A MULTINATIONAL, MULTICENTER, MASKED, RANDOMIZED, CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF LUCINACTANT FOR INHALATION IN PRETERM NEONATES 26 TO 32 WEEKS GESTATIONAL AGE WITH RESPIRATORY DISTRESS SYNDROME.

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To evaluate the safety and efficacy of lucinactant for inhalation, in comparison to nasal continuous positive airway pressure (nCPAP) alone, inpreterm neonates with RDS, as assessed by the time to, and incidence of, respiratory failure and/or death…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neonatal respiratory disorders
Study type	Interventional

Summary

ID

NL-OMON43417

Source
ToetsingOnline

Brief title
Lucinactant for inhalation

Condition

- Neonatal respiratory disorders

Synonym
lung problems in early born baby's, Respiratory distress syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Discovery Laboratories Inc
Source(s) of monetary or material Support: Discovery Laboratories Inc

Intervention

Keyword: Inhalation, Lucinactant, Neonates, RDS

Outcome measures

Primary outcome

The primary endpoint for this study is time to respiratory failure or death due

to RDS within the first 72 hours of life. Respiratory failure and death

due to RDS are defined in the *Efficacy Endpoints* section.

Secondary outcome

The secondary endpoints of this study include the evaluation of the incidence

of respiratory failure or death due to RDS, the incidence of BPD

at 36 weeks PMA, all-cause mortality, survival without BPD at 36 weeks PMA,

incidences of common complications of prematurity (especially air

leak), and change in FiO2 and/or PCO2.

Study description

Background summary

Preterm neonates are often surfactant deficient and receive surfactant replacement therapy (SRT) to treat respiratory distress syndrome (RDS).Currently, SRT is instilled directly into the neonate*s lung through an

endotracheal tube usually while receiving positive pressure mechanical ventilation (MV). However, data from studies in animal models of RDS suggest that positive pressure MV administered by an endotracheal tube may be injurious to the preterm lung. In an attempt to avoid endotracheal intubation and MV, to support preterm newborns with mild to moderate RDS, nasal continuous positive airway pressure (nCPAP) has become a widely accepted practice. However, use of nCPAP precludes delivery of SRT and deterioration in over one-third to one-half of preterm neonates receiving nCPAP has been observed in large multicenter trials, with most requiring endotracheal intubation, MV, and in many cases delayed administration of SRT. Meta-analyses of clinical surfactant studies indicate that SRT is most effective when administered early in the course of RDS, and the therapeutic benefit of SRT can diminish substantially when administered late. Therefore, the inability to administer SRT in preterm neonates with RDS who are initially supported with nCPAP and then deteriorate, requiring endotracheal intubation and delayed SRT results in suboptimal timing for SRT to treat RDS.

Study objective

To evaluate the safety and efficacy of lucinactant for inhalation, in comparison to nasal continuous positive airway pressure (nCPAP) alone, in preterm neonates with RDS, as assessed by the time to, and incidence of, respiratory failure and/or death due to RDS, incidence of bronchopulmonary dysplasia (BPD), and change in physiologic parameters (fraction of inspired oxygen [FiO2] and partial pressure of carbon dioxide [PCO2]) over the first 72 hours of life.

Study design

This study is a multinational, multicenter, masked, randomized, controlled study to evaluate the safety and efficacy of 2 different doses of lucinactant for inhalation (40 mg TPL/kg and 80 mg TPL/kg) in conjunction with nCPAP compared with nCPAP alone, in preterm neonates 26 to 32 completed weeks PMA who are being cared for in a neonatal intensive care unit (NICU) and who are within the first 20 hours after birth, who had successful implementation of controlled nCPAP within 90 minutes of birth, and who are candidates for SRT. Neonates will be enrolled by strata: 26 to 28 completed weeks PMA and 28 to 32 completed weeks PMA; approximately 2/3 of enrolled subjects will be in the 26 to 28 completed weeks PMA strata. There will be 2 phases in the study, a primary phase through 36 weeks PMA and a longer-term follow-up phase through 1-year corrected age. Before study enrollment, legal guardians will provide a signed written informed consent form (ICF) for each potential subject. Qualification for study enrollment will be established after confirmation that the subject has met all of the inclusion criteria and none of the exclusion criteria. The clinical criteria for

enrollment may be met prior to informed consent being obtained; however, no study-specific procedures that are not part of the usual standard care of the subject at the institution may be performed until the informed consent has been provided by a legally authorized representative of the subject. Inclusion criteria to be met within the first 20 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 6 cm H2O for at least 30 minutes to maintain oxygen saturation measured by pulse oximetry (SpO2) of 90% to 95%, with a fraction of inspired oxygen (FiO2) within a range of 0.25 to 0.45, also for at least 30 minutes. As soon as study eligibility has been confirmed and the informed consent is signed, subjects will be randomized to 1 of 2 active treatment groups or the control group (nCPAP only). Study therapy (lucinactant for inhalation or control) must be initiated as soon as possible after randomization, with the caveat that all subjects must continue to meet entry criteria at the time of initiation of study therapy (lucinactant for inhalation, or control).
Subjects may be eligible to receive up to 2 repeat doses. Repeat doses will be allowed 2 hours from completion of the previous dose up to 36 hours after completion of randomization if subjects meet repeat dosing criteria, as described in the *Treatment Groups* section. Subjects randomized to the control group will be continued on nCPAP alone. All subjects in the active treatment groups will receive the same drug
concentration of lucinactant for inhalation at the same rate delivery. The dose will vary by the volume of the nominal dose of lucinactant (30 mg TPL/mL) aerosolized and introduced into the nCPAP circuit, given over a predetermined time for each dose. The lucinactant for inhalation delivery will be facilitated by the investigational ADS device in conjunction with a commercially available nCPAP generator and patient interface.
Dose assignments will be masked to the principal investigator (PI); study staff (eg, site coordinator), as applicable; sponsor; and subject*s parents/legal guardians. All enrolled subjects will receive study treatment in a NICU, a specialized care center staffed by neonatologists, nurses, and respiratory therapists who are experienced in the delivery of emergent care to the preterm neonatal population. Neonates in the NICU are continuously monitored using advanced and sophisticated monitoring equipment, and there is ready and immediate access to equipment, medications, and skilled personnel that may be needed to address emergent developments. Interventions such as endotracheal intubation, MV, and surfactant administration will be readily available to all study subjects if clinically indicated in accordance with the high level standard of care customary in the NICU. Neonates will be followed through the primary phase efficacy and safety evaluations through 36 weeks PMA, NICU discharge, hospital transfer, or death, whichever occurs first. For the longer-term follow-up phase, neonates will be followed up to 1-year corrected age, at which time a physical examination will be performed, including an abbreviated neurologic assessment.

Intervention

This clinical study is intended for preterm neonates 26 to 32 completed weeks postmenstrual age (PMA). Currently, preterm neonates 29 to 34 weeks PMA have been studied in Protocol 03-CL-1201 in a dose escalation of 25, 50, and 75 mg total phospholipids (TPL)/kg (with an extension currently ongoing, which continues the dose escalation up to 150 mg TPL/kg and also allows a repeat dose if repeat dosing criteria are met). Similarly, a dose escalation study in preterm infants 26 to 28 weeks PMA has been initiated (Protocol 03-CL-1401). To date, lucinactant for inhalation has been generally well tolerated and there have been generally no safety signals of concern with escalating doses.

Study burden and risks

The inability to administer SRT without the need for endotracheal intubation represents an important unmet medical need. Aerosolized surfactant delivery potentially addresses this unmet medical need by providing a means to deliver SRT noninvasively to preterm neonates with RDS supported with nCPAP, thereby providing SRT early in the disease course while avoiding the need for endotracheal intubation.
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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Signed ICF from legally authorized representative
2. 26 to 32 completed weeks PMA
3. Successful implementation of controlled nCPAP within 90 minutes after birth
4. Spontaneous breathing
5. Chest radiograph consistent with RDS
6. Within the first 20 hours after birth, respiratory insufficiency requiring an nCPAP of 5 to 6 cm H2O to maintain SpO2 of 90% to 95%, with an FiO2 of 0.25 to 0.45 that is clinically indicated for at least 30 minutes. Transient (<10 minutes) FiO2 excursions below 0.25 or above 0.45 do not reset the 30-minute requirement.

Exclusion criteria

1. A heart rate that cannot be stabilized above 100 beats per minute (bpm) within 5 minutes of birth
2. Recurrent episodes of apnea requiring positive pressure ventilation (PPV) using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface
3. A 5 minute Apgar score < 5
4. Major congenital malformation(s), including and cranial/facial abnormalities that preclude delivery of nCPAP via nasal prongs, diagnosed antenatally or immediately after birth
5. Other diseases or conditions, including those potentially interfering with cardiopulmonary function (eg, hydrops fetalis or congenital infection, such as toxoplasmosis, rubella, cytomegalovirus, and herpes simplex [TORCH])
6. A known or suspected chromosomal abnormality or syndrome
7. Premature rupture of membranes (PROM) > 2 weeks
8. Evidence of hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis
9. A need for intubation and/or mechanical ventilation at any time before enrollment into the

study
10. The administration (or plan for administration) of any the following:
a) Another investigational agent or investigational medical device
b) Administration of any other surfactant agent
c) Steroid treatment (exposure before birth is acceptable; ie, antenatal steroids)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-12-2016
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aerosurf
Generic name:	Lucinactant

Ethics review

Approved WMO

Date:	21-04-2016
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003519-40-NL
CCMO	NL56044.078.16