MULTICENTRE BIOMEDICAL RESEARCH PROJECT

Exogenous surfactant in very preterm neonates presenting with severe respiratory distress in prevention of bronchopulmonary dysplasia

Sponsor Coordinator and Primary investigator

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Document created according to the criteria of the Edict of 24 May 2006 on the contents and methods of presentation of a protocol of biomedical research conducted on a medicinal product for human use. O.J. of 30 May 2006.
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1.6 Study Monitoring Committee

The study monitoring/steering committee will be made up of two Hospital Practitioners, Clinician-Researchers who are not participating in the study. This committee will analyse any adverse events. An evaluation will be performed at the halfway point of recruitment in the study (i.e., when 50 complete files of children have been validated), and if necessary, in case of occurrence of adverse events that are unexpected in their seriousness and/or their frequency. It will create a detailed report for the coordinating investigator, who will take appropriate measures if necessary.

Members of the monitoring committee:

- **Professor Olivier CLARIS**
  Neonatologie
  Hopital Femme Mere Enfant
  59, Boulevard Pinel
  69677 BRON Cedex

- **Professor Thierry DEBILLON**
  Neonatology Department
  Grenoble Teaching Hospital
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1.7 Methodological and statistical management of the study

This will be performed in partnership with CEC – INSERM of Nancy:

- **Professor. Rachel VIEUX, MD, PhD**
  Paediatrician, Neonatologist,
  Methodologist and Statistician (PhD)
  Maternite Regionale Universitaire - EA 4360 APEMAC,
  Université de Lorraine, Nancy

- **Professor Francis GUILLEMIN, MD, PhD**
  University Professor – Hospital Practitioner
  Coordinating Doctor of the CEC – INSERM of Nancy
  Department of Epidemiology and Clinical Evaluations, CIC-EC INSERM
  Marin Teaching Hospital – Nancy
1.8 Associated Analysis Laboratory (centralisation of biological analyses)

- Dr. Patricia FRANCK
  Hospital Practitioner; Department Head
  Laboratory of Medical Biology
  Maternité Régionale Universitaire – Nancy

1.9. Monitoring and secretarial work for the study

The Sponsor entrusts the Coordinating Investigator with the organisation of monitoring of the study, which will be performed by members of the research coordination team in Nancy.

- Marie Christine BUCHWEILLER
  Clinical Research Assistant
  Department of Neonatology, Neonatal Intensive Care and Resuscitation
  Maternité Régionale Universitaire – Nancy

- Sabine GUIGNON
  Clinical Research Assistant
  Department of Neonatology, Neonatal Intensive Care and Resuscitation
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- Anne-Fleur ANDRE
  Clinical Research Technician
  Department of Neonatology, Neonatal Intensive Care and Resuscitation
  Maternité Régionale Universitaire – Nancy

The Sponsor assigns part of the secretarial work of the Coordinating Investigator Centre to the research coordination team for the duration of the study.

- Sylvie VOIRIN
  Medical Secretary
  Department of Neonatology, Neonatal Intensive Care and Resuscitation
  Maternité Régionale Universitaire – Nancy

1.10 Partners

- CHIESI Farmaceutici S.p.A
  Via Palermo 26/A
  43100 PARMA - Italy

- ARAIRLOR (Regional Association for the Assistance of Persons with Respiratory Failure of Lorraine)
  2 Route de Mirecourt
  54500 Vandoeuvre Les Nancy

- APRESAN (Association for the Sponsorship of Research on Neonatal Care)
  Maternité Régionale Universitaire
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  54042 NANCY Cedex
1.11. Project summary

Advances in perinatal care have made it possible to improve the survival of the most immature neonates, but at the cost of an increase in the population at risk of developing bronchopulmonary dysplasia (BPD), which is responsible for respiratory and neurodevelopmental effects. Measures that have attempted to limit the development of BPD are not always effective, or related to major side effects. The physiopathological factors that are identified in BPD should, in theory, respond to surfactant. Therefore, the use of an exogenous surfactant, in a curative way, in neonates presenting with pulmonary disease requiring mechanical ventilation, leading to a significant risk of BPD, should allow earlier extubation and thus promote pulmonary healing and growth.

Objectives of the study:

Primary: to demonstrate a significant reduction of the duration of assisted ventilation in children presenting with severe respiratory distress.

Secondary:
- to reduce the incidence of BPD to 36 weeks of postconception age;
- to improve the inflammatory status of the lung and to restore its capacities for healing and growth;
- to improve development in stature and weight, psychomotor development, and to reduce respiratory sequelae leading to re-hospitalisation at the age of 1 years;

Method: a prospective, randomised French multicentre study, with double-blind, comparing traditional management (without surfactant) to the administration of an exogenous surfactant used in a curative manner.

Inclusion criteria: any neonate of gestational age less than 33 weeks of amenorrhea still on conventional assisted ventilation or HFOV (High Frequency Oscillatory Ventilation), after 14 ± 2 days of life, with FiO2 > 30% and/or an Oxygenation Index (OI) (OI = MAP x FiO2/PaO2 > 7 (MAP = mean airway pressure).

Exclusion criteria: active infection (CRP>30 mg/L) not controlled by appropriate antibiotic treatment; use of corticosteroids in the postnatal period, neurological or malformative disease jeopardising the appropriateness of extubation; surgical intervention < 72 hours; refusal of parental authorisation.

Number of subjects: 43 children/group are necessary to demonstrate a reduction of 10 days in the duration of ventilation, with an alpha risk of 0.05 and a power of 90%. Considering the usual risk of patients lost to follow-up, 20%, at least 50 children completing the study will be recruited in each group.
Evaluation endpoints:

Primary: the criteria of extubation will require a period of stability of at least 6 hours, and will involve:
. OI < 7 and/or FiO2 < 30% for SaO2 = 88-92% and/or PaO2 = 50-70 mmHg; and PaCO2 = 40-55 mmHg
. MAP < 7 mmHg and/or frequency < 25 /min in conventional ventilation; MAP < 9 mmHg in oscillations
. Extubation will be considered to be successful if it is maintained for at least 72 hours.
. Criteria for re-intubation = 6 episodes of apnoea/bradycardia requiring stimulation/6 hrs or at least one episode requiring resuscitation with positive pressure or FiO2 > 60% or PaCO2 > 60 mmHg for at least 6 hrs.

Secondary:
. Incidence of BPD on D28 (defined by FiO2 > 21%) and at 36 weeks of postconception age (PCA) (defined as a moderate, average, and severe according to Jobe and Bancalari (reference 20, page 13)).
. Laboratory evaluation using the Multiplex® technique on tracheal aspiration at randomisation, after 48 hrs, on D28 and just before extubation: inflammatory status of the lung (assay of levels of IL-6, TNF alpha, IL1 beta and IL10) and changes in capacities of pulmonary healing and growth (Metalloproteinases (MMP9) and their inhibitor (TIMP-1) and Vascular Endothelial Growth Factor (VEGF)).
. Rate of survival without neurological sequel at D28 and 36 weeks PMA (criteria of Papile and De Vries)
. Growth in height and weight at D28, 36 weeks PCA, 40 weeks PMA, 1 year
. Respiratory morbidity at 1 year PNA: total duration of supplementation with O2; number and duration of re-hospitalisations for respiratory disease. Recording of any administration of corticosteroids.

Statistics: analysis will be performed in intention to treat without crossover
2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1 Experimental medicinal product
The medicinal product studied is CUROSURF® from the CHIESI Co., a product which already has Marketing Authorisation (in the same population that being studied and at the same dosage), but for another indication, at an earlier postnatal age.

2.2 Summary of results of available, pertinent non-clinical and clinical trials

NA (first study on the topic in this indication)

2.3 Summary of foreseeable and known benefits and risks

Expected benefits:

Direct benefits are expected for patients participating in this work because the administration of the surfactant should make it possible to obtain earlier extubation, a reduction in the risk of BPD with a balancing of pulmonary inflammatory status, an improvement in healing and renewed pulmonary growth. Children in the 2 groups will also receive short-term, medium-term and long-term follow-up. This will make it possible to evaluate the impact of the curative surfactant prescribed in the neonatal period in premature children presenting with severe respiratory distress, as compared to control subjects:
- on growth and development, particularly cognitive development, at the age of 1, 2 and 7 years PNA.
This follow-up will make it possible to implement appropriate preventative or therapeutic measures if necessary.

A significant cognitive benefit is expected, because it should make it possible to position this treatment, which is already used in prevention and treatment of hyaline membrane disease in neonates, in a new indication of prevention of development of severe BPD for children requiring a prolongation of mechanical respiratory assistance. The study will make it possible to better understand the determinants of bronchial hyper-reactivity in dysplastic children born prematurely and to objectively quantify the incidence of exertion-induced airway obstruction in this population.
Foreseeable risks:

No particular foreseeable risk outside of temporary desaturation at the time of instillation of the surfactant as described in the M.A. of CUROSURF, and a possible obstruction of the intubation tube, which is easily prevented by prior tracheal aspiration. The other possible risks described in the Marketing Authorisation of the product are not applicable in this new indication because haemodynamic stability is acquired at this postnatal age, unlike the immediate neonatal period.

2.4 Route of administration, dosage, regimen of administration

The route of administration, the dosage and the regimen of administration are those described in the Marketing Authorisation:

**Route of administration:** the bottle should be heated to 37°C before use and shaken gently up and down in order to obtain a uniform suspension. It is then instilled, either in a single dose, directly into the lower trachea, or in 2 half doses, one half in the right main bronchus and the other half in the left main bronchus.

**Dosage:** the recommended dose is 200 mg/kg (i.e., 2.5 mL/kg).

**Regimen of administration:** After heating, the suspension must be withdrawn from the bottle using a thin needle and a sterile syringe, then instilled according to the procedure described above. After instillation, it is necessary to ventilate the child manually for a brief period (approximately 1 minute) using the same mixture of oxygen as that used before treatment, in order to allow uniform distribution. Then the child can be reconnected to a ventilator, and the mixture should be adjusted based on the clinical condition and analyses of blood gases.

The protocol calls for administration of a **single dose** without any additional dose.

2.5 Declaration of good practices

The biomedical research will be conducted in accordance with the protocol and will be performed according to the legislative and regulatory dispositions in force, in compliance with Good Clinical Practices and the Declaration of Helsinki.

2.6 Description of the study population

Neonates of both sexes, with gestational age less than 33 weeks of amenorrhea, still on conventional assisted ventilation or high-frequency oscillation ventilation after 14 ± 1 days of life, with FiO₂ > 30% and/or an Oxygenation Index (OI = MAP*FiO₂ / PaO₂) > 7 (MAP = mean airway pressure and PaO₂ = partial pressure of O₂ measured by bleeding or percutaneously, the sensor being placed in a postductal position).
2.7 References and scientific rationale of the study

Scientific rationale of the study

Bronchopulmonary dysplasia (BPD) is a dangerous complication of premature birth, responsible for incapacitating respiratory and neurodevelopmental handicaps. A chronic pulmonary effect of respiratory distress in the neonate, its incidence is still quite high (1-3). Indeed, measures to prevent or attenuate the onset of this disease, such as improvement in perinatal care, prenatal use of corticosteroids (4, 5) and the introduction of an exogenous surfactant (6, 7) have also made it possible to significantly improve the survival of the most immature neonates. This significant reduction in mortality has taken place at the cost of an increase in the population at high risk of developing a chronic pulmonary disease (8). BPD is a perinatal disease caused by multiple factors, for which multiple therapeutic approaches have been proposed. Postnatal corticosteroid therapy (4, 9), trials of antioxidant treatments (10, 11) and various strategies of assisted ventilation with the objective of reducing barotrauma or volutrauma lesions and/or preventing the onset of pulmonary fibrosis (12, 13). These measures have made it possible to limit somewhat the development of BPD, but are not always effective or devoid of major side effects in the long term, such as postnatal corticosteroid therapy, the interest of which is directly compromised by risks of worsening of neurological sequelae (5, 14). Thus, after a methodological analysis of the current state of knowledge, the American Pediatric Academy and the Canadian Fetus and Newborn Committee have recommended that the use of corticosteroids should be limited to serious, active forms dependent on the respirator and falling under the scope of well conducted clinical studies (14).

The physiopathological factors identified in serious forms of BPD include the presence of cellular debris in distal airways (15, 16); alterations in cellular functions such as those of type II pneumocytes (17) although the stock of surfactant seems to be little modified (18, 19); episodes of oedema and inflammatory episodes (13, 20); alteration in compliance and bronchomotor disorders (21); disorders of pulmonary healing and growth (13, 22) in a particularly vulnerable period, as well as increased oxidative stress in an immature organism at the level of its antioxidant defences (23). It is remarkable to observe that all these elements fall in the category of dysfunctions they can be treated or at least attenuated by exogenous surfactant. Finally, certain genetic variants lead to lower concentrations of surfactant specific proteins (SP), which are indicative of a more severe evolution of the disease and may respond in certain cases to the administration of surfactant (17).
On a basic level, disorders of pulmonary healing and growth, in a developing subject, appear to be the major mechanism leading to the characteristic pulmonary fibrosis resulting from BPD (13, 20, 22). This recognition has led to the definition of “new dysplasia”, relating to an imbalance in pulmonary inflammatory status, as opposed to “old dysplasia”, related to the aggressiveness of artificial ventilation causing barotrauma and volutrauma (20). This latter form of BPD has been considerably reduced by the more widespread use of prenatal maturation and introduction of surfactants very early after birth. Among the cytokines involved in the imbalance of pulmonary inflammatory status of “new” BPD, one notes particularly the role of Interleukins 6 (IL6) (24, 25) and 1 beta (IL1-beta) (24, 26), the latter probably also having a role in the arrest of pulmonary growth (27). TNF alpha (Tumour Necrosis Factor) also seems to play a major role in lesions in the lungs (28, 29). On the other hand, it is possible that IL10, normally involved in protection against inflammatory aggression, is expressed in a delayed manner in immature or premature neonates, contributing to the imbalance demonstrated in BPD (30). In terms of arrest and pulmonary growth, a block in the mechanisms of tissue remodelling has been suggested, illustrated by the relationship between metalloproteinases such as MMP9 (Matrix Metalloproteinase) (31, 32) and their inhibitors such as TIMP-1 (Tissue Inhibitor of Metalloproteinase) (33). Lastly, vascular abnormalities observed concomitantly in severe BPD may be associated with abnormalities of the primary pulmonary vascular growth factor, VEGF (Vascular Endothelial Growth Factor), which acts in synergy with nitric oxide (NO) (34). The projected study will evaluate the impact of treatment using exogenous surfactant on pulmonary inflammatory balance and capacities for renewed pulmonary and vascular growth.

Lastly, vascular abnormalities associated with BPD may have a functional impact ranging up to significant pulmonary arterial hypertension (35). We, along with other researchers, have shown that inhaled NO may be used safely in premature neonates, either in prevention (36) or in treatment of BPD (37, 38). While studies are not yet sufficient to recommend its systematic use in this indication, the results are sufficiently promising that inhaled NO is no longer withheld from children developing towards severe BPD with hemodynamic involvement (35). Since inhaled NO does not have any adverse effects on surfactant (39), this combination can only be synergetic in severe forms. This study will offer children developing toward particularly severe BPD with hemodynamic involvement confirmed by pulsed Doppler ultrasound (35), the use of inhaled NO in the 2 study groups.
Thus, the use of the exogenous surfactant in a curative manner in neonates presenting with pulmonary disease dependent on a respirator and risking development toward severe BPD should allow early extubation and promote healing and renewal of pulmonary growth, without the risks of long-term neurodevelopmental sequelae induced by corticosteroids, for example. Follow-up at 2 and 7 years of these prematurely born children will make it possible to verify the relevance of such treatment on their outcome.

References


8. Parker RA, Lindstrom DP, Cotton RB. Improved survival accounts for most but not all of the increase of BPD. Pediatrics 1992; 90:663-8


10. Frank L. Sosenko IR. Failure of premature rabbits to increase antioxidant enzymes during hyperoxic exposure: increased susceptibility to pulmonary oxygen toxicity compared with term rabbits. Pediatr Res 1991; 29:292-6


34. Thebaud B, Abman SH. Bronchopulmonary Dysplasia Where Have All the Vessels Gone? Roles of Angiogenic Growth Factors in Chronic Lung Disease. Am J Respir Crit Care Med 2007;175:978–85


3. OBJECTIVES OF THE RESEARCH

3.1 Primary objective
To demonstrate a significant reduction in the duration of assisted ventilation in children presenting with severe respiratory distress still requiring assisted ventilation with FiO2 ≥ 35% at 14 ± 1 days of life.

3.2 Secondary objectives
1. To reduce the incidence of BPD at 36 weeks of postmenstrual age (PMA)
2. To improve the inflammatory status of the lung and to restore its capacities for healing and growth, evaluated by assay of cytokines in the tracheal aspirations.
3. To improve development in height and weight, neuro/psychomotor development, and to reduce respiratory sequelae leading to re-hospitalisations at 1 and 2 years of age;
4. To improve stature development, psychomotor development and respiratory function at 7 years of age.

4. DESIGN OF THE RESEARCH

4.1 Evaluation endpoints

4.1.1 Primary evaluation endpoint:
Significant reduction in the duration of assisted ventilation in children presenting with severe respiratory distress:

Criteria for extubation: period of stability of at least 6 hrs
OI (= MAPxFiO2/PaO2 < 7 and/or FiO2 < 30%; for SaO2 = 88 – 92% and/or PaO2 = 50 – 70 mmHg and PaCO2 = 40 – 50 mmHg (arterial or percutaneous blood gases with sensor in postductal position).
MAP (mean airway pressure) < 7 mmHg with CMV (Conventional Mechanical Ventilation) or < 9mmHg with HFOV (High Frequency Oscillation Ventilation) and/or frequency < 25/min with CMV

Successful extubation = maintained for at least 72 hrs:
Criteria for re-intubation = 6 episodes of apnoea/bradycardia requiring stimulation / 6hrs or 1 apnoea/bradycardia requiring resuscitation with positive pressure, or FiO2 > 60%, or PaCO2 > 60 mmHg for at least 6 hrs (Coin Trial NEJM 2008)

Note: sPEEP and FiO2 = 21.5% (“medical” air), registered, but not standardised.
4.1.2 Criteria of secondary evaluation:

- **Incidence of BPD at D28 (FiO2) and at 36 weeks PCA (ref. 20, page 13):**
  - Moderate BPD: > 28D O2 and FiO2 = 21% at 36 weeks PCA (Note: SV-PEP and mask = 21.5%!)
  - Mean BDP: > 28D O2 and FiO2 \(\geq 21-30\] at 36 weeks PCA (total duration, non-consecutive)
  - Severe BDP: > 28D O2 and FiO2 > 30% at 36 weeks PCA

- **Survival without neurological sequel at D28 and 36 weeks TCA (Echo);**

- **Evaluation of pulmonary inflammatory status in tracheal aspiration:**
  - Balance pro-inflammation: IL6, TNF alpha, IL1 beta
  - anti-inflammation: IL10

- **Evaluation of healing and vascular/pulmonary growth in tracheal aspiration:**
  - MMP9, TIMP-1 and VEGF

- **Growth** at D28, 36 weeks, 40 weeks PCA, 1, 2 and 7 years;

- **Psychomotor and neurological** evaluation at 1 and 2 years (criteria selected from the Brunet-Lezine test (Fily A, Pierrat V, Delporte V, Breart G, Truffert P, EPIPAGE Nord-Pas-de-Calais Study Group. Factors associated with neurodevelopmental outcome at 2 years after very preterm birth: the population-based Nord-Pas-de-Calais EPIPAGE cohort. Pediatrics.2006;117:357-66))

- **Respiratory sequelae at 1 and 2 years:** total duration of O2 supplementation; numbers and duration of re-hospitalisations for respiratory disease. Recording of any administration of corticosteroids.

- Evaluation of **neuromotor development at 7 years**, and cognitive development using the WISC IV test, level of asthma and spirometry (functional respiratory tests \(\Rightarrow\) FEV1, TPC (total pulmonary capacity), effects of betamimetics). Recording of any administration of corticosteroids.

4.2 Methodology

4.2.1 Inclusion criteria:

- Any neonate of gestational age < 33 weeks on CMV or HFOV at \(14 \pm 2\) days of life;
- With FiO2 > 0.35 and/or \(\text{OI} = \text{FiO2xMAP/PaO2} > 7\) for at least \(6\) hrs;
- Informed authorisation from the parents or holders of parental authority.
- Centralised randomisation.

4.2.2 Exclusion criteria:

- Active infection (CRP>30 mg/L) not controlled by antibiotic treatment targeting the identified microbe (blood, urine, spinal tap);
- Surgical intervention (arterial canal or other) within the last 72 hrs
- Previous use of corticosteroids in the postnatal period;
- Disease (chromosomal, neurological (Intraventricular Haemorrhage (IVH) Grade II according to Papile), malformative) jeopardising the pertinence of extubation;
- Refusal of parental authorisation

4.2.3. Procedures:

4.3.2.1. Neonatal period:

- After randomisation, the child receives a tracheal aspiration for assay of cytokines and biological parameters. A practitioner not directly involved in the child’s care then opens the randomisation envelope and proceeds to the instillation of Curosurf® according to the methods described above, or air using a syringe filled with 2.5 ml/kg of air, without the knowledge of the personnel (medical and nursing) involved in the care of the child.
- Medical care is then continued according to the department’s routine.
- 48 hrs after the instillation of Curosurf® or air, a collection of tracheal aspiration fluid for assay of cytokines and biological parameters is performed during a routine tracheal aspiration.
- The same procedure is performed at D28 of postnatal age, unless the child has already been extubated (see below: extubation criteria)
- If the child is still intubated and ventilated on D28, they will receive Doppler echocardiographic evaluation (on D28±1) evaluating, in particular, the presence of any insufficiency or tricuspid regurgitation, on the one hand, and the ratio of time to peak velocity / right ventricular ejection time (TPV/RVET, reference 35 page 14), on the other hand. In case of the presence of insufficiency or tricuspid regurgitation and/or a TPV/RVET ratio < 0.54, treatment with 10 ppm of inhaled NO will be started in the 2 groups (references 37 and 38 page 14). The treatment will be maintained for 7 days (or until extubation) then the child will have an echocardiographic re-evaluation. If the criteria defined above persist, treatment is maintained for another period of 7 days (except in case of extubation). If not, gradual withdrawal will be performed over a period of 24 hrs. This procedure will be performed again up to a possible total duration of 21 days of treatment with inhaled NO (see reference 38 page 14).
- As soon as the child meets the criteria of extubation defined in paragraph 4.1.1 on page 21, they will receive a tracheal aspiration for assay of cytokines and biological parameters. They will then receive a loading dose of 10 mg/kg of caffeine and will be extubated according to the policy of the unit.
4.2.3.2. Follow-up at 1 and 2 years:

- Children participating in this study will receive routine follow-up at 1 and 2 years due to the particular risks that they present. During this visit, they will receive a standardisation of their examination in the context of the study.

- Growth in height and weight: at 1 and 2 years, information on height, weight, cranial circumference, cardiac frequency and resting arterial blood pressure (mean of 2 consecutive Dynamap measurements) will be collected.

- Respiratory evaluation will include the recording of the total duration of O2 supplementation and the number and duration of any hospitalisations for a respiratory disease. Notification of any administration of corticosteroids.

- Psychomotor and neurological evaluation: this study will use selected criteria from the Brunet-Lezine test, which were chosen during the EPIPAGE study and have demonstrated their pertinence and usefulness (Fily A, Pierrat V, Delporte V, Breart G, Truffert P, EPIPAGE Nord-Pas-de-Calais Study Group. Factors associated with neurodevelopmental outcome at 2 years after very preterm birth: the population-based Nord-Pas-de-Calais EPIPAGE cohort. Pediatrics.2006;117:357-66).

4.2.3.3. Follow-up at 7 years: (Ongoing; not part of the manuscript up to 1 year)

4.2.4 Data collection method:

Pre- and post-randomisation clinical data are collected by the investigator in a prospective manner and listed in the anonymous case report form provided for this purpose.

Tracheal aspiration fluids will be centrifuged and then the supernatant will be frozen at -20°C and transmitted to the Coordinator Centre where biological parameters will be measured in a centralised manner using a multiplex technique (R&D System®).

4.3 Inclusion procedures

Any neonates with GA < 33 weeks on CMV or HFOV at 14 ± 2 days of life will be considered to qualify for the protocol. The investigator will verify that the child meets the inclusion criteria and none of the exclusion criteria.

As soon as the child fulfils the conditions for participation in the study, the investigator will approach the parents and request their child’s participation in the study after a full explanation.

Once the authorisation has been obtained in writing, the investigator or his representative will call the Coordinator Centre using the telephone number reserved for this purpose (03 83 34 36 35), available 24 hours a day.

They will be asked for confirmation of the presence of inclusion criteria and the absence of exclusion criteria, and then the number of an opaque sealed envelope available in the centres will be given to them.

This envelope contains the notification of the assigned treatment and should only be opened by the practitioner not involved in the child’s care, who will perform the administration of Curosurf®.
or placebo. Once they have learned of the treatment, the Practitioner will place the notification in an envelope, which they will seal and which will be stored until monitoring of the centre, at which time it will be recovered.


4.4 Dosage and methods of administration
Administration of 1 dose of 200 mg/kg Curosurf® or Air, under blind (Doctors not directly involved in the patient’s care at the time of randomisation).
(The methods are those described in the MA of the medicinal product: see page 15).

4.5 Duration of participation of patients, including follow-up
Patients will first be evaluated at 36 weeks of postconception age and at the time of discharge to return home. They will then be seen in consultation for follow-up at the age of 1 year, 2 years and 7 years. The total duration of participation of patients, including follow-up, will therefore be 7 years.

4.6 Description of rules for definitive or temporary discontinuation

Premature discontinuation of participation of a person in the research:

Parental decision of premature discontinuation:
In accordance with the legislative dispositions in force (articles L.1122-1 of the French Public Health Code), parents may decide to interrupt the participation of their child in the research at any time without incurring any liability or prejudice and without having to give a reason; they must simply inform the investigator, who will make sure to continue optimal medical treatment.

Medical decision of premature discontinuation:
In case of occurrence of an adverse event, the Investigator may deem it necessary to prematurely discontinue the participation of a child in the research.
The Investigator will inform the parents of this decision immediately.
The Investigator will indicate the premature discontinuation in the case report form on the page intended for this purpose, will give a reason for their decision on the appropriate form and transmit it to the Primary Investigator immediately:
- document to be faxed:
  fax number: 03 83 34 44 11
- in parallel, inform the Primary Investigator by e-mail of the sending of the form:
  e-mail address: jm.hascoet@maternite.chu-nancy.fr
confirmation by a telephone using the number dedicated to the study
(03 83 34 36 35)
The Primary Investigator representing the Sponsor will evaluate the premature discontinuation with the members of the monitoring committee of the study. The latter may request an evaluation of the entirety of the study, including the lifting of the blind and will propose to the Coordinating Investigator the conduct that seems the most appropriate: continuing the study, continuing while informing the other investigators so that the unexpected side effect can be tested for systematically, possible discontinuation of the study (see below)

Premature termination of research:

Decision of the Sponsor to interrupt the research:
The sponsor will inform the AFSSAPS and the Ethics Committee CPP-Est III of the premature termination of the research in accordance with the legislative dispositions in force (articles L.1123-11 and R.1123-59 of the French Public Health Code), as well as all Investigators.
The Investigator will inform the parents of children participating in the research and will make sure to continue optimal medical treatment.

Decision of the AFSSAPS to interrupt the research:
The Sponsor will inform all the Investigators of the premature termination of research.
The Investigator will inform the parents of the children participating in the research and will make sure to continue optimal medical treatment.

4.7 Counting procedure for investigational medicinal product
The ampoules of Curosurf® are identical to those holding the MA for the treatment and prevention of hyaline membrane disease. The ampoules intended for this study will be labelled with an indication of their intended use. Used ampoules will be stored by the investigator in a container intended for this purpose and stored until a monitoring visit, at which time the study monitors will verify that the count of ampoules (unused and used) corresponds to the children treated and to the specified dosage.

4.8 Arrangement for maintaining the blind
The blind will be ensured at the time of randomisation by centralisation at the Coordinating Centre, to which the investigating centres will have access via a dedicated telephone number (see above).
The centres will be provided numbered sealed opaque envelopes containing the notification of the assigned treatment.
This envelope should only be opened by the Practitioner not involved in the child’s care, who will perform the administration of Curosurf® or Placebo. Once he has learned of the treatment, the
Practitioner will place the notification back in an envelope, which he will seal and which will be stored until monitoring of the centre, when it will be recovered. Throughout follow-up, the investigators will not be aware of which treatment has been allocated. Analysis will be performed in intention to treat without crossover.

4.9 Data to be collected in CRF (source data)
A case report form will be created and will include all of the classic perinatal data and those defined in paragraphs 4.1 and 4.2. The investigator will record the data, in a prospective manner, in the case report form based on source documents and will certify the accuracy of them. Data monitoring will be performed by the study coordination team (monitoring on-site and verification at the coordinating centre). Each page will be duplicated on carbon paper. The original will be sent to the coordinating centre and the copy will be kept by the investigator on site, according to the rules of archiving defined in Chapter 13.

5. POPULATION INVOLVED

5.1 Inclusion criteria
- Any neonate of gestational age < 33 weeks on CMV or HFOV at 14 ± 2 days of life;
- With FiO2 > 0.30 and/or OI (= FiO2xMAP/PaO2) > 7 for at least 6 hrs;
- Informed authorisation from the parents or holders of parental authority.
- Centralised randomisation.

5.2 Exclusion criteria
- Active infection (CRP>30 mg/L) not controlled by antibiotic treatment suited to the identified microbe (blood, urine, spinal tap);
- Surgical intervention (arterial canal or other) within the last 72 hrs
- Previous use of corticosteroids in the postnatal period;
- Disease (chromosomal, neurological (Intraventricular Haemorrhage (IVH) > Grade II according to Papile), malformative) jeopardising the pertinence of extubation;
- Refusal of parental authorisation

5.3 Procedure for early discontinuation of treatment
- Since this is a protocol with administration of a single administration of treatment, by bolus, it is not necessary to set up a procedure for discontinuation of treatment.
6. TREATMENT

6.1 Treatment necessary for research
Two treatments are necessary for the research in addition to normal management:
1. Curosurf®, a medicinal product with an MA in the study population, and at this dosage, but for a different indication at an earlier gestational age
2. Inhaled nitric oxide, a medicinal product with an MA for another indication in slightly more mature children. Widely used in the population of children being studied in this project, two published scientific studies confirm its interest in this indication at this gestational age. It is not the subject of study, and children able to receive it will receive it in the 2 groups (see scientific rationale of the study and references).

6.2 Permitted and non-permitted treatments
• All treatments used routinely are authorised and will be recorded, except for postnatal corticosteroids (see below).
  In particular:
• Lasilix®, which will be authorised at the local investigator’s discretion and recorded
• Caffeine, which is recommended in premature neonates before activation
• Non-permitted postnatal corticosteroids:
  Before randomisation, this is a criterion for exclusion from the study; After randomization, hydrocortisone is allowed only in cases of corticotropic axis immaturity (documentation is recommended); 3 days betamethasone treatment is allowed for extubation

6.3 Monitoring of compliance with treatment
Since this is a protocol with administration of a single dose of treatment, by bolus, it is not necessary to set up a particular procedure for compliance with treatment. Counting of empty ampoules will make it possible to verify that they have been used.

6.4 Storage of investigational medicinal products
Since this is a medicinal product that is already present in hospital pharmacies, the conditions of preservation and storage will be identical to ampoules of Curosurf® used in routine therapy. The only difference will come from labelling specifying the destination of ampoules intended for the study.

  Note: in case of error, since it is the same medicinal product in the same presentation, the “routine” ampoules that have been used in error will be kept in the same way as those intended for the study, and the error will be recorded at monitoring. This error will not be considered to be a reason for excluding the child from the study as long as the rest of the
procedure has been followed. On the other hand, routine ampoules will not be replaced by ampoules dedicated to the study, which must keep this designation.

7. EVALUATION OF EFFICACY

7.1 Parameters of evaluation of efficacy
The primary parameter of evaluation of efficacy is the duration of assisted ventilation. The evaluation endpoint is therefore the date of successful extubation defined by extubation maintained for at least 72 hours. Criteria of extubation are defined as follows:

For a period of stability of at least 6 hrs
OI (= MAPxFiO2/PaO2 < 7 and/or FiO2 < 30%; for SaO2 = 88 – 92% and/or PaO2 = 50 – 70 mmHg and PaCO2 = 40 – 50 mmHg (arterial or percutaneous blood gases with sensor in postductal position).
MAP (Mean Airway Pressure) < 7 mmHg with CMV (Conventional Mechanical Ventilation) or < 9mmHg with HFOV (High Frequency Oscillation Ventilation) and/or frequency < 25/min with CMV

The criteria of failure of extubation indicating the necessity for re-intubation are the following: 6 episodes of apnoea/bradycardia requiring stimulation / 6 hrs or one episode of apnoea/bradycardia requiring resuscitation with positive pressure, or FiO2 > 60%, or PaCO2 > 60 mmHg for at least 6 hrs

7.2 Method and calendar of collection of efficacy parameters
The method of evaluation of efficacy is the notification of the date of extubation, this being maintained for at least 24 hours. This date will be recorded in the case report form on the page intended for this purpose.

8. EVALUATION OF SAFETY

(article L. 1123-10 of the French Public Health Code)
The investigator shall follow the legislative and regulatory dispositions regarding notification to the Sponsor of any new fact involving the research or the investigational medicinal product that might have an impact on the safety of persons who are subjects in it as well as any modification made in this context.
The Sponsor shall follow the legislative and regulatory dispositions regarding the transmission to all investigators, to CPP EST III and to the AFSSAPS of any suspected serious adverse reaction, of any new fact and any information that might affect the safety of patients participating in the research, have an impact on the conduct of the trial or modify the clinical trial authorisation granted by the AFSSAPS for the conduct of the trial.
The Monitoring Committee of the study will be informed of the occurrence of any suspected serious adverse reaction, of any new fact and of any information that might affect the safety of persons participating in the research. Lifting the blind may be requested. The verification of safety will constitute part of the parameters systematically evaluated during the evaluation that is scheduled for the halfway point in recruitment. The committee may offer the sponsor the discontinuation or the continuation of the study, depending on the case.

8.1 Safety evaluation parameters

The parameters for safety evaluation will be all adverse events. An adverse event is any harmful reaction occurring in a person participating in biomedical research, whether or not this reaction is related to the research or to the product being studied in the research (article R.1123-39 of the French Public Health Code). A serious adverse event is any event or effect that leads to death, is life-threatening for the person participating in the research, requires a prolongation of hospitalisation or leads to a serious or lasting disability or handicap (article R.1123-39 of the French Public Health Code). It is possible that other events not meeting the above mentioned qualifications could also be considered as potentially serious, and the investigator’s judgment may lead to declaration of these effects or events to the Sponsor.

The investigator will evaluate the adverse event with regard to the nature, its severity, its outcome and its causal relationship with the research, by filling out the corresponding page of the patient’s case report form.

8.2 Method and calendar of collection of safety parameters

If an event is considered to be serious, the investigator will inform the Sponsor represented by the Primary Investigator at the coordinating centre. Within 24 hours following the occurrence of the serious adverse event:

The Investigator will complete the narrative report of the serious adverse event on the form adapted to the research and will send it to the Primary Investigator:
- document sent by fax:
  fax number: 03 83 34 44 11
- at the same time, inform the Primary Investigator by e-mail of the sending of the report:
  e-mail address: jm.hascoet@maternite.chu-nancy.fr

The Primary Investigator representing the Sponsor will evaluate the serious adverse event with the members of the monitoring committee of the study:
- lifting of the blind, if appropriate.

The Investigator will send additional information necessary for evaluation, if needed (clinical outcome, laboratory testing or diagnostic testing, or any other pertinent material).
8.3 Procedures of recording and notification of adverse events

The procedures of notification of the Primary Investigator, representing the Sponsor, by the investigator are described above.

The information will be recorded in writing, in duplicate on pages of the case report form intended for this purpose.

The Sponsor will declare to the AFSSAPS and to the CPP-Est III Ethics Committee any unexpected serious adverse event within the required deadlines and according to the regulations in force (article R.1123-47 of the French Public Health Code).

8.4 Methods of follow-up after the occurrence of adverse events

Any patient presenting with an adverse event will be followed until resolution or stabilisation, and the data from this follow-up will be recorded in the case report form on the page intended for this purpose.

In case of a serious adverse event, the Investigator will inform the Primary Investigator of the outcome of the patient in a follow-up report.

The Primary investigator will maintain a registry of serious adverse events occurring during the research.
9. STATISTICAL ANALYSIS PLAN

9.1 Planned statistical methods

Data entry will be performed on an EpiData database developed for the study, access to which will be protected by a login with a password. Double data entry will be performed with comparison, verification and correction of all discrepancies. Analysis of data will be performed using SAS software version 9.1 (SAS Institute Inc., Cary, North Carolina USA).

For all analyses, the alpha risk is set at 0.05, and the tests will be two-sided.

- **Validation of randomisation:**

  The general characteristics of children in the two groups will be compared using a chi-square test of comparison of percentages for qualitative variables and a test of comparison of means for quantitative variables. An equal distribution of these variables between the two groups is expected.

**Primary evaluation endpoint:**

- **Descriptive analysis:**

  The duration of ventilation will be presented per randomisation group, and per gestational age in weeks of amenorrhea, by the mean, the standard deviation, the median and the range.

- **Bivariate analysis:**

  The duration of intubation of children in the two groups will be compared using a student t-test of comparison of means.

- **Multivariate analysis:**

  If a difference of the duration of intubation is demonstrated, multivariate linear regression will be performed. This regression will use the duration of intubation as the dependent variable. The independent variables chosen will be those having an association with duration of intubation with a significance limit of <0.10 in the bivariate phase.

  This regression will make it possible to determine perinatal and neonatal factors that, combined with Curosurf® treatment, may prolong or reduce the duration of mechanical ventilation.

**Secondary evaluation endpoints:**

- **Descriptive analysis:**

  The qualitative variables will be presented using the number of subjects, and percentages, and quantitative variables will be presented using the mean, standard deviation, medium and interquartile range.

- **Bivariate analysis:**

  Qualitative variables will be compared using a chi-square test (or a Fisher exact test if necessary), for the comparison of percentages; quantitative variables will be compared using a student t-test (or a rank test if necessary), for comparison of means between the groups.

- **Multivariate analysis**
When it is appropriate, for all of the analyses repeated over time (such as, for example, analyses pertaining to inflammatory status of the lung, or to healing ability or growth capacity of the lungs, with several repeated measurements), and analysis of variance with repeated measurements may take into account the effect of time, defined as a “maturation” effect.

9.2 Population sizes
In a recent study conducted on a population of 860 premature neonates similar to those of this study (reference 36, page 14), 16% of children were ventilated for more than 14 days and 75% of them later presented with BPD versus 21% for the entire population. The mean duration of ventilation was 34 days with a standard deviation of 14 days. In this project, to demonstrate a difference of ten days of mechanical ventilation between the two groups, in a two-sided test, with an alpha risk of 5% and a power of 90%, the number of subjects necessary is 43 children per group.
Considering the risk of subjects lost to follow-up, estimated at 20%, a sample population of 50 children per group having completed the initial analyses is necessary.

9.3 Planned degree of statistical significance
For all analyses, the alpha risk is set at 0.05 and the tests will be two-sided.

9.4 Statistical criteria for discontinuation of research
There is no statistical criterion for early discontinuation of research.

9.5 Method for accounting for missing or invalid data
Missing data will be analysed as missing data. If more than 20% of the data are missing, a post hoc calculation of power may be performed. Invalid data will be excluded from analysis, regardless of the randomisation arm of the child, and the number of these excluded data will be specified during analysis.

9.6 Management of changes in the initial analysis design
In case of a need for changes in the analysis design, these changes will be performed before any analysis takes place, and defined by Dr. Rachel Vieux with the agreement of professor Francis Guillemin of the CIC-EC INSERM of Nancy.

9.7 Choice of subjects to be included in analyses
Analysis is in the intention to treat population. All children will be included in the analyses.
10. RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

(GCP for biomedical research on medicinal products for human use – Official Journal of 30 November 2006)

The Investigator will make the documents and individual data that are strictly necessary for follow-up, for quality control and audit of the biomedical research available to persons responsible for quality control duly assigned by the Sponsor and persons called upon to collaborate in the trial with access to these documents in accordance with the legislative and regulatory dispositions (articles L. 1121-3 and R.5121-13 of the French Public Health Code).

11. QUALITY CONTROL AND QUALITY ASSURANCE

The biomedical research will be performed in accordance with the legislative and regulatory dispositions in force and according to the rules of Good Clinical Practices.

(GCP for biomedical research on medicinal products for human use – Official Journal of 30 November 2006)

The Sponsor and the Investigator will ensure compliance with the principles of GCP in the context of their respective obligations.

The Sponsor is responsible for the setup and follow-up of a quality system (quality assurance and quality control) including standard operating procedures (SOP). This system ensures that the research will be performed, that the data will be generated, documented, recorded and reported in accordance with the protocol, with the principles of GCP and in compliance with the legislative and regulatory dispositions in force.

12. ETHICAL CONSIDERATIONS

The biomedical research will be performed in accordance with the legislative and regulatory dispositions in force and in compliance with the rules of Good Clinical Practices.

The research will be conducted in compliance with the declaration of Helsinki, version in force, adopted in General Assembly of the World Medical Association.

Declaration of Helsinki: (version 2008 – annex no. 1)

The study will be conducted in accordance with the principles and rules set forth in the declaration of Helsinki.

Opinion of Community Ethics Committee:

(article L.1123-6 of the French Public Health Code)

The protocol will be submitted for prior opinion to the CPP EST-III Ethics Committee.
Opinion of the Ethics Committee of the Hospital:
The protocol will be submitted for prior opinion to the Committee on Ethical Research and Teaching of Maternité Régionale Universitaire of Nancy.

Consent to participate in biomedical research performed on a minor:

(article L.1122-1 and L.1122-2 of the French Public Health Code)
Informed consent of the parents will be required before the child enters the study:
Parents will receive necessary explanations during an interview with the investigator, who will give them a document summarising the information provided. After this discussion, they will be able to take time to think about it before giving their agreement for the participation of their child in the project by signing the consent form, of which they will keep a copy. (Information letter – annex no. 2 and consent form – annex no. 3)

Protection of the confidentiality of the subject:

(article 53 to 61 of the law on “Informatique et libertés”)
The confidentiality of subjects will be preserved; each child will receive an identification code reserved for the study ensuring anonymity, and the data collected will not under any circumstances allow direct identification.
Any person called upon to collaborate in the research is subject to professional secrecy.
The computer file for the processing of personal data, used in the context of the research, will be declared beforehand to the French Data Protection Authority (CNIL).

13. PROCESSING OF DATA AND STORAGE OF DOCUMENTS AND DATA RELATED TO THE RESEARCH

Data processing
Case report form:
A case report form for collection of patient data will be created for the study and will include all the data necessary for analysis. The Investigator will record the data in the case report form from source documents and will certify the accuracy of it. Inspection of data will be performed by the study coordination team (on-site monitoring and inspection at the coordinating centre).
The pages of the form will have self-copying carbon paper; the original will be sent to the coordinating centre, and the duplicate will be kept by the Investigator.
Requests for corrections or clarifications of data may be made to the investigator on the forms, the certified original of which will be sent to the coordinating centre and a copy kept in the case report form.

Computer data entry:
Data entry will be performed at the coordinating centre into an anonymous computer database developed under the responsibility of the statistician.
The computer file for data processing used in the context of the research will be declared beforehand to the French Data Protection Authority (CNIL).

Storage of documents and data related to the research
Documents and data related to the research are essential documents that comprise the permanent dossier of the research, allowing the evaluation of the conduct of the research and of the quality of the data produced.
In application of article R.1123-61 of the French Public Health Code, the sponsor and the investigator will keep the documents and data related to the research that are specific to them for at least 15 years after the end of the research.
The documents and the person responsible for their storage are listed in the annex on Good Clinical Practices in accordance with the legislative and regulatory dispositions in force. (*GPC for biomedical research conducted on medicinal products for human use – Official Journal of 30 November 2006*).

**14. FINANCING AND INSURANCE**

**Financing:**
A financial agreement for the research will be created in the form of a contract between the Sponsor in the following parties: investigator, management of the investigating centres.

**Insurance:** (*article L.1121-10 of the French Public Health Code*)
Insurance contract covering the civil liability of the Sponsor of biomedical research: before the start of research, the sponsor takes out an insurance policy with SHAM, covering its indemnity for any harmful consequences of the research, in accordance with the legislation in force.
15. RULES ON PUBLICATION

Maternité Régionale Universitaire of Nancy is the owner of the data, and no use or transmission to a third party can be made without its prior written consent.

Each investigator accepts the agreement that the results of the study shall appear in a joint publication, with other investigators, before any individual publication, which must be subject to prior written agreement by the sponsor. This is in order to avoid divulging confidential information that might bring prejudice to the protection of individual property.

One investigator per centre (or one of the co-investigators designated by them in writing) will be named as a co-author of any publication about the research, on the condition that the centre in question has recruited at least two patients with a complete file. This investigator permits the use of their name (or that of the co-investigator designated by them, if applicable) in a publication, after they (or the co-investigator designated by them) have given their agreement in writing.

The first author of the publication will be the primary investigator/coordinator of the study, who is responsible for writing the manuscript. The order of co-authors will then be based on the number of enrolments in each centre, including the coordinating centre. The last author will be the statistician in charge of analysis. The statistician will provide a complete statistical analysis report in writing beforehand.

The CHIESI pharmaceutical company will be mentioned and thanked explicitly in all publications related to this study.

The ARAIRLOR association will be thanked in the main publication on the study.

The Sponsor reserves the right to add to the list of co-authors if necessary.