An unblinded data manager will be assigned to process the unblinded data.

11.3 Database Quality Assurance

All databases will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

12 STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, covariates, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis

methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

12.1 Treatment Groups

For this study the following treatment groups will be assessed:

Group	Description
Active-Low Dose	AeroFact 108 mg/kg (Aerosolized SF-RI 1)
Active-High Dose	AeroFact 216 mg/kg (Aerosolized SF-RI 1)
Control	nCPAP or nIMV alone

12.2 Description of Study Endpoints

12.2.1 Primary Efficacy Endpoint – Part I

- Proportion of infants requiring intubation/cannulation and bolus surfactant instillation in the first 7 days after birth

12.2.2 Secondary Efficacy Endpoints – Part I

- Time to first intubation/cannulation and bolus surfactant instillation between study treatments for first 7 days of life
- Compare the proportion of infants across groups receiving multiple doses of surfactant
- Number of days on mechanical ventilation from the day of birth to 40 weeks PMA or discharge.
- Number of days on supplemental oxygen administration from the day of birth to 40 weeks PMA or discharge
- Survival without bronchopulmonary dysplasia (BPD) at 36 and 40 weeks PMA

12.2.3 Additional Efficacy Endpoints – Part II

- Length of Stay (LOS) in NICU
- Assessment of pulmonary outcomes at 3, 6, 9 and 12 months corrected age
- Proportion of subjects with any respiratory resource utilization at 3, 6, 9 and 12 months corrected age
- Respiratory morbidity per quarter till 12 months of corrected age
- Assessment of modified GMFS at 12 months of corrected age

12.2.4 Safety and Tolerability Assessments

Safety and tolerability will be assessed through the monitoring of oxygenation, bradycardia, nasal congestion/aspiration (AeroFact dosing and bolus instillation of surfactant), and other adverse events (AEs) to 40 weeks PMA or discharge. Incidence of comorbidities of prematurity/AE's will be assessed. Tolerance of the AeroFact dosing administration and all doses of bolus surfactant will be assessed during and up to 24 hours following each AeroFact dose or bolus instillation. Tolerance monitoring will end and begin anew with any AeroFact dose or bolus surfactant dose administered within the 24 hour assessment period. Only SAE's resulting in death wil be recorded in Part II.

12.3 Sample Size Determination and Rationale

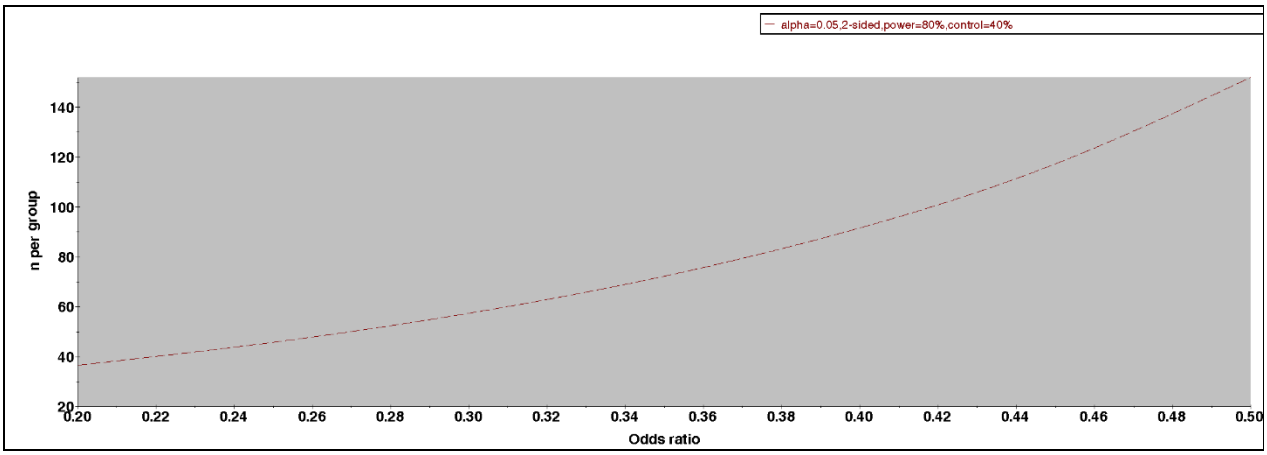
Two hundred and sixty-one (261) subjects (87 in each arm) will be randomized in a 1:1:1 ratio in order to assure that 246 subjects (82 in each arm) complete the study. The randomization will be stratified by site, gestational age and dosing group.

Infants requiring treatment escalation in the AeroFact dose groups is estimated to be 20% and in the control group is estimated to be 40%, with an odds ratio of 0.375.

Under the above assumptions, 82 subjects in each treatment group will be required, to meet the Type I error rate of 0.05 and 80% statistical power. To accommodate the potential dropouts, a 5% dropout rate is included in this sample size calculation.

The sample size is depicted in Figure 12.1.

Figure 12-1: Sample Size



12.4 Randomization

Infants will be block randomized in a 1:1:1 partially-blind fashion to receive one of two doses of AeroFact (Active) or Control. The randomization will be stratified by site and gestational age. There will be two sets of randomization envelopes, one for each gestational age group and they will be color-coded. If twins or triplets are enrolled, only the first sibling will be randomized and subsequent siblings will receive the same treatment assignment.

Treatment group will be randomly assigned using a predetermined randomization schedule created by an independent individual who is not on the study team. The randomization schedule will be generated using an appropriate block size to help maintain treatment groups of equal size within each age strata. Subjects who do not complete the study will not be replaced.

12.5 Stratification

The randomization will be stratified by site and gestational age (26 0/7 to 28 6/7; and 29 0/7 to 31 6/7 weeks.

12.6 Blinding and prevention of Bias

For the active dose groups, clinical and research staff will remain blinded to dose level being administered. AeroFact drug delivery circuit will remain in line for the duration of dosing or a minimum of 2 hours, regardless of dose volume being administered.

Treatment unblinding for investigator site personnel will occur after the completion of Part II and all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for emergency unblinding due to safety reasons. For all other study personnel (sponsor, vendors, stats, data management, etc.), active dose unblinding will occur after the completion of Part I and all clinical data for Part I have been received, data inconsistencies have been resolved, and the database of Part I is locked, except for emergency unblinding due to safety reasons.

The control group for this study are infants treated with nCPAP or nIMV alone.

12.7 Interim Analysis (IA)

A blinded interim analysis is planned and will be conducted when approximately 60% of subjects have been randomized and completed first 7 days of life or early termination, whichever occurs first.

The main purpose of this interim analysis will be:

- sample size re-assessment to evaluate the final sample size needed to proceed with the study based on the control responder rate at interim analysis, and;
- to evaluate the safety of AeroFact primarily on the frequency of adverse events, nasal congestion/aspiration, dosing tolerance events, and serious adverse events

The results of the interim analysis are to be reviewed by an independent DSMB who would assess the data for both safety and efficacy. The DSMB responsibilities are further elaborated in the DSMB charter. The DSMB will make recommendations to the sponsor on the sample size adjustment and any safety concerns. The details of the interim analysis will be included in the statistical analysis plan.
There will be no statistical penalty or statistical adjustment due to this interim analysis as this is a blinded interim analysis with no interim unblinding.

12.8 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

12.9 Analysis Populations

The details of the analysis population to be used for the study are described in the below sections.

12.9.1 Intent-to-Treat (ITT) population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. The ITT population will be the primary population for the primary, secondary and additional efficacy analysis.

12.9.2 Per Protocol (PP) Population

The Per Protocol (PP) population is defined as all randomized subjects who were not associated with a major protocol violation that affects patient safety or the integrity of the data. The PP analysis of primary, secondary and additional endpoints will be considered supportive.

12.9.3 Safety Population

The Safety population is defined as all randomized subjects. This population will be used for the analysis of safety parameters.

12.10 Covariates

The covariates planned for this study will be detailed in the statistical analysis plan.

12.11 Adjustment due to Multiple Comparisons

There are two comparisons for the primary endpoint because of the two active dose groups compared with a control. Hence, a closed test procedure will be used to protect the type I error rate, the order of testing will be:
1) AeroFact 216 mg/kg (Aerosolized SF-RI 1) vs. Control (nCPAP or nIMV alone)
2) AeroFact 108 mg/kg (Aerosolized SF-RI 1) vs. Control (nCPAP or nIMV alone)

Similarly, since there are multiple secondary endpoints a closed test procedure will be used to project the Type I error rate. The order of the secondary endpoints will be specified in the statistical analysis plan.

12.12 Statistical Methods

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial. All inferential statistical analysis will be based on a two-sided test with a Type I error rate of 0.05.

All the efficacy analyses presented here will be conducted using both ITT and PP populations. All safety analyses will be conducted using the Safety population. All data collected will be summarized according to the variable type.

12.12.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

12.12.2 Demographics and baseline characteristics analysis

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

12.12.3 Concomitant Medications/Therapies of Interest

Concomitant medications of interest/therapies will be summarized separately for the Safety population. All prior and concomitant medications of interest recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of WHO Drug. Descriptive summaries by treatment group will be prepared using the coded term. All concomitant medications of interest/therapies recorded in the case report form will be listed.

12.13 Efficacy Analyses

The primary analyses of the primary and secondary efficacy endpoints will be conducted on the ITT population. The PP population analyses of primary and secondary endpoints will be considered supportive.
For the efficacy endpoints the data will be summarized and compared according to the variable type:

- Continuous data summaries will include:
  - Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values.
  - Analysis of Covariance (ANCOVA) or Mixed Model Repeated Measures (MMRM) adjusted for stratification factors for inferential statistics.
- Categorical data summaries will include:
  - Frequency counts and percentages
  - Logit model or Generalized Estimating Equation (GEE) method adjusted for stratification factors and clustering of multiple births within a mother for inferential statistics
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and to depict the time to event data.

12.14 Safety Analyses

12.14.1 Adverse Events

Adverse events will be coded using MedDRA. TEAEs will be summarized for subjects who received at least one dose of AeroFact for the active group or received bolus instillation for the control group. AEs and TEAEs will also be summarized for up to 7 days after birth.
TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

12.14.2 Clinical Laboratory Data

There are no required laboratory tests for this study.

12.14.3 Other Safety Data

All changes in safety data will be listed and summarized over time.

12.15 Extent of Exposure

Exposure data will be summarized by treatment group using frequencies and percentages.

12.15.1 Adverse Events

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the CSR.

AEs will be summarized by presenting, for each treatment group, the incidence of AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only one time in the incidence count for that MedDRA term.

12.16 The Procedure for Revising the Analysis Plan

Any changes to the statistical analysis plan will be formalized and dated in an amendment and documented in the CSR.

12.17 Data Safety Monitoring Board

Safety oversight will be provided by a physician Medical Monitor who will provide study supervision for any safety concerns.

An independent DSMB will be comprised of at least three members consisting of at least two physician experts and one statistician who are not investigators in the study nor otherwise associated with the study. The DSMB will perform an evaluation of the data if requested by the Medical Monitor. Safety parameters will be assessed. The DSMB will establish its own charter, procedures, and criteria for recommendations regarding sample size adjustments and safety.

13 ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

13.1 Ethics

13.1.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with International Conference on Harmonization (ICH) E6, Section 3, and any local regulations, i.e., Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval (except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start and the release of any study medication to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

13.1.2 Regulatory Notification

The requirements for the conduct of clinical trials in accordance with the applicable US FDA regulations under an Investigational New Drug application (21 CFR 312) will be met before commencement of this study.

13.1.3 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices of Aerogen Pharma (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.
- US CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

13.1.4 Patient Information and Informed Consent

In some cases, a potential parent(s) will be approached and given information about the study prior to birth of the infant, and prenatal consent will be obtained. In others, consent will be obtained postnatally.

As part of administering the informed consent document, the Investigator must explain to the parent(s) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. The parent(s) must be informed that participation in the study is voluntary and that they may withdraw their infant from the study at any time and that withdrawal of consent will not affect their infant's subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The parent(s) should understand the statement before signing and dating it and will be given a copy of the signed document. The parent(s) will be asked to sign an informed consent prior to any study-specific procedures being performed. No infant can enter the study before informed consent has been obtained.

Due to the COVID-19 pandemic, informed consent may be conducted by phone or video-conference, rather than in-person. Discussion of study and consent may be done remotely. Consents may be given to parent to sign or sent via email for electronic signature. If remote process of consent and signatures are used, they must be witnessed using process approved by site IRB.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. The parent(s) must sign an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each infant will be verified by the Sponsor and kept in the study center's investigational site files.

The parent(s) should be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation of their child in the trial. The communication of this information should be documented.

13.2 Administrative Procedures

13.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, by the FDA. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all patients included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator for safety reasons, the

Sponsor's Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed as soon as possible.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the site for forwarding on to the IRB/IEC detailing such changes.

13.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5). Any requests for a planned deviation from the protocol must be discussed with Aerogen Pharma so that a protocol waiver may be generated.

13.2.3 Monitoring Procedures

The Sponsor or Sponsor's representative will maintain contact with the Investigator and designated staff by telephone, letter, and/or email between study visits. Monitoring visits (blinded and unblinded) may be done either remotely or by visits to each investigational site and conducted by a Sponsor representative or CRA. The Investigator will allow the CRA to inspect the clinical and pharmacy facilities to assure compliance with GCPs and local regulatory requirements. The CRFs and patient's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with federal regulations and local regulations. All records at the investigational site are subject to inspection by the FDA.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts.
- Copies or transcribed health care provider notes which have been certified for accuracy after production.
- Recorded data from automated instruments such as x-rays, and other imaging reports, e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnographs, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives).
- Records of telephone contacts.
- Diaries or evaluation checklists.
- Study medication distribution and accountability logs maintained in pharmacies or by research personnel.
- Laboratory results and other laboratory test outputs, e.g., serum pregnancy test result documentation.
- Correspondence regarding a study patient's treatment between physicians or memoranda sent to the IRBs/IECs.

- CRF components (e.g., questionnaires) that are completed directly by patients and serve as their own source.

13.2.4 Recording of Data

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained. The Investigator will enter the information required by the protocol onto the CRFs in accordance with the CRF Completion Guidelines provided by the Sponsor, report the CRFs to the Sponsor, and preserve the copy of the CRFs after the Investigator signs to the CRFs.

13.2.5 Quality Assurance and Quality Control

To ensure compliance with ICH GCP and all applicable regulatory requirements, the sponsor (or a designated third party), may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to notify the sponsor as soon as possible following awareness of an impending regulatory inspection. The Investigator and Institution agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The sponsor (or its designee) will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the Investigator (and delegate(s)) generating the data.

Prior to the study initiation, the sponsor (or its designee) will explain the protocol, Investigator's Brochure, and CRF to the Investigator and clinical facility staff involved in this study. In addition, the assigned study monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

13.2.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of CRFs, Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. In addition, the Sponsor will send a list of treatment codes by study patient to the Investigator after the clinical database for this study has been secured after the completion of Part II. The investigational site should retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified, or as required by their site IRB.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contacts the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

13.2.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the Sponsor's Quality Assurance department or representative conducts audits of clinical research activities in accordance with the Sponsor's or representative's SOPs to evaluate compliance with the principles of ICH GCPs and all applicable

local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

13.2.8 Handling of Study Investigational Product

All study investigational product (IP) will be supplied to the Principal Investigator (or designated pharmacist) by the Sponsor or Sponsor representative. Study investigational product supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the study investigational product labels. The Investigator (or designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study investigational product (s) in an IP accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study IP dispensed to each patient must be available for inspection at any time.

All study IP supplies are to be used only for this protocol and not for any other purpose. The Investigator (or designated pharmacist) must not destroy any study investigational product labels or any partly used or unused study supply. At the conclusion of Part I of the study and as appropriate during the course of the study, the Investigator (or designated pharmacist) or a sponsor representative will return all used and unused study investigational product containers, study investigational product labels, and a copy of the completed study investigational product disposition form to the Sponsor or their designee.

13.2.9 Publication of Results

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Aerogen Pharma, as appropriate.

13.2.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

13.2.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a trial is prematurely terminated or suspended, the Sponsor should promptly inform the Investigator/Institution and the regulatory authority(ies) of the termination or suspension, and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and should provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

13.2.12Patient Insurance and Indemnity

The Sponsor will provide the insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study.

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15 APPENDIX I- PART I DISCHARGE BREATHING QUESTIONNAIRE

Aerogen Pharma

Study ID: 1-___ ___ ___- ___ ___ ___ - ___

Protocol Part I

Form 13 – Breathing Questionnaire at Discharge from NICU

(Answer questions as if your baby went home today (if still in hospital))

13.1. Information received from (list primary caregiver): *(select one)*

☐ Mother ☐ Father ☐ Grandparent ☐ Foster Parent ☐ Other

13.2. How many people normally live in your home including your baby (for at least 6 months of the year)?
(select one)

☐ 2-3 ☐ 4-6 ☐ 7-10 ☐ >10

13.2.1. Are the infants < 5 years, other than your baby that live in the home? *(select one)*

☐ None ☐ 1-2 ☐ 3-5 ☐ 6-8 ☐ >8

13.3. Do you have any pets? *(select all that apply)*

☐ None ☐ Dog ☐ Cat ☐ Other Furry Animal ☐ Fish ☐ Birds ☐ Other _____

13.4. Will your child receive child care outside the home in the next year?

☐ Yes ☐ No ☐ Unknown

13.4.1. Who will provide care? *(select all that apply)*

☐ Relatives ☐ Daycare ☐ Friends ☐ Other

13.4.2. Will other children that are not siblings be present at the outside site?

☐ Yes ☐ No ☐ Unknown

13.5. Please describe the situation regarding smoking in your child's home: *(select one)*

☐ Smoking is allowed in any room in the house

☐ Smoking is limited to part of the house where the child will rarely go

☐ Occasionally there is smoking inside the house (visitor, family member)

☐ There is no smoking inside the house at all

☐ Other

13.6. Dose either parent smoke? ☐ Yes ☐ No ☐ Don't know

13.6.1. If yes, estimate the number of cigarettes per day:

☐ < 5 ☐ 5-10 ☐ 11-20 ☐ > 1 pack/day ☐ Unknown

Aerogen Pharma Study ID: 1-___ ___ ___- ___ ___ ___ - ___

Protocol Part I

Form 13 – Breathing Questionnaire at Discharge from NICU (cont'd)

13.7. Altogether, how many people who live in the house smoke?

☐ None ☐ 1-2 ☐ >2

13.8. Will your child travel regularly (at least once a week) in a vehicle (car or truck) that someone smokes in, even when the child is not in the car?

☐ Yes ☐ No

13.9. Please tell us what breathing and allergy problems run in the family.

13.9.1. Biological parents – one or both: *(select all that apply)*

☐ Asthma/recurrent lung infections ☐ Medication Allergies ☐ Other
☐ Allergies/Hayfever ☐ Eczema ☐ None

13.9.2. Grandparents – one or both: *(select all that apply)*

☐ Asthma/recurrent lung infections ☐ Medication Allergies ☐ Other
☐ Allergies/Hayfever ☐ Eczema

13.9.3. Siblings – one or both: *(select all that apply)*

☐ Asthma/recurrent lung infections ☐ Medication Allergies ☐ Other
☐ Allergies/Hayfever ☐ Eczema

13.10. Please tell us more about your family background

13.9.1. Maternal education: *(select one)*

☐ Some education, high school not complete ☐ College Graduate
☐ High School Graduate ☐ Graduate Study
☐ Some College

13.9.1. Paternal education: *(select one)*

☐ Some education, high school not complete ☐ College Graduate
☐ High School Graduate ☐ Graduate Study
☐ Some College

13.10. How will your child's health care be paid for? *(select one)*

☐ Private Insurance ☐ Medicaid/Public ☐ No Insurance

_____ _____
Principal Investigator Signature Date

13.11. Form Signed ☐ Yes ☐ No

16 APPENDIX II – PART II QUESTIONNAIRE

Part II Follow Up Questions	**3 months Corrected Age**	**6 months Corrected Age**	**9 months Corrected Age**	**12 months Corrected Age**
Respiratory symptoms	X	X	X	X
Dr visit/ER/hospital visit	X	X	X	X
Oxygen/ventilator use	X	X	X	X
Respiratory Medications	X	X	X	X
Home living situation	X	X	X	X
Type and route of feedings		X		X
Care outside home		X		X
Smoking in home		X		X
Family/social history				X
Medical history, vision hearing				X
Medications for chronic conditions				X
Allergies				X
Motor milestones				X
Growth parameters				X
Modified Gross Motor Function Score				X

Aerogen Pharma Protocol Number APC-AF-CLN-002

AeroFact 2b – Part II – Follow-Up

1. Corrected Age at current Interview:

☐ 3 Months ☐ 6 Months ☐ 9 Months ☐ 12 Months

History of last interview

2. Date of last interview ___/___/___

2a. Date of NICU Discharge: ___/____/_____ ☐ N/A

3. Which was last interview conducted:
☐ Discharge ☐ 3 Months ☐ 6 Months ☐ 9 Months

4. Was the interview conducted for the current period?
☐ Yes
i. Date of this interview ___/___/___
ii. Where was questionnaire performed?
1. In hospital as in-patient
2. In person at follow-up clinic
3. Over the telephone
☐ No
i. Reason this interview was not conducted *(select one)*
1. Child died
2. Unable to Contact
3. Family refused this contact
4. Consent withdrawn. No further follow-up
5. Other (Describe): _____

_____

5. Information received from:

☐ Mother ☐ Father ☐ Grandparent ☐ Foster Parent ☐ Other

Aerogen Pharma Protocol Number APC-AF-CLN-002

6. Since discharge (or last interview), has your child had a cough without a cold?
☐ Yes ☐ No

6.a. If Yes, how often do you notice a cough without a cold?
a. Every day
b. Not every day, but more than once per week
c. Once a week
d. Not every week

6.b. When does your child have this cough without a cold ? (select one)
a. More often during the day
b. The same amount whether it is day or night
c. More often at night

7. Since discharge (or last interview), has a medical person (nurse or doctor) told you he/she heard wheezing when listening to your child's chest?
☐ Yes ☐ No

7.a. If Yes, when has a medical person heard wheezing in your child's chest? (select one)
a. Only when my child has a cold
b. Only when my child has NOT had a cold
c. Both when my child has a cold and without a cold

8. Since discharge (or last interview), has your child been treated in the Emergency Department or by another doctor in the office or clinic because of a breathing problem or a change in his/her breathing?
☐ Yes ☐ No ☐ N/A

8.a. If yes, how many times was your child treated in the Emergency Department, office or clinic?
☐ ≤ 2 ☐ 3-5 ☐ 6-10 ☐ >10

9. Since discharge (or last interview), has your child been admitted to the hospital overnight?
☐ Yes ☐ No ☐ N/A

9a. How many times was your child admitted to the hospital overnight?
___ ___ ___

9b. How many times was this because of a breathing problem or a change in his/her breathing?
___ ___ ___

Aerogen Pharma Protocol Number APC-AF-CLN-002

10. Is your child currently on oxygen or a breathing machine (ventilator) at home (or in hospital)?

☐ Yes →
- 10.a. Is child currently on oxygen? ☐ Yes ☐ No
- 10.b. Is child currently on a ventilator? ☐ Yes ☐ No

☐ No →
- 10.c. Has your child been on oxygen at home since discharge (or last interview)? ☐ Yes ☐ No
- 10.d. Has your child been on a ventilator at home since discharge (or last interview)? ☐ Yes ☐ No

11. Since discharge (or last interview), has your child been diagnosed with a respiratory syncytial virus (RSV) infection?

☐ Yes ☐ No

12. Which of these medications has your child been prescribed (at home or in the hospital) since discharge (or last interview)? *(Select all that apply)*

☐ Inhaled bronchodilators ☐ Systemic Steroids
☐ Inhaled steroids ☐ Pulmonary vasodilators
☐ Diuretics ☐ None of the above

See Medications list on last page

13. How many people normally live in your home including your baby (for at least 6 months of the year)? *(select one)*

☐ 2-3 ☐ 4-6 ☐ 7-10 ☐ >10

13.a. Are there any children < 5 years of age (other than your baby)? *(select one)*

☐ None ☐ 1-2 ☐ 3-5 ☐ 6-8 ☐ >8

14. Do you currently have any pets? *(select all that apply)*

☐ None ☐ Dog ☐ Cat ☐ Other furry animal ☐ Fish ☐ Birds ☐ Other

Questionnaire Completed by *(staff)*: _____ Date: _____

Aerogen Pharma Protocol Number APC-AF-CLN-002

Complete at 6 and 12 months ONLY:

15. What type of milk does your child drink?
☐ Breast milk only ☐ Breast milk and Formula ☐ Formula Only ☐ Other ☐ No enteral feedings

16. What is the route of feedings? *(select one)*

☐ 100% Nipple (breast or bottle)

☐ Naso-gastric or Gastric tube (any NG counts as NG or gastrostomy)

☐ Parenteral (any parenteral counts as parenteral)

17. Was breast milk discontinued since last interview? ☐ Yes ☐ No

17a. If Yes, how old (in months) was the child when breast milk was discontinued? (approximate corrected age in Months ___ ___ *(months)*

18. Does your child receive any care outside the home? ☐ Yes ☐ No

18.a. If yes, who provides care? *(select all that apply)*

☐ Relatives ☐ Daycare ☐ Friends ☐ Other

18.b. Are other children that are not siblings present at outside care site?

☐ Yes ☐ No

19. Please describe the situation regarding smoking in your child's home.

19.a. Which of the following statements best describes the situation regarding smoking in your child's home?

☐ Smoking is allowed in any room in the house

☐ Smoking is limited to part of the house where the child will rarely go

☐ Occasionally there is smoking inside the house (visitor, family member)

☐ There is no smoking inside the house at all

☐ Other Specify: _____

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Complete at 6 and 12 months ONLY:

19.b. Dose either parent smoke? ☐ Yes ☐ No ☐ Don't know

19.c. If yes, estimate the number of cigarettes per day:

☐ < 5 ☐ 5-10 ☐ 11-20 ☐ > 1 pack/day ☐ Unknown

20.3. Altogether, how many people who live in the house smoke?

☐ None ☐ 1-2 ☐ >2

20.4. Does your child travel regularly (at least once a week) in a vehicle (car or truck) that someone smokes in, even when the child is not in the car?

☐ Yes ☐ No

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Complete 12 months ONLY:

21. Family/Social history at time of assessment:
    a. ☐ One Parent
    b. ☐ Two Parents
    c. ☐ Foster Home
    d. ☐ Other Describe: _____

22. Primary language spoken in the home:
    a. ☐ English spoken as first language
    b. ☐ English spoken as second language *Specify 1st language* _____
    c. ☐ English spoken very little or none at all*Specify 1st language* _____
    d. ☐ Unknown

23. Maternal education
    a. ☐ Some education, high school not complete
    b. ☐ High school graduate
    c. ☐ Some college
    d. ☐ College graduate
    e. ☐ Graduate study
    f. ☐ Unknown/Unavailable

24. Maternal employment:
    a. ☐ Employed as: *Specify:* _____
    ☐ Full time homemaker
    b. ☐ Student
    c. ☐ Unemployed
    d. ☐ Unknown

25. Medical history at time of assessment:
    a. Since hospitalization or last follow-up exam, has child received any of the following diagnoses or surgeries? *(select all that apply)*
    ☐ Gastrostomy tube placement
    ☐ Ventriculoperitoneal (VP) shunt
    ☐ Seizure disorder requiring treatment
    ☐ Failure to thrive
    ☐ Tympanostomy tubes
    ☐ Eye surgery
    ☐ PDA ligation or other closure of PDA
    ☐ None of the above diagnoses or surgeries received since initial hospitalization or last follow up exam

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26. How many times has child been hospitalized for non-respiratory illness or surgery? *(total hospitalizations, including those identified on Question 25a)*

    Total number of hospitalizations: ___ ___ ___ ☐ None ☐ N/A (infant still in hospital)

27. Is child taking any of the following medications for a chronic medical condition? *(select all that apply)*
    a. ☐ Anti-reflux medications
    b. ☐ Prokinetics
    c. ☐ Anti-epileptics
    d. ☐ Other *Specify:* _____
    e. ☐ Not taking any medications listed above

28. Has your child ever had hay fever or another condition that makes his/her Nose or eyes runny, stuffy or itchy, **without a cold**?

    ☐ Yes ☐ No

29. Has your child ever been allergic to any food?

    ☐ Yes ☐ No

    (these are reactions that include rash and swelling, not vomiting or diarrhea)

30. Has your child ever been allergic to any medicine?

    ☐ Yes ☐ No

    (these are reactions that include rash and swelling, not vomiting or diarrhea)

31. Has your child ever had eczema diagnosed by a doctor?

    ☐ Yes ☐ No

32. Has your child ever been diagnosed with asthma by a doctor?

    ☐ Yes ☐ No

33. Milestones:
    a. Is child able to sit without support? ☐ Yes ☐ No
        i. Corrected age at which child sat without support: _____ *(months of age)*
    b. Is child able to crawl independently? ☐ Yes ☐ No
    c. Is child able to walk independently? ☐ Yes ☐ No
        i. Corrected age at which child walked independently: _____ *(months of age)*

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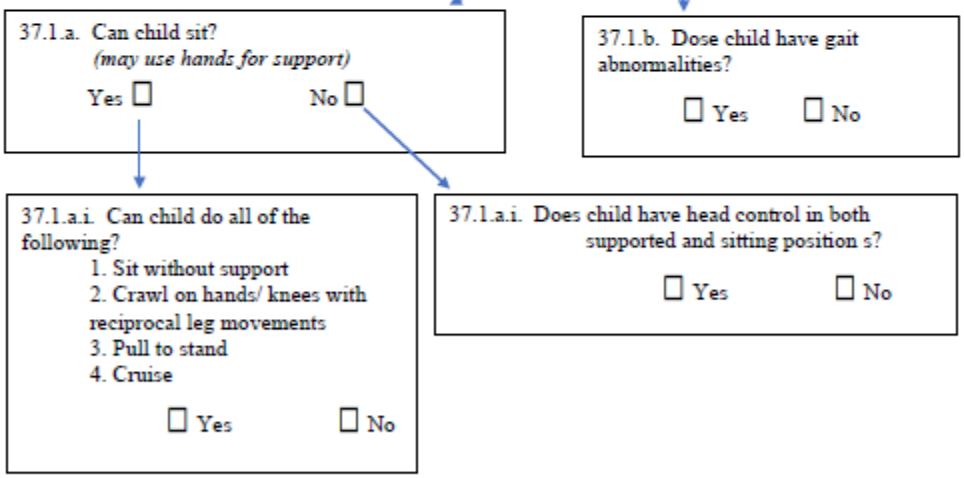
34. Child growth parameters at time of assessment (questionnaire)?
    a. Weight (kg) ___ ___ . ___ ☐ Unknown

35. Child's vision at the time of assessment:
    a. Visual function: *(Select one)*
    ☐ Normal ☐ Unilateral blindness ☐ Bilateral blindness ☐ Prescription glasses

    b. Visual problems at time of assessment: *(Select one)*
    ☐ None ☐ Cataracts
    ☐ Strasbismus ☐ Glaucoma
    ☐ Cortical blindness ☐ Retinal detachment
    ☐ Optic atrophy ☐ Other *Specify:* _____

36. Childs hearing:
    a. Hearing function: *(Select one)*
    ☐ Normal
    ☐ Unilateral hearing loss *36.a.i. Requires amplification?* ☐ Yes ☐ No
    ☐ Bilateral hearing loss *36.a.ii. Requires amplification?* ☐ Yes ☐ No

37. Was Modified Gross Motor Function Test Performed? ☐ Yes ☐ No



38. Has a physician diagnosed this child with cerebral palsy? ☐ Yes ☐ No
    a. Cerebral palsy is characterized by:
    ☐ Diplegia ☐ Hemiplegia ☐ Quadriplegia ☐ Other

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Medication List:

Bronchodilators
Examples: albuterol (Ventolin)
levalbuterol (Xopenex),
ipratropium bromide (Atrovent)

Inhaled steroids
Examples: beclomethasone (Qvar)
budesonide (Pulmicort),
flunisolide (Aerobid),
fluticasone (Flovent)
triamcinolone (Azmacort)

Diuretics
Examples: furosemide (Lasix)
chlorothiazide (Diuril)
hydrochlorothiazide (Hydrodiuril)
aldactone

Systemic steroids
Examples: cortisone
dexamethasone
prednisone
prednisolone
methylprednisolone

Pulmonary vasodilators
Examples: sildenafil (Revatio)
tadafil (Adcirca)
bosentan (Tracleer)
ambrisentan (Myogn)
inhaled iloprost (Ventavis)
beraprost
trepoprostenol
epoprostenol (Flolan)
inhaled nitric oxide