**DRUG RESEARCH PROTOCOL INVOLVING HUMANS – TYPE 1 RESEARCH**

***Respiratory effect of the LISA (Less Invasive surfactant administration) method with sedation by propofol versus absence of sedation: Double-blind comparative randomized clinical trial***

***PROLISA***

**Multicentric study**

N°UE d'essai clinique : 2024-518836-36-00

**Version n° 7.0 of 17/02/2026**

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|---|---|
| **Coordinating investigator** | Pr Chevallier Marie<br>Grenoble France<br>Grenoble Alps University Hospital. Neonatal Intensive Care Unit<br>Email: MChevallier3@chu-grenoble.fr<br>Phone: + 33 (0)4 76 76 55 77<br>Speciality: Neonatologist |
| **Sponsor** | Grenoble Alps University Hospital (CHU Grenoble Alpes),<br>Clinical Research and Innovation Delegation<br>Pavillon Dauphiné<br>CS 10217, 38043 Grenoble Cedex 09 |

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# PRINCIPAL STAKEHOLDERS

| | |
|---|---|
| **Sponsor:** | Grenoble Alps University Hospital (CHU Grenoble Alpes),<br>Pavillon Dauphiné,<br>CS 10217, 38043 Grenoble Cedex 09<br>Email : LChambon@chu-grenoble.fr<br>arcpromoteur@chu-grenoble.fr |
| Coordination | Noëlle BROSILLE<br>CIC Grenoble – Antenne Pédiatrique du CIC – Hôpital Couple Enfant<br>CHU de Grenoble, CS 102017<br>38043 Grenoble Cedex 09<br>Email : NBrosille@chu-grenoble.fr<br>Phone: 04 76 76 71 32 |
| **Coordinating investigator:** | Pr Chevallier, Marie<br>Grenoble France<br>Grenoble Alps University Hospital<br>Email: MChevallier3@chu-grenoble.fr<br>Phone: 04 76 76 55 77 |
| **Investigators** | Co investigateurs (See Annex 1) |
| **Pharmacy coordinator** | Dr Audrey LEHMANN<br>Essais Cliniques<br>Pole Pharmacie<br>CHU Grenoble Alpes<br>Email : ALehmann@chu-grenoble.fr<br>Phone: 04 76 76 92 09 (or 04 76 76 81 51, available 24/7) |
| **Pharmaceutic supplier** | Dr Mazet Roseline<br>Pharmacotechnie<br>Pole Pharmacie<br>CHU Grenoble Alpes<br>Email : RMazet@chu-grenoble.fr |
| **Clinical Research Vigilance** | Drs Marylaure GAVARD, Laura LEO<br>CHU Grenoble Alpes, Pavillon Dauphiné DRCI<br>Phone: 04 76 76 68 21<br>Télécopie : 04 76 76 83 54<br>Email : vigilance-essaiscliniques@chu-grenoble.fr |

| | |
|---|---|
| **Methodology** | Dr Ego Anne<br>Département de Méthodologie de l'Information de Santé<br>CHU GRENOBLE ALPES<br>Phone: 04 76 76 53 39<br>Email : AEgo@chu-grenoble.fr |

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| 1.1 | 20/09/2018 | Answers to ANSM and CPP |
| 1.2 | 01/10/2018 | Answers to ANSM |
| 1.3 | 26/12/2018 | Second exam by CPP |
| 1.4 | 25/02/2019 | Answers to CPP |
| 2.0 | 25/06/2019 | Substantial amendment n°1 |
| 2.1 | 29/08/2019 | Answers to CPP |
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| 6.0 | 16/10/2024 | Substantial amendment n°6 |
| 6.1 | 17/03/2025 | 1st RFI – Part I |
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# PROTOCOL SIGNATURE PAGE

***Respiratory effect of the LISA (Less Invasive surfactant administration) method with sedation by propofol versus absence of sedation: Double-blind comparative randomized clinical trial***

***PROLISA***

This protocol has been read and approved.

Both parties undertake to carry out the clinical trial in accordance with the protocol, Regulation (EU) 536/2014 of April 16, 2014 on clinical trials on medicinal products for human use and the principles of good clinical practice.

**Principal Investigator**

Pr CHEVALLIER Marie
Neonatal Medicine and Resuscitation
Couple-Child Hospital
Grenoble Alps University Hospital

Date :

**Sponsor**: Grenoble Alps University Hospital

Représented by:
Mme Monique SORRENTINO
General Manager

Date :

## ABREVIATIONS

| | | |
|---|---|---|
| **ADR** | **:** | Adverse drug reaction |
| **AE** | **:** | Adverse event |
| **AESI** | **:** | Adverse event of special interest |
| **ANSM** | **:** | Agence Nationale de Sécurité du Médicament et des produits de santé |
| **ASQ :** | **:** | Ages and Stages Questionnaire |
| **BDP** | **:** | Bronchopulmonary dysplasia |
| **BiPAP** | **:** | Bilevel Positive Airway Pressure |
| **CHU** | **:** | Centre Hospitalier et Universitaire (University Hospital) |
| **CFR** | **:** | Code of Federal regulations |
| **CIC** | **:** | Centre d'Investigation Clinique = clinical research center |
| **CPAP** | **:** | Continuous Positive Airway Pressure |
| **CPP** | **:** | Comité de Protection des Personnes (Ethics committee) |
| **CRF** | **:** | Case Report Form |
| **DRCI** | **:** | Délégation à la Recherche Clinique et à l'Innovation |
| **DSMB** | **:** | Data safety monitoring board |
| **FANS** | **:** | Faceless acute neonatal pain scale |
| **FDA** | **:** | Food and Drug administration |
| **FiO2** | **:** | Fraction of inspired oxygen |
| **FRG** | **:** | Fetal growth restriction |
| **GA** | **:** | Gestational age |
| **GABA** | **:** | Gamma aminobutyric acid |
| **GCP** | **:** | Good Clinical Practice |
| **GMFCS** | **:** | Gross Motor Function Classification System |
| **ICH** | **:** | International Conference of Harmonization |
| **INSERM** | **:** | Institut National de la Santé et de la Recherche Médicale |
| **INSURE** | **:** | INtubation SURfactant Extubation |
| **ITT** | **:** | Intention to treat |
| **LISA** | **:** | Less Invasive Surfactant Administration |
| **MV** | : | Mechanical Ventilation |

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|---|---|---|
| **NICU** | **:** | Neonatal Intensive Care Unit |
| **NIPPV** | **:** | Nasal Intermittent Positive Pressure Ventilation |
| **PEEP** | **:** | Positive end expiratory pressure |
| **PIP** | **:** | peak inspiratory pressure |
| **PO2** | **:** | Oxygen pressure |
| **RDS** | : | Respiratory Distress Syndrome |
| **SAE** | : | Serious Adverse Event or Reaction |
| **SpO2** | : | Pulse Oxygen saturation |
| **SPC** | : | Summary of product characteristics |
| **SUSAR** | : | Suspected unexpected serious adverse reaction |
| **TcPCO2** | : | Transcutaneous Pressure of CO2 |
| **UADR** | : | Unexpected Adverse Drug Reaction |
| **wGA** | : | Weeks of gestational age |

# 1 RESARCH SUMMARY

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|---|---|
| **TITLE** | Respiratory effect of the LISA (Less Invasive surfactant administration) method with sedation by propofol versus absence of sedation: Double-blind comparative randomized clinical trial |
| **SHORT TITLE** | PROLISA |
| **PROJECT COORDINATOR** | Pr Chevallier Marie |
| **AFFILIATED INSTITUTION FROM THE MINISTRY OF HEALTH** | CHU GRENOBLE ALPES |
| **RATIONAL (CONTEXT AND HYPOTHESIS)** | Respiratory Distress Syndrome (RDS) affects 85% of preterm babies born < 32 weeks of gestational age (wGA). To limit mechanical tracheal ventilation (MV), the LISA (less invasive surfactant administration) procedure consists of the tracheal insertion of a thin tube to administer the surfactant. Two meta-analysis evaluating LISA reported a 30% reduction in (i) MV within the first 72 hours and (ii) bronchopulmonary dysplasia (BPD) at 36 weeks. However, the LISA premedication procedure is still under debate, and is often performed without analgesia or sedation. This reflects neonatologists concerns about the potential adverse effects (apnea and the need for MV) of this premedication.<br>Despite a few publications reporting hospital series using different drugs especially Propofol, no comparative prospective studies exist on premedication before LISA. Research to identify adequate strategies for LISA premedication that preserve respiratory function is urgently needed.<br>We propose to evaluate premedication with Propofol compared to a control strategy including a placebo with a possible rescue treatment with ketamine to ensure pain control. We hypothesize that sedation with Propofol, compared to no sedation during the LISA procedure |

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| | for preterm babies less than 32 wGA will improve the neonate's comfort without increasing respiratory side effects. |
| **EXPERIMENTAL DESIGN** | Phase III, Multicenter, Double Blind, Randomized, controlled vs placebo trial |
| **MAIN OBJECTIVE** | Randomized trial in preterm babies < 32 weeks of gestation, to compare sedation by Propofol versus placebo during the LISA procedure, on the need for MV within 72 hours of life and on pain reduction before and following procedure. An open-label ketamine treatment as rescue is possible in each group. |
| **PRIMARY END POINT (LINKED TO MAIN OBJECTIVE)** | Rate of MV from the start of the LISA procedure up to 72 hours of life.<br>Pain before procedure (need of ketamine administration) or within 1 hour following 1st injection of propofol/placebo (FANS score ≥ 6) |
| **SECONDARY OBJECTIVES** | 1. To compare sedation by Propofol versus placebo during the LISA procedure, evaluating the need for MV within 72hours of life, in each class of GA (<28, 28-31 wGA)<br>2. To assess the rate of ketamine administration for rescue in each group<br>3. To assess quality conditions of the procedure: per procedure events (tolerance) and clinician's satisfaction (efficacy) during the LISA procedure<br>4. To assess BPD at 36 wGA<br>5. To assess in-hospital neonatal morbidity and mortality.<br>6. To evaluate neurodevelopmental outcome at two years corrected age among survivors. |
| **SECONDARY END POINTS (LINKED TO SECONDARY OBJECTIVES)** | 1. Rate of MV from the start of the LISA procedure up to 72 hours of life in each class of GA (<28, 28-31wGA)<br><br>2. Rate of ketamine administration for rescue<br>3. Tolerance and efficacy (Per procedure events):<br>• Number of laryngoscopies needed to perform LISA |

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| | • Cardiorespiratory parameters at 1, 3, 5, 15, 30, 60 and 120 min after the drug injection: heart rate, respiratory rate, pulse oxymetry, blood pressure, FiO2, TcPCO2, with comparison between the two groups<br>• Apnea requiring bag mask ventilation<br>• Emergency intubation after the drug injection before the LISA procedure can be performed (or within 1h following the drug injection)<br>• Clinician's satisfaction during laryngoscopy with the score Viby Mogensen<br>4. BPD at 36 wGA<br>5. In-hospital morbidity and mortality:<br>• Pneumothorax within 72h<br>• necrotizing enterocolitis<br>• proven early and late infections<br>• retinopathy of prematurity<br>• periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage<br>• treatment of a patent ductus arteriosus<br>• death at 36 wGA and in-hospital mortality<br>7. At two years of corrected age :<br>• ASQ questionnaire,<br>• Gross Motor Function Classification Scale<br>• Visual and hearing function. |
| **INCLUSION CRITERIA** | – Preterm Infants < 32 wGA<br>– Presenting a RDS<br>o in the first 48 hours of life<br>o treated by CPAP or BiPAP<br>o requiring surfactant :<br>• FIO2 :<br>if 28 - 31 wGA : FiO2 ≥30% for a duration ≥ 10mn |

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| | if <28 wGA FIO2 ≥25% for a duration ≥10mn<br>• SpO2 :<br>To obtain a SpO2 between ≥88 and ≤ 95%<br>– Available IntraVenous line (peripheral, umbilical or central catheter)<br>– Recipient of the French Social Security<br>– Informed consent form signed |
| **NON INCLUSION CRITERIA** | • Congenital and/or major malformations<br>• FIO2 >60% at the time of the inclusion<br>• Silverman score >6<br>• Contraindication to the use of Propofol :<br>  • Low Blood Pressure with 2 successive measurements (Mean < Gestational Age expressed in Weeks of Gestation) persisting after one volume expansion,<br>  • Use of inotropic medication to maintain a normal blood pressure.<br>• Use of sedative or analgesic drugs (except paracetamol and ibuprofen) in the previous 24h<br>• Coma, convulsions, areactivity at neurological examination |
| **DESCRIPTION OF THE DESIGN** | In each participating unit, information will be given to parents of preterm babies <32 wGA upon their admission to the delivery room or to the NICU, and informed consent will be sought as soon as possible. Eligible babies presenting a RDS will be included and randomized to the control (placebo) group or Propofol group. While benefiting from Nasal Intermittent Positive Pressure Ventilation (NIPPV) the newborn will be prepared as usual for tracheal intubation. Trialists will be blinded to treatment allocation.<br>The drug administration in the two groups will be titrated according to weight (0.5mg/kg per dose of Propofol or a similar volume of placebo). After each dose, a pain score (FANS) will be quickly evaluated within 2 minutes of the injection, to assess the need for a |

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| | supplementary dose (up to a predefined limit) or rescue treatment by Ketamine.<br>After the steps of sedation, the LISA procedure will be performed, with detailed data collection of per procedure events up to 72 hours of procedure. Babies will be subsequently managed as usual in each NICU and data will be collected about respiratory, neurological and hemodynamic outcomes during the hospital stay, and especially at discharge, 28 days, and 36 weeks. At two years of corrected age, a final examination will be performed to evaluate neurodevelopmental outcomes. |
| **NUMBER OF SUBJECTS** | Recruiting 204 neonates allows to obtain a power greater than 80% to answer each of the following two statistical questions asked in the main objectives' hierarchy:<br>(i) showing the non inferiority of Propofol compared to placebo on MV within the 72 1st hours of life: we expect a 30% MV rate in the control group and the non-inferiority margin is set at 18%,<br>(ii) showing the superiority of Propofol versus placebo on pain (no need of ketamine before LISA and FANS score <6 within 1 hour after intervention) associated with the LISA procedure, with the hypothesis of 76 and 22% of painful neonates respectively in the intervention and control arm. |
| **NUMBER OF CENTERS** | **15 centers (see Annexe 1)** |
| **DURATION OF THE STUDY** | Anticipated Duration of Recruitment: 54 months<br>Duration of treatment: 15min but monitoring of the patient during the 72 hours following the LISA procedure<br>Duration of participation of each patient: 2 years<br>Total duration of the research: 6.5 years |
| **STATISTICAL ANALYSIS OF THE DATA** | A comparison between baseline characteristics in each arm will be performed.<br>Considering the non-inferiority assumption and the superiority hypothesis respectively on the 1st and 2nd questions included in our hierarchical analysis strategy, randomized patients will be included |

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| | in a modified intention to treat analysis (m-ITT) in the group they were initially allocated to. A per-protocol analysis will be carried out subsequently to confirm the results of the m-ITT analysis performed to answer to the first question.<br><br>Primary outcome<br>The primary objectives consist in 2 different questions, which are organized hierarchically. Therefore, the 2nd level of the hierarchy will only be tested if the null hypothesis of the 1st level is rejected.<br>• If the upper limit (one-sided 97.5% confidence interval) for the difference of MV rate at 72 hours of life difference is less than 18%, then we will retain the non-inferiority of the experimental strategy. If non-inferiority is confirmed, the rates of MV up to 72h life will be compared using a conventional superiority test.<br>• Rates of painful neonates will be compared by a chi-square or Fisher test with a significance level set at 0.05.<br><br>Secondary outcomes<br>The analysis of primary outcomes will be repeated in each class of GA (<28, 28-31wGA). Means and standard deviations (or median and 25th and 75th percentile) of FANS, cardio-respiratory parameters, number of laryngoscopies, number of apneas, clinician's satisfaction, neurodevelopmental outcomes at 2 years (ASQ, GMFCS, visual and hearing function), will be calculated and compared using the Student test (or Mann-Whitney test).<br>Numbers and frequencies of ketamine administration for rescue and emergency intubation, pneumothorax within the first 72h post procedure, BPD at 28 days and 36wGA, other outcomes of neonatal morbidity and in-hospital mortality will be calculated, and compared using the Chi2 test (or Fischer exact test). |

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| | The threshold $p<0.05$ will be considered to define the significance of the statistical tests performed with Stata MP15. Blinding will be maintained during statistical analysis. |
| **EXPECTED PATIENT OR PUBLIC HEALTH BENEFIT** | Currently, the absence of guidelines on sedation is a major barrier to performing LISA. This study will be particularly useful for neonatologists, enabling them to develop a new strategy for surfactant administration with a high degree of safety. If our hypothesis is confirmed (non-inferiority of Propofol on MV within 72 hours and superiority on neonatal comfort and pain), our study will support the development of the LISA procedure.<br>Moreover, this study is timely, and will enable us to draw up clear recommendations on the use of sedative drugs in newborns. At present they are used anyway, but at the discretion of the clinicians and without enough scientific justification. This study should lead to the better management of pain, particularly as we know that LISA is currently frequently performed without sedative drugs. Painful events during the hospitalization of neonates contribute to the occurrence of some adverse complications in preterm infants and everything must be implemented to minimize stressful procedures. Through this study, we hope to demonstrate that the LISA procedure with Propofol does not increase tracheal intubation and ventilation in the first days of life and improve neonatal comfort. This condition is absolutely necessary to preserve the respiratory benefit of LISA on BDP at 36wGA. |

# 2 RATIONALE

## 2.1 MANAGEMENT OF RESPIRATORY DISTRESS SYNDROME AMONG PRETERM BABIES

Respiratory Distress Syndrome (RDS) affects 85% of preterm babies born < 32 weeks of gestational age (wGA). Currently, the strategy to manage RDS relies on the use of surfactant and noninvasive nasal ventilation, to limit tracheal mechanical ventilation (MV). Because the use of intra tracheal ventilation is associated with an inflammatory pulmonary response, the reduction of the duration of mechanical ventilation is one of the ways to limit the risk of bronchopulmonary dysplasia (BDP) (Reiterer 2017). Several protocols have been studied during recent years aimed at the optimization of nasal ventilation during the RDS (SUPPORT 2010, Morley 2008, Sandri 2010, Dunn 2011) with differing results on the rate of BDP (Wright 2016, Schmölzer 2013, Isayama 2016).The conclusion of a 2013 meta-analysis is that "One additional infant could survive to 36 weeks without bronchopulmonary dysplasia for every 25 babies treated with nasal CPAP in the delivery room rather than being intubated" (Schmölzer 2013). At the same time the InSurE strategy (Intubation Surfactant Ventilation and Early Extubation) involving the early administration of surfactant followed by quick extubation and stabilization on CPAP has been introduced. No significant difference in BDP was observed with InSurE and CPAP compared to standard management with mechanical ventilation (Pfister 2012). However, non-invasive ventilation has become a standard of care for preterm babies in most Neonatal Intensive Care Units (NICU) (Owen 2016), because neonatologists are always looking for new strategies to avoid the use of mechanical ventilation and limit its side effects, in order to reduce the rate of BPD.

## 2.2 THE LISA (LESS INVASIVE SURFACTANT ADMINISTRATION) PROCEDURE

The latest progress in RDS management in preterm babies relies on the LISA (less invasive surfactant administration) procedure. It consists of the insertion of a thin tube to administer intra-tracheal surfactant in spontaneously breathing preterm infants, this catheter is then immediately removed to avoid MV. The major advantage of this strategy is the total lack of ventilator-induced lung injury. In the last 10 years, several randomized trials compared respiratory outcomes of the LISA procedure versus InSurE among babies <32-34 wGA, spontaneously breathing with FiO2≥0.3-0.4 and moderate to severe RDS. Two meta-analyses reported a 30% reduction in MV within the first 72 hours and in BPD at 36 weeks (Aldana-Aguirre 2017, Rigo 2016).

While premedication before endotracheal intubation is becoming a standard of care for newborns, the question was not resolved for the LISA procedure in these publications. The need for premedication was inconsistently reported in the 2 meta-analysis, and only 1 in 6 trials used analgesia or sedation in that of Göpel et al. (2015). A recent narrative review highlighted the need of data about premedication during LISA. (Murphy, 2024) This reflects neonatologists' concerns, balancing advantages and drawbacks of premedication (baby's comfort, quality conditions of the procedure, *versus* adverse effects of sedation) against bradycardia and/or desaturation episodes during LISA. A few trials reported an increased incidence of desaturation and bradycardia among procedure-related outcomes (Mohammadizadeh 2015, Kribs 2015). In contrast, laryngoscopy without sedation is stressful and associated with apnea, hyper- or hypotension, decreased heart rate and decreased PO2, leading to early intubation.

## 2.3 SEDATION DURING THE LISA PROCEDURE

A survey conducted in European NICUs is illustrative of the ongoing debate over whether or not sedation during LISA should be used (Klotz 2017). According to this survey, 52% of units perform LISA with sedation, and this rate is fivefold higher than in 2010. Premedication was performed with atropine (29%), opioids (23%), and ketamine (9%) or Propofol (8%). Propofol is known for its short-acting powerful sedative effect and maintenance of spontaneous breathing (Klotz 2017). Nevertheless, hypotension and respiratory depression have been reported. In a recent retrospective study, Dekker showed a more favorable COMFORTneo score, a validated score for measuring the comfort of a preterm infant (Caljouw 2007), with Propofol versus without (Dekker 2016). Similar rates of intubation, hypotension, and bradycardia during LISA were observed, despite longer desaturation with Propofol (3 versus 1 minute) (Dekker 2016). We recently reported a retrospective analysis of 35 preterm infants sedated with Propofol for LISA in the NICU of Grenoble Alps University Hospital. The intubation rate in the 1st hour was estimated as 14%, and side effects (bradycardia, hypotension) were transient and mild (Descamps 2017).

According the experience of some French NICU, Ketamine infusion has been used for LISA but no prospective data are published in the literature on this subject. However, ketamine infusion is used for preterm babies in other indications, with few reported effects on respiratory function (Walter Nicolet 2010, Barois 2013, Durrmeyer 2010).

Research to identify adequate strategies for LISA premedication that preserve respiratory function is urgently needed (Kribs 2016). We propose to evaluate premedication with Propofol compared to a control strategy including a placebo, associated with a possible rescue treatment with ketamine in the two groups to ensure that sedation does not increase the need for MV.

## 2.4 PROPERTIES OF PROPOFOL

Propofol (2,6-diisopropyl phenol) is an alkyl phenol derivative dissolved in a lipid emulsion. It is a **hypnotic agent** acting by inactivation of the central inhibitory neurotransmitter gamma aminobutyric acid (GABA). When the molecule binds to its receptors, one of the main mechanisms is an increase in chloride ion influx and hyperpolarization of the neuron, leading to unresponsiveness to external stimuli (Chidanbaram 2015). In adults or older children Propofol is known to have rapid effect, **short action**, and few side effects, like post-operative nausea. Controversies about Propofol essentially come from animal studies. In vitro studies has demonstrated an apoptotic effect on neuronal cells, possibly irreversible lesions to GABAergic neurons and decreased dendritic growth (Spahr-Schopfer 2000, Honegger 1996, Vutskits 2005). One recent in vivo study on macaques showed neuron and oligodendrocyte apoptosis in the cortex and white matter after an unknown dose of Propofol (Creeley 2013). Others authors have reported an increased risk of apoptosis of mouse neurons after one dose of 10mg/kg of Propofol in association with sevofurane versus sevofurane alone (Tagawa 2014).

Propofol seems to be **more like a hypnotic agent than an analgesic** in its action but is often studied in neonates without a co-analgesic agent and this could be criticized (Kudchadkar 2014). Its utilization is increasing in preterm babies. In a German prospective study, Mehler et al reported that in 35% of sedated infants in their cohort Propofol was used in 0.7% of infants between 2003-2007 versus 3% of infants in 2010 (Mehler 2013). Another prospective study found that Propofol was used in between 3.2 and 12.9% of the NICU in France in 2011, depending on reason for sedation (Bissuel 2013).

Marketing authorization in France has been obtained for children ≥ 1 month of age (HAS 2015) whereas the Food and Drug administration (FDA) has approved it for maintenance of anesthesia only in children ≥2 months (Smith 2012). Propofol is marketed in many forms throughout the world. In France the generic molecule or a brand name (Diprivan® 1% from Astra-Zeneca,

United Kingdom) are available. For all preparations Propofol appears white in color because light is scattered by the small droplets of lipid suspended in the liquid medium.

In preterm infants, the **appropriate dose of Propofol** is not very clear in the literature because clearance seems to be affected by gestational age, postnatal age (Allegaert, Peeters 2007, Allegaert, Hoon 2007) and the existence of cardiomyopathy (Rigby-Jones 2002). Neonatal clearance is estimated at about 25% of adult clearance (Allegaert, Hoon 2007). Most studies used between 1 and 2.5 mg/kg of Propofol for relatively deep sedation, such as for endotracheal intubation. In 2016 Smit *et al* calculated the best effective dose for successful intubation according to gestational age for an INtubation SURfactant Extubation (INSURE) procedure. For a newborn of <28 weeks GA this corresponded to 0.8 mg/kg; then for 28-31 weeks GA to 0.7 mg/kg and for 32-37 weeks GA to 1.35 mg/kg (Smits 2016). All patients in this study were extubated one hour after INSURE. Finally, some authors have suggested dilution (for preterms <1000g) (Simons 2013) or slow infusion of Propofol (Welzing 2010) in order to limit side effects of the molecule, but there is no robust published data on this.

Among preterms, the **clinical advantages of Propofol** over other hypnotic drugs are numerous. In case of an emergency procedure its preparation seems to be easier and faster than for other drugs (Ghanta 2007). Recovery time of spontaneous movement and breathing are very short (Smits 2016, Ghanta 2007). It could be even used when neonates breathe spontaneously during minimally invasive surfactant therapy procedures for example (Dekker 2016). Two randomized controlled studies showed that Propofol is as effective as others agents like morphine-atropine-suxamethonium (Ghanta 2007) or midazolam (Papoff 2008) for successful intubation and reduction of pain. However, there were only a small number of infants in the last study. In prospective observational pilot studies, good conditions of intubation were related (Dekker 2016, Welzing 2010, Papoff 2008), but Simons *et al* founded that only 37% infants in their population (preterms <1000g needing intubation) had a sufficient sedation with the first dose of Propofol of 2 mg/kg (Simons 2013). They explained their findings by a theory of a higher proportion of “slow responder babies” as postnatal age increases.

A first retrospective cohort study compared comfort levels in infants receiving propofol sedation (1mg/kg) versus no sedation. The authors found that 56% of infants had a COMFORTneo score<14 (considered pain-free) in the sedated group versus 11% in the non-

sedated group. The second study by *Dekker et al* (randomized and controlled) showed that the percentage of infants with a COMFORTneo score <14 during LISA was significantly higher in the sedated group than in the unsedated group (32/42 (76%) vs. 8/36 (22%), p<0.001) (Dekker 2018).

In prospective clinical studies, **the most frequently reported side effect of Propofol** is **hypotension**. Except for one French study for which results are ongoing, there is no randomized study which evaluates hypotension a long time after stopping Propofol infusion (See Clinicaltrials.gov.). Hypotension is more likely to appear in first hours of life as has been shown in survey by Welzing *et al*, and seems to be less disturbing in more mature preterm infants (after five post-natal days.) (Welzing 2010). Some authors explained hypotension by a dip in endogenous catecholamines 10-15 min after a painful procedure and this could be the reason why fluid replacement did not improve tension in this case (Kudchakar 2014). Concerning cerebral oxygenation, only one recent study using near infrared spectroscopy showed a transient decrease cerebral oxygenation 2 minutes after Propofol infusion but no change on oxygen cerebral extraction (Vanderhaegen 2010). In some cases, Propofol could lead to profound **desaturation** concomitant with hypotension (Papoff 2008, Veyckemans 2001). This could be explained by a reduction in vascular systemic resistance more than pulmonary resistance and could increase right to left shunting with a transient return to fetal circulation (Veyckemans 2001). Dekker and al. showed a higher proportion of need for non-invasive ventilation in the context of Minimally Invasive Surfactant Therapy (MIST) in the group sedated with Propofol than in the non-sedated group (Dekker 2016).
One case of **Propofol infusion syndrome** has been reported in neonates who have received 10 times the normal doses of Propofol. The authors also warned of the need for care in patients who have prolonged parenteral nutrition or cholestasis because Propofol is cleared by the liver (Sammartino 2010).

In conclusion, Propofol with sugar solution seems to be a promising candidate for spontaneous breathing procedures in neonates. Sugar solution, which is well used in neonates (Stevens 2016) before painful procedure, could then palliate to the lack of analgesic effect of propofol. We should be careful about the doses used to avoid side effects. Randomized controlled studies are necessary to evaluate its benefit for procedures such as MIST and its impact on subsequent neurocognitive development.

## 2.5 HYPOTHESIS, EXPECTED BENEFITS AND RISKS

Even though the benefit of LISA has been demonstrated to improve pulmonary morbidity among preterm babies, the lack of evidence as to whether sedation should be given during minimally invasive surfactant therapy is currently a major limitation to the widespread use of this strategy. Previous studies analyzing specific types of sedation were mostly observational studies and hospital series. Various strategies of sedation have already been adopted by concerned neonatologists for human and ethical reasons, but powerful well-conducted trials are urgently needed to support the choice of premedication.

Our hypothesis is that premedication with **Propofol compared to no sedation during the LISA procedure for preterm babies less than 32 wGA will improve the neonate's comfort without increasing respiratory side effects**. To demonstrate our hypothesis, we will perform a phase III, double blind trial comparing Propofol versus placebo during the LISA procedure. For ethical reasons, ketamine treatment will be possible as rescue in each group. The primary endpoint will focus on the need for MV during the LISA procedure and up to 72 hours of life and the pain before and following the procedure.

Several individual benefits for the participating newborns offset the risks of premedication:

- Each participating baby will be assured management of stress and pain during the intra-tracheal administration of surfactant: in the sedated group by Propofol and in the placebo group for which a rescue treatment with ketamine is planned. Currently, because premedication is not widely used in France, this protocol will allow participating children to benefit from comfortable care.
- Conclusive findings would support the widespread use of the LISA procedure in NICUs, leading to an improvement in the respiratory outcomes of preterm babies.
- Respiratory outcomes following premedication by Propofol are reassuring, and our trial will consolidate the immediate and middle-term safety of sedation on pulmonary function. The target of our trial is focused on preserving in-hospital respiratory outcomes, but we cannot exclude a possible reduction in the duration of mechanical ventilation and BPD at 36wGA compared to the literature, considering the improvement in quality of LISA procedure.
- Propofol and ketamine are two drugs for which some data on their use in preterm newborns are already available (see paragraph 2.2).

- There is no major individual risk identified from the literature, excluding immediate adverse effects of the sedation on respiratory function. Because the protocol will be performed achieved in Neonatal Intensive Care Units, mechanical ventilation will be readily achievable if severe apnea occurs during the procedure. All other potential side effects (especially hemodynamic effects) are currently monitored in NICU and in our experience they are transient and mostly non-serious events (Descamps 2017).

  The dosage for the procedure LISA is very low (decrease with a factor of 50 in comparison with the administration in clinical practice). Moreover, because the administration of lipid is systematically performed during first days and weeks of life for the usual clinical practice, the surveillance of lipid administration will be made according the protocols of each center.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 MAIN OBJECTIVE

In a population of preterm babies less than <32wGA, our objective is to compare sedation by Propofol versus placebo during the LISA procedure on the need for MV within 72 hours of life and on pain reduction before and following procedure.

The following hypotheses will be tested sequentially:

- Propofol is not inferior to placebo regarding the need for MV within 72 hours
- Propofol is superior to placebo regarding pain before and following procedure

An open-label ketamine treatment as rescue is possible in each group.

## 3.2 PRIMARY ENDPOINT

**Rate of MV from the start of the LISA procedure up to 72 hours of life** in each group.

The need of MV will be indicated by these guidelines:

- Repeated and severe apnea with bradycardia and/or low oxygen saturation, according the American Academy of Pediatrics Guidelines (American Academy of Pediatrics, 2003):
  - Respiratory pause during 20 sec
  - Or a shorter respiratory pause if accompanied by bradycardia or cyanosis
- High FIO2 justifying intubation for a second administration of surfactant and mechanical ventilation

- Respiratory complications such pneumothorax, with an aggravation of the respiratory distress syndrome
- Any other cause where the clinician judges the necessity for mechanical ventilation: the motive for the respiratory assistance must be indicated in the case report form

All delays associated with reintubation for MV will be recorded (per procedure, within the 1st hour, and from the 1st hour to 72 hours of life).

**Pain before procedure and within 1 hour following procedure**

Each neonate requiring ketamine administration before procedure or with a Faceless Acute Neonatal Scale (FANS) ≥6 within 1 hour following first injection of propofol/placebo will be considered as painful.

## 3.3 SECONDARY OBJECTIVES

1. To compare sedation by Propofol versus placebo during the LISA procedure, evaluating the need for MV within 72hours of life, in each class of GA (<28, 28-31wGA)
2. To assess the rate of ketamine administration for rescue in each group
3. To assess the quality conditions of the procedure: per procedure events (tolerance) and the clinician's satisfaction (efficacy) during the LISA procedure
4. To assess BPD at 36wGA
5. To assess in-hospital neonatal morbidity and mortality.
6. To evaluate the neurodevelopmental outcome at two years corrected age among survivors.

## 3.4 SECONDARY ENDPOINTS

1. Rate of MV from the start of the LISA procedure up to 72 hours of life in each class of GA (<28, 28-31wGA)

2. Rate of ketamine administration for rescue: This administration will be indicated after two (< 28 wGA) or 3 (28 – 31 wGA) administrations of the drug, if adequate comfort is not achieved (FANS≥6 or baby not comfortable) (See paragraph 5.3)

3. Quality conditions:

**Per procedure events:**

- Number of laryngoscopies needed to perform LISA, reflux of surfactant through mouth or nose
- Evolution of cardiorespiratory parameters from baseline to 1, 3, 5, 15, 30, 60 and 120 min after the drug injection: heart rate, respiratory rate, pulse oxymetry, blood pressure, FiO2, inspiratory and end-expiratory ventilation pressures, TcPCO2
- Presence of apnea requiring bag mask ventilation or additional nasal pressure with NIPPV (Nasal Intermittent Positive Pressure Ventilation), and defined according to the American Academy of Pediatrics Guidelines (American Academy of Pediatrics, 2003):
  - Respiratory pause during 20 sec
  - Or a shorter respiratory pause if accompanied by bradycardia or cyanosis
- Emergency intubation after the drug injection before the LISA procedure indicated for severe apnea

**Clinician's satisfaction during laryngoscopy** (especially ease of the exposure of the glottis) according to the Viby Mogensen scale (Viby Mogensen 1996). This score based on 5 items (scored from 1 to 4), explores the facility to expose the larynx and the baby's behavior.

4. BPD at 36 wGA according the definition proposed by Jobe with the distinction between severe, moderate and mild BPD (Jobe 2001)
   Final Evaluation at a post-conceptional age of 36wGA
   BPD: Oxygen supplementation during 28 days associated with the following situation at the final evaluation:
   - Mild BPD: ventilation with room air
     Moderate BPD: Oxygen supplementation with FI02 < 30%
   - Severe: Oxygen supplementation with FI02 > 30% and/or ventilation with positive pressure

5. In-hospital neonatal morbidity and mortality:

- Pneumothorax within 72h
- necrotizing enterocolitis
- proven early and late onset sepsis

- retinopathy of prematurity
- periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage
- treatment of a patent ductus arteriosus
- death at 36 wGA and in-hospital mortality

6. At two years :

- ASQ questionnaire, completed by the parents
- Gross Motor Function Classification Scale in cases of motor impairment
- Visual and hearing function

# 4 EXPERIMENTAL DESIGN

Phase III, pivotal, double blind, randomized, multicentric, trial comparing Propofol versus placebo during the administration of surfactant preterm babies less than 32wGA. In each group, a rescue treatment with ketamine will be possible, to avoid, as much as possible, a pain during the procedure.

This trial will involve 15 geographically dispersed NICU in France. These neonatal units are used to participating in health research and have a varied case mix of patients. They are all centers used to performing the LISA procedure. In each center, a neonatologist will be identified as the PROLISA referral professional.

A learning phase involving junior and senior neonatologists will be planned in all centers to ensure the homogeneity of practice including sedation/placebo injection, monitoring during the procedure, and rescue analgesia. Training will be supported by videotapes illustrating various scenarios with and without procedure events, need for rescue analgesia etc. and relayed by the referral neonatologist. It will also include examples of scoring the FAN Scale.

**Parental information, consent, and randomization:**

- Inclusion and exclusion criteria will be applied in the 1st 48 hours of life. Most of the eligible babies will already be hospitalized in the NICU, while a few others will present with RDS in the delivery room. To ensure a high rate of participation and recruitment despite the emergency context of premature birth and neonatal resuscitation in the first

hours of life, parents of preterm babies <32 wGA will be informed about the trial as soon as possible on their admission to the delivery room or to the NICU.

- Considering the emergency context of most situations, anticipated informed consent will be sought from mothers and ideally parents, as soon as possible after the admission of the mother into the delivery room or at admission of the neonate to the NICU. It is possible to discuss about the study before the birth, if the mother is previously hospitalized in the obstetrical unit. A single signature a parent is sufficient to include the newborn in the protocol. The recovery of the second signature will be sought within 48 hours.
- Preselected babies who finally do not have an indication for LISA, will not be included in the end.

Randomization will be performed only for eligible preterm babies presenting a RDS. The randomization will be stratified by center and by class of GA (<28, 28-31wGA).

Stratified randomization according to gestational age:

The main hypothesis of the trial arises in a different way depending on the term of the newborn. First, the rate of BDP is linked to gestational age, being higher the shorter the term. For example, in the French Study EPIPAGE 2 (a nationwide cohort of preterm babies born in 2011) the rate of severe BDP was 37%, 22% and 8% (respectively at 24, 26 and 28 wGA) whereas it decreased from 3 to 1.5% at 29 and 31wGA (Ancel 2015). Second, the need for MV is also associated with the gestational age. In the COIN Trial which compared the respiratory outcome between preterm babies treated by Nasal CPAP vs. intubation at birth, the rate of intubation for MV in the CPAP group was 55% for infants born at 25 or 26 weeks' gestation and 40% for those born at 27 or 28 weeks' gestation (Morley 2008). This result can be explained by a risk of apnea that is greater the lower the gestational age (Lorch 2011). Third, global severity of apnea syndrome (duration, low saturation and bradycardia) is worse for extremely premature babies (Darnall 1997, Eichenwald 1997). Conservation of respiratory function is all the more difficult during sedation. Fourthly, concerning the pain expression it can also vary according to gestational age. In fact some studies showed that the responses to pain may be with smaller magnitude as gestational age decreases. (Maxwell, 2019).

For all these reasons the results of our trial must be analyzed according the gestational age.

A predefined randomization list with a **1:1 ratio**, obtained with a random number generator with a **random size of blocks from 2 to 6**, will be established. **Drugs** will be delivered by the

hospital pharmacy as required in sequentially numbered containers. Medialipide will be used in the control group to ensure that the 2 arms will be indistinguishable.

**Follow-up:**

The **subsequent management** of preterm newborns will be left to the discretion of clinicians in both arms of the trial. The follow-up of participants will include the hospitalization in the neonatal unit until hospital discharge, and a clinical examination planned at two years. In France, preterm babies are systematically enrolled in a perinatal network, and this organization will facilitate this last visit. According to the parents' place of residence and perinatal networks in French regions, babies might be transferred from the initial NICU, corresponding to the place of birth and a participating center, to another NICU, closer to the parents' residence. In this case, data collection will remain under the responsibility of the investigator of the participating center which included the newborn.

**Endpoint collection:**

Primary and secondary endpoints will be evaluated by neonatologists, and data collection will be carried out by clinical research assistants recruited in each center, who will record data in an electronic case report form.

# 5 INCLUSION AND EXCLUSION CRITERIA

## 5.1 INCLUSION CRITERIA

- Preterm Infants < 32 wGA
- Presenting a RDS
    - in the first 48 hours of life
    - treated by CPAP or BiPAP
    - requiring surfactant:
        - FIO2 :

– if 28 - 31 SA : FiO2 ≥30% for a duration ≥ 10mn

– if <28 SA FIO2 ≥25% for a duration ≥10mn

- SpO2 :

To obtain a SpO2 between ≥88 and ≤ 95%

- Available Intra-Venous line (peripheral, umbilical or central catheter)
- Covered by French Social Security
- Informed consent form signed

## 5.2 NON-INCLUSION CRITERIA

- Congenital and/or major malformations
- FIO2> 60% at the time of the inclusion
- Silverman score > 6
- Contraindication to the use of Propofol :
  - Low Blood Pressure with 2 successive measurements (Mean < Gestational Age expressed in Weeks of Gestation) persisting after one volume expansion
  - Use of inotropic medication to maintain normal blood pressure.
- Use of sedative or analgesic drugs (except paracetamol and ibuprofen) in the previous 24h
- Coma, convulsions, areactivity at neurological examination

## 5.3 MANAGEMENT OF INCLUDED BABIES

**Management before the LISA Procedure:**

After verifying the newborn's eligibility, obtain mothers and ideally parents' consent. A single signature a parent is sufficient to include the newborn in the protocol. The recovery of the second signature will be sought within 48 hours. After allocation to the intervention or control treatment, the newborn will be prepared as in usual practice for tracheal intubation, whether admitted to the NICU or resuscitated in the delivery room equipped with cardio-respiratory monitoring, SpO2 monitoring (right hand), prepared material for tracheal intubation (ET tube, laryngoscope and Magill Forceps). Non-invasive respiratory support (with local devices) will be maintained throughout the procedure with a Non Invasive Positive Pressure Ventilation (NIPPV): Positive End Expiratory Pressure (PEEP) ≥ 4 cm H20. In case of BiPAP: Positive Inspiratory Pressure (PIP) ≥ 6 cm H20 and Respiratory Frequency remains at the discretion of the clinician, according to the condition of the child. We propose a respiratory rate around 30/min.

In the two groups, when the intervention team is ready, proceed with following administrations before the LISA

- atropine (dose used in routine care – for example 10µg/kg),
- caffeine (dose used in routine care – for example 20 mg/kg). If this drug could not been administered before LISA (for example when LISA is performed in birth room), it is tolerated that caffeine is injected within 30 minutes of the procedure
- oral sugar solution (unless contraindicated): 30% or 24%, depending to local available solutions: the solution is deposited on the tip of the tongue (using a 1 mL enteral syringe or directly the individual dose), drop by drop, about 2 minutes before the procedure. The recommended dose is 5 to 10 drops, according to local protocol. (Barrington 2011, *Stevens* 2016).

According to international guidelines atropine is commonly used before any intubation procedure. The aim of the atropine administration is to reduce the risk of bradycardia associated with an exacerbation of vagal tone. Sugar solution is given as an analgesic agent.

**LISA procedure**

**Sedation before the administration of surfactant**

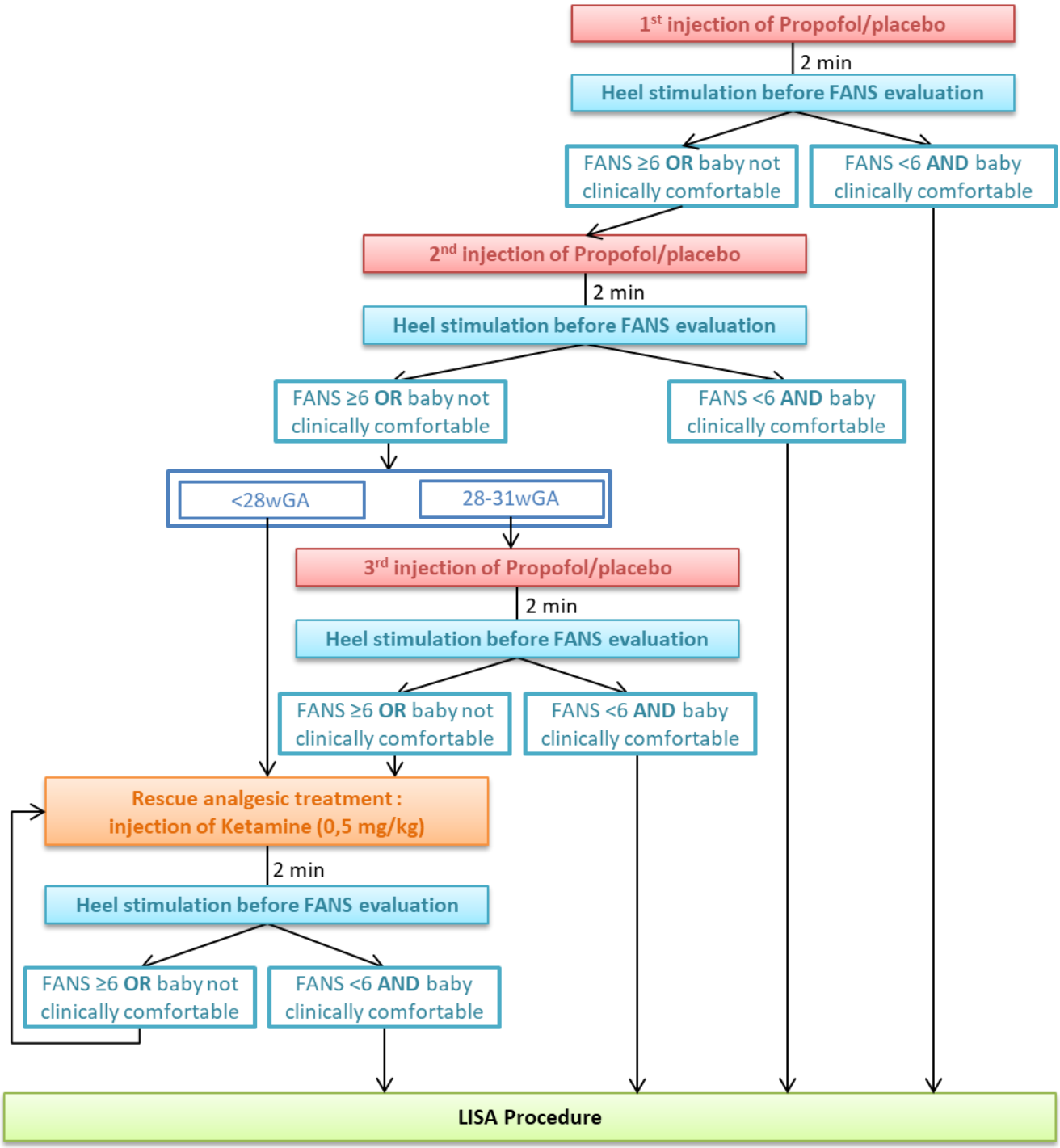
• The administration of Propofol (experimental group) or placebo (control group) will then be performed with a titration: (0.5 mg/kg per dose of Propofol or a similar volume of placebo (20% Medialipide, which has the same appearance as Propofol).

• Within 2 minutes of the injection of the 1st dose, a FANS pain score will be quickly evaluated after firmly rubbing the heel of the patient's feet:

<u>If the FANS score is ≥ 6 OR if the baby is uncomfortable during the foot arch stimulation</u> the second dose of 0.5mg/kg will be injected.

After two (< 28 wGA) or 3 (28 – 31 wGA) administrations of the drug (or placebo), if adequate comfort is not achieved (FANS ≥ 6 or if the clinician considers that the sedation is not sufficient to proceed with LISA), a rescue treatment will be given: ketamine 0.5mg/kg. One or two injections are recommended but in some rare cases, the clinician can decide to go further and administer more ketamine doses. This has to remain an exceptional case, and 1 or 2 doses must be sufficient in most cases.

<u>If the FANS score is < 6 AND if the baby is comfortable during the foot arch stimulation</u>, no further injection of propofol (or placebo) will be given




**Administration of surfactant**

An aspiration probe (CH6) or the **LISAcath®** (Catheter for oral endotracheal instillation) from CHIESI SAS, will be used. The type of probe is left to the choice to each investigator of the center. If the used probe does not have numbered graduations, a wound closure strip (such as Steristrip®) should be placed at the desired insertion depth (using a graduated probe):

- 7 cm + weight in kg when the probe is introduced through the nose

- 6 cm + weight in kg when the probe is introduced through the mouth.

Direct laryngoscopy (or indirect with videolaryngoscopy, according local practices) will be performed with the probe inserted to beyond the vocal cords to the required depth, and held in position at the lips. Once the probe is correctly positioned, surfactant will be slowly infused (at the dose used in routine care – for example 200mg/kg). At the end of the administration, the probe will be immediately withdrawn. The newborns will be continuously on NIPPV throughout the procedure.

Apnea during the procedure, is defined according to the American Academy of Pediatrics Guidelines (American Academy of Pediatrics, 2003):

- Respiratory pause during 20 sec
- Or Respiratory pause shorter if accompanied by bradycardia or cyanosis

If the newborn develops transient apnea, additional positive pressure inflations given by respiratory support (NIPPV), an AMBU® bag or a T-piece resuscitator device (Neopuff®) will be possible.

**Management until 72 hours of life:**

- MV will be indicated according to the definition given in paragraph 3.2.
- If a second dose of surfactant is indicated, usually occurring 12 to 24 hours following the 1st administration, the indications and modalities of administration will be performed according to the guidelines usually followed by the NICU.
- All other aspects of care (nutrition, hemodynamics, neurological monitoring etc.) will be left to the discretion of the neonatologists. For the management of low blood pressure, the general strategy will include volume expansion with physiologic saline 0,9% (10-20ml/kg, IV administration) and/or amine / hydrocortisone hemisuccinate.

## 5.4 RECRUITMENT MODALITIES

Considering the sample size (see the paragraph 11 on data management and statistical analysis) the study will be multicentric, with the involvement of 15 motivated neonatal units in university hospitals, listed in appendix 1. Recruitment estimation was estimated thanks to the usual level of activity of the NICU.

# 6 STUDY ARMS

## 6.1 INTERVENTION ARM

Name of studied treatment: Propofol (Propofol LIPURO 1% 100mL)

Pharmacologic form: 10mg/ml. Considering the birthweight of most preterm babies, Propofol will be diluted to a final concentration of 1mg/ml by the nurse ($1/10^{th}$ dilution: 1 part of Medialipid 20% with 9 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution).

Treatment initiation: the $1^{st}$ dose will be injected following usual management of LISA procedure included the installation of the newborn and the atropine and caffeine injection

Dose per administration: 0.5mg/kg per dose of Propofol.

Number of administrations: Several administrations of 0.5 mg/kg are possible, according the level of sedation achieved, as evaluated by the FANS score and the physician feeling. If the FANS score is ≥6 AND the baby is not comfortable, a new dose will be injected up to a total of two (before 28 wGA) or 3 (between 28 – 31 wGA) administrations of the drug. (See paragraph 5.3)

Modalities of preparation in accordance with SPC (See RCP (SPC) in annex)

## 6.2 CONTROL ARM

Name of treatment for placebo: Medialipide® (B. BRAUN)

Pharmacological form: 20g/100ml

Medialipide 20% will be used as the placebo. This is an emulsion of medium and long triglycerides based on soya oil and having same appearance organoleptics characteristics as Propofol.

Dose per administration: Same volume as for the Propofol administration

The volume to be given will be the same as that for Propofol. For example, for a preterm baby with a birth weight of 1kg, the volume of Medialipide 20% to be administered will be 0.5mL, which contains 0.01g of lipids. This dose is 300 times less than the dose usually used for parenteral nutrition during a day.

Number of administrations: according to the same protocol that for the Propofol administration.

Modalities of preparation: The same dilution procedure as Propofol lipuro 1% SPC: 1 part of Medialipid 20% with 9 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution

as shown in parenteral nutrition which is in accordance with medialipide 20% SPC (See RPC (SPC) in annex).

## 6.3 OTHERS DRUGS

Other drugs are used during this study but they are not of particular interest for the main objective of the study.

- Atropine and caffeine is commonly used before any procedure of intubation in the international guidelines. The aim is to reduce the risk of bradycardia associated with an exacerbation of the vagal tone.
- Sugar solutions 30% and 24 % are commonly used before any painful procedure in NICU. It has been well studied in preterm infants to reduce pain before these types of procedure. In some of protocols about LISA procedure the use of Sugar solutions before procedure is often encouraged by the investigator (Dargaville 2014, Dekker 2016)
- If adequate comfort is not achieved, a rescue treatment will be administrated: ketamine 0,5mg/kg, renewable once. in each group (placebo or propofol) if the sedation is considered inadequate by the clinician

Name of rescue treatment: ketamine

Pharmacologic form: 10mg/ml

Dose per administration: 0,5 mg/kg

Number of administration: renewable once.

## 6.4 PHARMACY CIRCUIT

The circuit is described in a specific pharmacy manual prepared for the study.

### A) PRODUCT SUPPLY AND RECEPTION

Propofol Lipuro 10mg/ml and placebo (medialipide 20%) are ordered by Pharmacy Department, Universitary Hospital of Grenoble with the budget allocated for the clinical trial at the start of the study. Supply may be made in several times.

The drugs are received in the Pharmacy of Grenoble Alps University Hospital.

B) PACKAGING

Each vial will be packaged in specific study packaging allowing the maintenance of the double-blind. (link). The packaging will be done by the Pharmacy of Grenoble Alps University Hospital before dispatch to each center.

C) PRODUCT SHIPMENT AND MANAGEMENT

Specific supplying procedures will be detailed in the study pharmacy manual as appropriate.
Briefly, centers will be automatically supplied after each inclusion and resupplied if necessary at the request of the pharmacist with a specific document.
Treatment accounting will be carried over to a specific traceability document.

D) PRODUCT DISPENSATION

Specific dispensation modalities will be detailed in the study pharmacy manual as appropriate.

E) STORAGE

All drugs must be stored at a temperature not exceeding 25 °C in accordance with SPC and in a secured place in accordance with the internal procedure of the Pharmacy at each center.

F) RETURN AND DESTRUCTION OF PRODUCTS

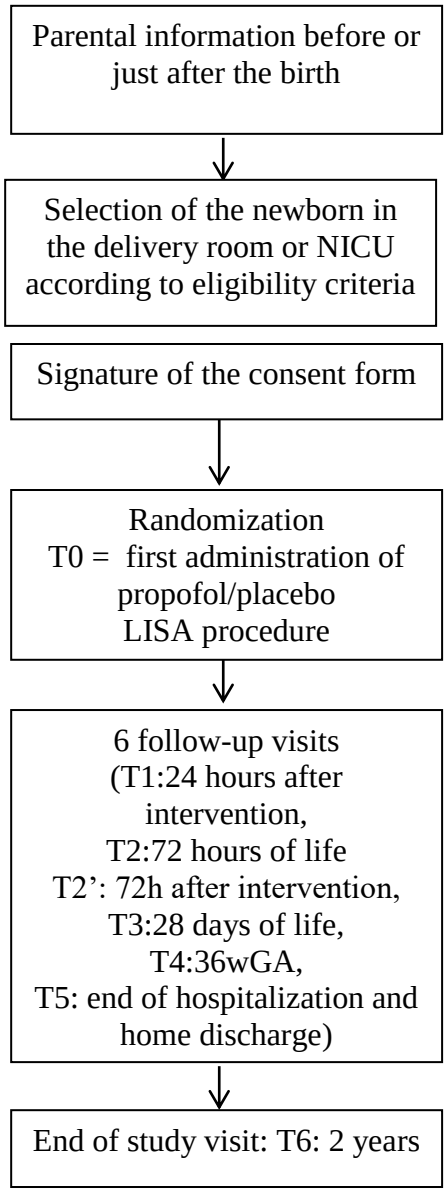
Expired, unused and returned products will be destroyed according to the internal procedure of the Pharmacy at each center and after approval from the Pharmacy of Grenoble Alps University Hospital.

# 7 STUDY PROGRAMME

## 7.1 SCHEDULE

- Start of inclusions: October 2019
- Duration of the inclusion period: 54 months
- Duration of treatment: 15 min
- Duration of participation for each patient: 2 years
- Total duration of the research: 6.5 years
- End of inclusions: 2024.
- End of research: 2026.

## 7.2 PLANNED VISITS AND EXAMINATIONS



Summary of visits and data collection

| | Screening | LISA Procedure T 0 | H24 post intervention T1 (+/-6h) | H72 of life T2 (+/-6 h) | H72 post intervention T2' (+/-6 h) | Day 28 T3 (+/-1d) | 36wGA T4 (+/-1d) | End of hospitalization T5 | Follow Up Visit : 2 years T6 (+/- 2 months) |
|---|---|---|---|---|---|---|---|---|---|
| Consent form | X | | | | | | | | |
| Inclusion – Non-inclusion criteria | X | | | | | | | | |
| Baseline maternal characteristics, Obstetric management, Neonatal characteristics | X | | | | | | | | |
| Cardiac and Rrespiratory monitoring * | X | X | X | X | X | | | | |
| Silverman Score | X | | X | | X | | | | |
| Ventilation : Need, type and settings | X | | X | X | X | X | X | | |
| Neurological examination | X (Apgar) | | | | | | X | | |
| Biological analyses especially blood gases | X | | X | | X | | X | | |
| Chest X ray | X | | | | X | | X | | |
| Per-procedure events (pre-medication and heel stimulation), FANS and rescue treatment by ketamine ** | | X | | | | | | | |

| | Screening | LISA Procedure T 0 | H24 post intervention T1 (+/-6h) | H72 of life T2 (+/-6 h) | H72 post intervention T2' (+/-6 h) | Day 28 T3 (+/-1d) | 36wGA T4 (+/-1d) | End of hospitalization T5 | Follow Up Visit : 2 years T6 (+/- 2 months) |
|---|---|---|---|---|---|---|---|---|---|
| Brain Ultrasound | | | | | X | | X | | |
| Sensorial examination (auditive and/or ophthalmic) | | | | | | | | X | X |
| ASQ Score and motor examination | | | | | | | | | X |
| Status for chronic lung diseases | | | | | | X | | | X |
| Neonatal Co-morbidities | | | | | | | | X | |
| Treatments | | | | | X | | | X | X |
| Adverse events | | X | X | X | X | X | X | X | X |

* Blood pressure, heart rate, FIO2

** + clinician's satisfaction

### 7.3 INCLUSION AND PROCEDURE EVENTS

The examination at inclusion will be performed by the neonatologist, assisted by the nurse in the delivery room or in the neonatal unit, and will include:

- Control of the RDS (Respiratory Distress Syndrome):
  - Silverman Score
  - FI02, ventilation type and settings
  - Chest X ray to determine the severity of the RDS
  - Blood gases
- Control of hemodynamic function (severe alterations are a non-inclusion criteria)
  - Blood pressure
  - Heart rate
  - Clinical signs of circulatory failure
- Neurological examination: APGAR score.

Considering that endpoints will be collected during and immediately after the LISA procedure, the neonatologist will be assisted by the nurse and by one or two other colleagues. The monitoring of babies will include:

- Heel stimulation and FANS scale assessed before and after LISA, indicating whether ketamine administration is needed for rescue or not. This score is an evaluation of pain. It could be used to evaluate the possible local pain during propofol infusion. Moreover, because there is an item concerning the limb movement, it could be used to identify a possible unusual event which is hyper excitability with involuntary movements
- Per procedure events:
  - number of laryngoscopies needed to perform the LISA,
  - Cardiorespiratory parameters at 1, 3, 5, 15, 30, 60 and 120 min after the drug injection: heart rate, respiratory rate, pulse oxymetry, blood pressure, FiO2, TcPCO2
  - Apnea requiring bag mask ventilation
  - Emergency intubation after the drug injection but before the LISA procedure can be performed (or within 1h following the drug injection )
- Clinician's experience of LISA and clinician's satisfaction during laryngoscopy using the Viby Mogensen scale (appendix 2)
- Organizational data: date and place of the LISA procedure, type of the used LISA probe, recovery of the vial and probe packaging premedication.

### 7.4 OTHER EXAMINATIONS DURING THE HOSPITALIZATION

All the clinical visits performed for participants correspond to current monitoring of preterm babies <32wGA admitted to the NICU. Five visits are programmed during the hospitalization:

- at 24 hours post intervention (= 24h post first administration of propofol/placebo): Cardiac and respiratory status of the newborn will be evaluated. Blood gas analysis will be performed.
- at 72 hours of life: Evaluation of the main criteria (the need of mechanical ventilation), the administration of potential new dose(s) of surfactant and in a more comprehensive way, the cardiac and respiratory status of the newborn.

- at 72h post intervention (= 72h post first administration of propofol/placebo): Cardiac, hemodynamic and respiratory status of the newborn. Possible icterus requiring exsanguino-transfusion will be recorded. Blood gas analysis, chest X-ray and brain ultrasound will be performed. Possible additional administration of surfactant will be recorded.
- at 28 days of life: Evaluation of bronchopulmonary dysplasia status and need of ventilation.
- at 36wGA: to evaluate especially bronchopulmonary dysplasia status (with chest X ray and blood gases), and the need of ventilation. Brain ultrasound will be performed. Neurological examination.
- at the end of hospitalization: summary of ventilation days, usual complications of the premature: cerebral lesions (intraventricular hemorrhage and cystic periventricular leukomalacia), treatment for ductus arteriosus, necrotizing enterocolitis, proven early and late onset sepsis, retinopathy of prematurity or death. Hemodynamic and respiratory status will be evaluated. Possible icterus requiring exsanguino-transfusion will be recorded. Brain ultrasound and sensorial examination will be performed.

### 7.5 FOLLOW UP VISIT AT 2 YEARS

The 2-year examination is a standard medical examination to identify the motor development of children. This visit is to assess respiratory events during the two first years (especially any viral infections, Synagis immunoprophylaxis), and neurological development with a medical examination and one standardized test: the Ages and Stages Questionnaire (ASQ) which will be filled-in by the parents. Several recent publications attest to his interest in monitoring neurodevelopment (Pierrat 2017; Halbwachs 2014 ; Halbwachs 2013). In cases of motor impairment, the Gross Motor Classification scale will be used. An assessment of visual and auditory function will also be made.

## 8 DATA COLLECTION

### 8.1 CLINICAL EXAMINATION

In addition to the study endpoints, previously detailed, data collection will include:

- Baseline maternal characteristics: mother birth month and year, employment, smoking habits, body mass index, obstetric history, complications of the current pregnancy, antenatal treatments
- Obstetric management: labor and delivery mode, provider initiated delivery (pre-labor caesareans, place of birth (maternity level, inborn)
- Neonatal characteristics: date and hour of birth, gender, gestational age, birthweight and height, Apgar scores, small for gestational age (defined as birthweight below the 10$^{th}$ percentile according the EPOPé curves (Ego 2015), pH and lactate at the umbilical cord, resuscitation in delivery room, inspiratory and end-expiratory ventilation pressures
- Characteristics of hospital stay: dates and lengths of hospital stay in NICU, secondary transfer
- Neonatal morbidity and mortality: bronchopulmonary dysplasia, necrotizing enterocolitis, proven early and late onset sepsis, retinopathy of prematurity, periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage, treatment of a patent ductus arteriosus
- Treatments up to 72H after LISA and during whole hospitalization: caffeine, doxapram, ibuprofen, sedation, analgesia, corticosteroid for respiratory disease (only at the end of hospitalization), inotropic medications, NO administration and volume expansion.
- Subsequent follow-up: growth (9-months and 2-years), hospitalizations and treatments, neurodevelopmental assessment (ASQ questionnaire, Gross Motor Function Classification Scale if motor impairment, visual and hearing functions)

## 8.2 IMAGING ANALYSES

- Chest X ray at inclusion to confirm the diagnosis of RDS, and during hospitalization to monitor respiratory function, especially at 72h post procedure, 28 days of life and 36wGA to detect the bronchopulmonary dysplasia
- Brain US at H72 post procedure and 36wGA to screen for the occurrence of cerebral lesions (intraventricular hemorrhage and/ or periventricular leukomalacia)

Imaging performed corresponds to current monitoring of preterm babies of <32wGA admitted to NICU. They will be analyzed and interpreted by the radiology department of the center, with the usual practices of the hospital.

## 8.3 LABORATORY PARAMETERS

### 8.3.1 Local Biology and pathology analysis (BPA) overview grid

| Local testing by usual procedure | Sample to be drawn | Hour 24 post procedure | Hour 72 post procedure | Day 28 of life | 36 weeksGA |
|---|---|---|---|---|---|
| Venous Blood gas | according to standard local laboratory <2.5ml of blood | HC | HC | HC | HC |
| | HC : health care related procedure. | | | | |

### 8.3.2 Health care related BPA:

Biology testing described with HC marking are done according to §8.3.1 as standard health care related to assess respiratory status. They are assessed according to standard local laboratory procedure (samples to be drawn, labelling, analysis, result delivery).

They are cited here because their results will be registered in the CRF. All the laboratory analyses performed correspond to current monitoring of preterm babies of <32wGA admitted to NICU.

### 8.3.3 Local research related BPA (in associated center)

NA.

### 8.3.4 Central research related BPA and biological collection

NA.

### 8.3.5 Person contact of laboratory analyses

Referent / contact: Pierre AUDOIN paudoin@chu-grenoble.fr 04 76 76 95 98.

### 8.3.6 Collection of biological samples

NA.

### 8.3.7 Total blood sample

Blood sample will be drawn at each visit according to § 8.3.1 < 2.5mL by visit, a maximum over 30 days of 5mL. We are under the limit according to Jardé's Law (for any subject over 1kg).

# 9 BIOLOGICAL SAMPLE COLLECTION

Not applicable

# 10 PHARMACOVIGILANCE AND SAFETY

## 10.1 DEFINITIONS

### 10.1.1 Adverse event (AE)

Any harmful event occurring in a person participating in research involving humans, irrespective of whether or not the event is related to the experimental drug or procedure.

### 10.1.2 Adverse Drug Reaction (ADR)

Any harmful and undesirable reaction to the experimental drug, whatever the administered dose.

### 10.1.3 Unexpected Adverse Drug Reaction (UADR)

Any ADR for which the nature, severity, or course does not conform to the information given in the reference documents (see list in 10.**2**. **Reference documents**).

### 10.1.4 Serious Adverse Event or Reaction (SAE)

A Serious Adverse Event or Reaction is an event that:
- results in death,
- or is life-threatening for the person participating in the research,
- or results in permanent or significant disability or incapacity,
- or requires in-patient hospitalization or prolongation of existing hospitalization
- or results in a congenital anomaly or birth defect
- or any other event that does not meet the definitions listed above but may be considered as "potentially serious", in particular some laboratory tests results

- or a medically pertinent event in the judgment of the investigator
- or an event requiring medical intervention to prevent one of the outcomes listed above.

### 10.1.5 New Safety Issue

This is any new data that may lead to:

- a reassessment of the benefits and risks of the research or experimental drug,
- changes in the use of this drug, or in the conduct of the research,
- or to suspend or interrupt or modify the protocol of the research or of similar research.

A New Safety Issue may also correspond to a suspected unexpected serious adverse reaction (SUSAR).

### 10.1.6 Causality

This defines the relationship between the adverse event and the experimental product (drug) under study or the procedure. The adverse event linked to the experimental product becomes an adverse reaction according to factors that should be considered when determining causality, such as chronological or semiological factors.

### 10.1.7 Severity

The severity of adverse events is evaluated by the investigator using the following classification:

- grade 1, mild: a generally transient adverse event with no impact on normal daily activities
- grade 2, moderate: adverse event sufficiently troublesome to affect normal daily activities
- grade 3, severe: an adverse event that significantly alters the normal course of the subject's daily activities, or is disabling, or constituting a threat to the life of the subject.

## 10.2 REFERENCE DOCUMENTS

- Summary of product characteristics (SPC) of propofol, medialipid and ketamine
- Investigator’s Brochure of experimental drug (PROPOFOL) and placebo (MEDIALIPID)
- Study protocol

## 10.3 RESPONSIBILITIES

### 10.3.1 Responsibilities of the Investigator

For each adverse event the investigator must:

- notify the sponsor of all serious adverse events occurring during the trial within a maximum delay of 24h after becoming aware of the event. The investigator must use the adverse event report form provided by the establishment's clinical trials Vigilance service that appears in annex of the protocol and/or clinical report book (e-crf):
- provide an etiological diagnosis
- evaluate the severity
- evaluate the extent
- determine whether there is a causal link between the experimental product or procedure, the treatments used for comparison, other treatments associated with the research and the SAE.
- inform the sponsor of any additional relevant information regarding the SAE within 8 days of the initial declaration.
- follow-up the patient presenting an SAE until it's resolution, stabilization at a level judged as acceptable by the investigator or return to a previous state, even if the patient has withdrawn from the trial.

The investigator records and documents all adverse events, unless otherwise specified in the protocol. The investigator shall inform the sponsor of all serious adverse events occurring in the participants whom he has treated in the clinical trial, unless otherwise specified in the protocol.

### 10.3.2 Responsibilities of the Sponsor

The sponsor must assess:

- whether there is any causal link between the SAE and the experimental drug or procedure

If the assessments of the sponsor and the investigator differ, then the two opinions are to be mentioned in the declaration addressed to the competent authorities (if a declaration is necessary).

- whether the SAE was expected or unexpected, using the reference documents in force for the study (see ch **10.2. Reference documents**)
- determine the degree of causality of the experimental drug or procedure

Sponsor must report suspected SIEs electronically to the Eudravigilance database.

- Eudravigilance database:

o - either via EVWEB,

o - or by electronic transmission ICSR E2B(R3),

- According to the procedures described on the EMA website at the following link: https://www.ema.europa.eu/en/humanregulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-electronicreporting.

It is therefore no longer necessary to declare EIGIs /SUSARs by e-mail to the ANSM.

The sponsor of a clinical trial conducted in at least one Member State shall notify electronically and without delay to the database referred to in Article 40(1) of European Regulation 536/2014 all relevant information on the following suspected serious and unexpected adverse reactions:

a) All suspected serious unexpected adverse reactions to investigational medicinal products occurring in the context of the said clinical trial, whether they occur at a clinical trial site in the European Union or in a third country;

b) All suspected serious unexpected adverse reactions related to the same active substance, whatever its pharmaceutical form and strength or the indication studied, in investigational medicinal products used in the clinical trial, occurring during a clinical trial conducted exclusively in a third country, if the said clinical trial is promoted:

i) by the said sponsor; or

ii) by another sponsor which belongs to the same parent company as the sponsor of the clinical trial or which develops a medicinal product jointly with the sponsor of the clinical trial on the basis of a formal agreement. For these purposes, the provision of the investigational medicinal product or information on safety issues to a potential future marketing authorisation holder cannot be considered as joint development;

c) all suspected serious and unexpected adverse reactions related to investigational medicinal products, occurring in any clinical trial participant, which are identified by the sponsor or which are brought to the sponsor's attention after the end of the clinical trial.

Follow up: (follow-up reports)

If the initial notification of a suspected life-threatening or fatal SAE is incomplete (for example, if the sponsor has not provided all the information within seven days), the sponsor has a further 8 days to submit a completed report based on the initial information.

In cases where a suspected serious adverse event has led to the death or endangered the life of the participant but was not initially considered to lead to the death or endangered the life of the

participant, a combined report (including the initial report and the new report) is drawn up if the initial notification has not yet been submitted.
The initial notification period (day 0 = Di 0) begins as soon as the sponsor receives the information containing the minimum notification criteria.

If significant new information on a suspected IGRA that has already been notified is communicated to the sponsor, the countdown starts again on day 0, i.e. on the date of receipt of the new information. This information is notified by means of a follow-up report within 15 days.

Minimum criteria for notification of suspected IGIEs
In accordance with Annex III (2.3) of the ECR :
A suspected serious adverse reaction may be notified if the notification includes at least the following information:
a) a valid trial number (EudraCT No or EUCT No)
b) the sponsor's study number ;
c) an identifiable participant code ;
d) an identifiable notifier ;
e) an EIGI (= SUSAR) ;
f) a suspected ME (including the name/code of the active substance);
g) a causality assessment.

If necessary, in order to meet the notification deadlines, the sponsor may transmit an initial incomplete report followed by a complete report, in accordance with section 2.4 of Annex III. 27.5.2014 EN Official Journal of the European Union L 158/37 3.
If the sponsor, due to lack of resources, is unable to transmit the notification to the database referred to in Article 40(1) of European Regulation 536/2014 and receives the agreement of the Member State concerned, it may transmit it to the Member State in which the suspected serious unexpected adverse reaction occurred.
That Member State shall report the suspected serious unexpected adverse reaction in accordance with paragraph 1 of this Article.

Other notification obligations required for the safety of participants

The sponsor notifies the Member States concerned, via the EU portal, of all 'unexpected events' that have an impact on the risk-benefit balance of the clinical trial but do not constitute suspected serious unexpected adverse reactions.
The notification shall be made without undue delay and no later than 15 days after the sponsor becomes aware of the event.
The sponsor shall make available to the Member States concerned, via the EU portal, all inspection reports from third country authorities relating to the clinical trial. At the request of a Member State concerned, the sponsor shall submit a translation of the report or its summary in the official language of the Union indicated in the request.

Urgent safety measures
If an unexpected event is likely to have a serious impact on the risk-benefit balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the participants.
The sponsor shall notify the Member States concerned, via the EU portal, of the event and the measures taken. The notification shall be made without undue delay and at the latest within seven days of the date on which the measures were taken.

Blinded trial
In the case of a blinded trial, as a general rule, the sponsor reports the serious unexpected adverse reaction to the health authority and the CPP after unblinding the investigational medicinal product.

## 10.4 PROCEDURES AND DELAYS IN REPORTING BY THE INVESTIGATOR

### 10.4.1 Reporting procedure

To comply with the regulations in force regarding the reporting of serious adverse reactions to the health authorities, the investigator agrees to document the event, to meet the deadlines for notification and to provide all the information necessary for the analysis of the event.
All serious adverse events (SAE) **must be reported by the investigator** to the sponsor's service in charge of safety (Vigilance):
Clinical Trials Vigilance: Dr Marylaure GAVARD / Dr Laura LEO, Pavillon Dauphiné, CHU Grenoble Alpes. Tel : 04 76 76 68 21 Fax : 04 76 76 83 54

email: vigilance-essaiscliniques@chu-grenoble.fr

and regardless of the causal relationship concerning the drug under investigation or the research The investigator must use the **SAE report form**, in the appendix of the case report booklet (ecrf) (VIGEC-FOR-001) or in annex of the study protocol, signed and dated, and include copies of laboratory test results and the reports of clinical examinations or hospitalizations concerning the SAE. Pertinent negative results should also be included. **These documents should be anonymized** and contain the code and number of the patient.

The initial report must be followed by additional relevant information within 8 days.

### 10.4.1 Reporting period

All SAE occurring to a person participating in the research must be reported.

- From the date of signing consent to participate,
- During the entire follow-up period for the participant in the trial,
- After the end of scheduled follow-up of the participant, when the event is susceptible to be due to the research, and without a time limit when it might be due to the experimental drug(s) (e.g. serious reactions that can appear a long time after drug exposure, such as cancer or birth defects).

If the investigator becomes aware of a serious adverse event, suspected to be causally related to the investigational medicinal product, occurring after the end of the clinical trial in a participant whom he has treated, he shall inform the sponsor without undue delay.

## 10.5 SPECIFIC FEATURES OF THE PROTOCOL

### 10.5.1 Related events subject to reporting / Adverse Events of Special Interest (AESI)

All non-serious or serious adverse events related to the drug or procedure under study and for which information from the investigator to the sponsor appears appropriate and / or the abnormal analytical results defined in the protocol as determinants of the safety of the subjects in the clinical trial, must be notified to the sponsor by the investigator, in accordance with the procedures and time limits specified in the protocol.

### 10.5.1 Expected events and/or reactions

Known events listed in the SPC of the propofol lipuro 1% in adults and infants are:

| System Organ Class | Undesirable Effects | Frequency |
|---|---|---|
| Immune system disorders: | Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension | Very rare (<1/10 000) |

| | | |
|---|---|---|
| Metabolism and Nutritional disorder: | Metabolic acidosis (5),<br>hyperkalaemia (5),<br>hyperlipidaemia (5) | Frequency not known (9) |
| Psychiatric disorders: | Euphoric mood, drug abuse and drug dependence (8) | Frequency not known (9) |
| Nervous system disorders: | Headache during recovery phase<br>Epileptiform movements,<br>including convulsions and opisthotonus during induction, maintenance and recovery<br>Postoperative unconsciousness<br>Involuntary movements | Common (>1/100, <1/10)<br>Rare(>1/10 000, <1/1000)<br>Very rare (<1/10 000)<br>Frequency not known (9) |
| Cardiac disorders: | Bradycardia (1)<br>Pulmonary oedema<br>Cardiac arrhythmia (5),<br>cardiac failure (5), (7) | Common (>1/100, <1/10)<br>Very rare (<1/10 000)<br>Frequency not known (9) |

| | | |
|---|---|---|
| Vascular disorders | Hypotension (2)<br>Injection site thrombosis and phlebitis | Common (>1/100, <1/10)<br>Uncommon(>1/1000, <1/100) |
| Respiratory, thoracic, and mediastinal disorders: | Transient apnoea during induction<br>Respiratory depression<br>(dose-dependent) | Common (>1/100, <1/10)<br>Frequency not known (9) |
| Gastrointestinal disorders: | Nausea and vomiting during recovery phase<br>Pancreatitis<br>Hepatobiliary, disorders<br>Hepatomegaly (5) | Common (>1/100, <1/10)<br>Very rare(<1/10 000)<br>Frequency not known (9) |
| Musculoskeletal and connective tissue disorders: | Rhabdomyolysis (3), (5) | Frequency not known (9) |
| Renal and urinary disorders | Discolouration of urine following prolonged administration | Very rare (<1/10 000) |
| | Renal failure(5) | Frequency not known (9) |

| | | |
|---|---|---|
| Reproductive system and breast | Sexual disinhibition | Very rare (<1/10 000)<br>Very common (>1/10) |
| General disorders and administration site conditions: | Local pain on induction (4)<br>Tissue necrosis (10) following accidental extravascular administration<br>Local pain, swelling, following accidental extravascular administration | Very rare (<1/10 000)<br>Frequency not known (9) |
| Investigations | Brugada type ECG (5), (6) | Frequency not known (9) |
| Injury, poisoning and procedural complications: | Postoperative fever | Very rare (<1/10 000) |

Since the specificity of the population studied in the Prolisa study, all these effects mentioned are not directly extrapolable to the newborn population. The pharmacological occurrence is still possible and it is necessary to know how to identify them, but most of the events listed in this SPC have not been observed in the premature population, so their occurrence, although possible, will be considered as unexpected. Only the events listed in the table below are considered as expected.

The expected events are especially those associated with the administration of Propofol and the possible co-administration of Ketamine

- Low blood pressure (Propofol administration)
- Low Oxygen Saturation during low blood pressure (Propofol administration)
- Apnea (Propofol administration and co-administration of Propofol-ketamine)
- Apnea associated with Low Oxygen Saturation (Propofol administration and co-administration of Propofol-ketamine)
- Apnea associated with Bradycardia (Propofol administration and co-administration of propofol-ketamine).

| **System Organ Class (Meddra SOC)** | **adverse effects (Meddra PT)** | **Frequency** |
|---|---|---|
| Vascular disorders | Hypotension | Common (>1/100, <1/10) |
| Investigations | Low $0_2$ saturation | Frequency not known |
| Respiratory, thoracic and mediastinal disorders: | Transient apnoea during Induction, neonatal apnea | Common (>1/100, <1/10) |
| Cardiac disorders | Bradycardia | Common (>1/100, <1/10) |
| General disorders and administration site conditions: | Local pain on induction | Very rare (<1/10 000) |
| Nervous system disorders: | Involuntary movements | Frequency not known (9) |
| Metabolism and Nutritional disorder: | Metabolic acidosis | Frequency not known (9) |

Some expected events could be associated with the LISA procedure and common to any tentative of intubation

- Traumatic lesion of the glottis or the oropharynx (oedema, wound, ulceration, perforation) during the introduction of the laryngoscope or probe
- Bleeding of the nasal pits during the introduction of the probe
- Infections

Since Medialipide is not used at a therapeutic dose, neither adverse effect with this product is expected.

All adverse effects mentioned in the Summary of product characteristics (SPC) of the different concomitant products used in this study (atropine, ketamine, sugar solution) are considered as expected.

### 10.5.2 Expected non-serious events

Hematomas during the sampling of blood for blood gases

## 10.6 INDEPENDENT SUPERVISORY COMMITTEE

A data safety monitoring board (DSMB) will be convened for the study to assess safety related to the study. The DSMB will be met first after around 50 inclusions, once a year if necessary since the last inclusion, and may eventually meet at the request of the investigator or the sponsor, or, for example, in case of SUSAR.

This committee may propose to the sponsor and coordinating investigator that the study is stopped or the study protocol modified if the safety of persons participating in the study seems inadequate.

## 10.7 IN UTERO EXPOSURE

Not applicable.

## 10.8 ANNUAL SAFETY REPORT

At the anniversary date of authorization issued by the Health Authorities, the study sponsor must submit a safety report that includes:

- The list of serious adverse reactions that may be related to the trial drug or procedure, including both unexpected and expected reactions.
- A concise and critical analysis of the safety of persons participating in the research

This report can be submitted to the coordinating investigator for approval.
This report is sent to the competent authority (ANSM) and to the ethics committee (CPP) within 60 days after the anniversary date of authorization of the research.

# 11 DATA MANAGEMENT AND ANALYSIS

## 11.1 DATA MANAGEMENT

An electronic CRF will be created for this study with a login and password for the investigators in each center. The sponsor will supply the logins and passwords. In each center, the persons authorized to collect the data will be clearly identified. The database will reflect the data collected in the electronic CRF. The database will be the property of Grenoble Alps University Hospital.

## 11.2 SAMPLE SIZE CALCULATION

In this controlled double-blind trial aimed at comparing the LISA procedure with sedation versus the LISA procedure with placebo, our hypothesis is that the improvement in neonatal comfort and procedural conditions will be offset by a reasonable increase in the necessity for mechanical ventilation during the first 72 hours of life,

The sample size was estimated according to the following assumptions:

- A balanced randomized ratio of 1:1
- According to NONA-LISA protocol (Breindahl 2024) and other previous studies (Aldana-Aguirre 2017, Kribs 2015, Göpel 2015 and Göpel 2011), the lowest rate of MV in the first 72h of life was estimated at 30% but heterogenous results close to 50% were reported in the LISA arm with sedation. Thus, we make the hypothesis of a rate of 30% and we propose to set the non-inferiority margin for the difference at 18%, corresponding to the upper limit of the one-sided 97.5% confidence interval.
- A previous randomized trial evaluating pain during LISA procedure reported rates of painful neonates of 76 vs 22% with placebo without sedation versus Propofol (Dekker 2018).

Under these hypotheses, recruiting 204 neonates allows us to obtain a power greater than 80% to answer each of the following two statistical questions asked in the main objectives' hierarchy: (i) showing the non-inferiority of Propofol compared to placebo on MV within the 72 1$^{st}$ hours of life, (ii) showing the superiority of Propofol versus placebo on pain associated with the LISA procedure.

## 11.3 RANDOMISATION

The randomization will be stratified by center and by class of GA (<28, 28-31wGA). Allocation will be predefined by the Department of data management and biostatistical analysis of the Grenoble Alps University Hospital according to one list per participating center, with a 1:1 ratio, obtained with a random number generator number using a random size of block from 2 to 6. Drugs will be prepared by the pharmaceutical department of the Grenoble Alps University Hospital and then delivered to each participating NICU in sequentially numbered containers according to the randomization list of the center. NICUs will be provided with 2 or 4 blinded bottles for each class of GA. Once a participant is included, the investigator will take the first blinded bottle in the ascending order of inclusion number.

## 11.4 ANALYSIS STRATEGY

**Baseline characteristics of study sample**

Descriptive statistics (means and proportions) will be calculated to check for any major imbalances between the study's two groups of neonates at baseline. These characteristics will be presented as numbers and frequencies for categorical variables and means and standard deviations for continuous variables or median and 25th and 75th percentile if the parameters do not follow a normal distribution (graphic verification of the symmetry of the distribution). Comparison between baseline characteristics in each arm will be performed by using a Chi2 test (or Fischer exact test) for qualitative data, and Student test (or Mann-Whitney test) for quantitative data.

**Statistical methods**

Considering recent guidelines supporting ~~that~~ intention to treat (ITT) analysis in non-inferiority assumption (Bai 2021) and the superiority hypothesis on the 2nd question included in our hierarchical analysis strategy, all randomized patients will be included in an ITT analysis in the group they were initially allocated to.

However, this implies obtaining complete data for all randomized patients, which in practice is rarely possible. We propose an analysis on the modified ITT population (mITT), which will include patients for whom the following protocol deviations will be observed:

- Patients assigned to an intervention group who finally did not receive the (or received incomplete) intervention, whatever the reason, but who completed follow-up within the 1st 72 hours of life, will be analyzed in the corresponding intervention group;
- patients allocated to the control group who would benefit from another intervention will be analyzed in the control group;

A per-protocol analysis will be carried out subsequently to confirm the results of the ITT analysis performed to answer to the first question, and will involve patients who satisfactorily complied with the assigned treatment and who had no major protocol violations (see paragraph 13.2).

The threshold $p<0.05$ will be considered to define the significance of the statistical tests performed with Stata MP15. Blinding will be maintained during statistical analysis.

**Primary outcome**

The primary objectives consist in 2 different questions, which are organized hierarchically. Therefore, the 2nd level of the hierarchy will only be tested if the null hypothesis of the 1st level is rejected.

- The MV rate at 72h of life will be estimated in each group. Our trial aims to show that the experimental arm with sedation is not less effective than the control arm with placebo, and we made the hypothesis that the MV rate within 72h of life will not exceed 48%, compared to 30% in the control group, corresponding to a non inferiority margin of 18%. If the upper limit of the one-sided 97.5% confidence interval for the treatment difference by the experimental treatment is less than this equivalence margin, then we will retain the non-inferiority of the experimental strategy . If non-inferiority is rejected, the rates of MV up to 72h life will be compared using a conventional superiority test.
- Rates of painful neonates (FANS) will be compared by a chi-square test with a significance level set at 0.05. A sensitivity analysis of pain rates using logistic regression adjusted for stratification variables (center and GA) will also be performed.

**Secondary outcomes**

The analysis of primary outcomes will be repeated in each class of GA (<28, 28-31wGA). Means and standard deviations (or median and 25th and 75th percentile) of cardio-respiratory

parameters, number of laryngoscopies, number of apneas, clinician's satisfaction, neurodevelopmental outcomes at 2 years (ASQ, GMFCS, visual and hearing function), will be calculated and compared using the Student test (or Mann-Whitney test).
Numbers and frequencies of ketamine administration for rescue and emergency intubation, pneumothorax within the first 72h post procedure, BPD at 28 days and 36wGA, other outcomes of neonatal morbidity and in-hospital mortality will be calculated, and compared using the Chi2 test (or Fischer exact test).

**Documentation of missing data and guarantee of integrity of the data**

An inspection of the database will be conducted to detect possible outliers. After checking with contributors to the study, these will be corrected if necessary in agreement with the contributors. Thus, a new database will be created taking into account these changes. These modifications and the missing data will be listed in a document. The freezing of the database will be made on this new version, which will be archived. The statistician will work on a copy.

**Missing data handling:**

Considering the design and endpoints will be recorded mostly during hospitalization, there are unlikely to be high rates of missing data. Nevertheless, in case of rates between 5% and 20%, missing data will be replaced. The replacement of missing data will either be according to an analysis strategy for the worst case scenario, or by multiple imputation. If multiple imputation is used, 5 imputations will be made, using a logistic regression model taking into account the main factors related to the outcome.

# 12 BLINDING

## 12.1 ORGANIZATION OF BLINDING

The preparation of containers containing Propofol or placebo will be centralized (Pharmacy, Grenoble Alps University Hospital). Both the propofol and the placebo will be physically identical, and investigators will not have access to the randomization list or to preparation records. This ensures proper blinding. Treatment kits will subsequently be given to the medical unit. Blinding will be maintained during statistical analysis.
The vigilance unit will hold the unblinding list.

### 12.2 UNBLINDING

In case of suspected adverse reactions and if the knowledge of the treatment administered allows a specific management, unblinding can be requested by the investigator even in case of emergency. Unblinding may be done 24/24h by the Pharmacy.

In order to lift the blind, the physician has to call the coordinating pharmacy:

- during business hours at: 04 76 76 92 09
- outside business hours at: 04 76 76 81 51

A specific form, containing date of request, contact details, name of the trial and nature of the treatment will be completed. The sponsor must be informed within 24 hours.

This unblinding is possible during the whole study, indeed randomization list will be available at the Pharmacy until the end of the trial.

Unblinding by the study sponsor could be done at the vigilance unit in case of suspected unexpected serious adverse reactions before drawing up the statement to the competent authorities, or for another safety reason.

## 13 STUDY STOPPING RULES

### 13.1 STUDY STOPPING CRITERIA FOR A PARTICIPATING SUBJECT

Criteria for exclusion from the study are:

- One or both parents withdraw consent to participate in the study
- Protocol Violations include the following conditions, and exclude the patient from the mITT analysis and / or the per-protocol analysis.

| Criteria excluding patients from the mITT analysis | Criteria excluding patients from the per-protocol analysis |
|---|---|
| - Patient included but not randomized<br>- Incomplete or missing evaluation of MV or pain | - Criteria excluding patients from the mITT analysis<br>- Inadequate or delinquent informed consent<br>- Inclusion criteria not met<br>- Non Inclusion criteria present<br>- Improper breaking of the blind |

| | |
|---|---|
| | - Use of prohibited medication<br>- Evaluation outside permissible window (72h of life +/- 6h for MV and within 60 minutes after 1st injection of propofol/placebo for pain)<br>- Allocation to the intervention or control group without finally receiving the adequate intervention (or receiving incomplete intervention), whatever the reason, with completed follow-up within the 1st 72 hours of life |

Protocol deviations, which refers to any other, unplanned, instance(s) of protocol noncompliance, may not render a patient ineligible, and will be discussed by the scientific committee

### 13.2 EARLY DISCONTINUATION OF THE EXPERIMENTAL PROCEDURE BY THE SUBJECT

In case of premature termination of the study, data from all the visits are collected in the eCRF until the premature termination of the study.

### 13.3 STOPPING RULES BY THE SPONSOR

The sponsor may stop the study at any time, for the following reasons:

- Inability of the investigator to include subjects according to the planned schedule.
- Absence of signed consent.
- Major violations of the protocol.
- Incomplete or incorrect data.

The sponsor notifies each Member State concerned of the end of a clinical trial relating to that Member State. This notification shall be made within 15 days of the end of the clinical trial in relation to the Member State concerned.

The sponsor notifies each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries where the clinical trial has been conducted. The

notification shall be made within 15 days of the end of the clinical trial in the last Member State concerned and in the third countries where the clinical trial was conducted.

Where the sponsor temporarily discontinues a clinical trial, it shall inform each Member State concerned within 15 days, giving reasons for its decision. Where a clinical trial which has been temporarily stopped restarts, the sponsor shall notify each Member State concerned within 15 days of the restart of the clinical trial.

Where the sponsor terminates a clinical trial early, it shall inform each Member State concerned, giving reasons for its decision and specifying any follow-up measures for participants.

Where the sponsor temporarily interrupts or prematurely terminates a clinical trial for safety reasons, it shall inform all the Member States concerned, without undue delay and within 15 days at the latest.

### 13.4 STOPPING RULES BY THE INVESTIGATOR

In the case of adverse events judged as severe by the investigator and that could jeopardize the health of subjects, the investigator may stop the study with the agreement with the sponsor.

### 13.5 INCONVENIANCE/CONSTRAINTS OF THE STUDY AND POSSIBLE COMPENSATION OF SUBJECTS /PATIENTS

The newborn will not be able to simultaneously participate in another interventional research study up to 1 week after the end-of-study visit.

## 14 STRENGTHS AND LIMITATIONS

### 14.1 DEFINITION OF CONTROL ARM

For human and ethical reasons, it might seem questionable to plan a control arm without sedation during “less invasive surfactant administration”. Indeed, attitudes and experiences of neonatologists support a growing recourse to various medications allowing improved neonatal comfort. Policies concerning premedication might be quite heterogeneous when considering the European observational survey of Klotz et al. or the first few hospital series describing

outcomes with various drugs. However, on the other hand, according to currently published randomized trials the "standard" LISA procedure excludes the use of sedation. In view of this state of knowledge, we made the choice to develop the possibility of a rescue administration of analgesia in both groups.

This rescue administration will probably be more frequent in the control group, but ketamine has been retained for its moderate sedative versus analgesic properties. Its use has also been specifically defined, and will intervene only after 2 (<28wGA) or 3 doses (28-31wGA) of the supposedly active drugs. Consequently we hope to maintain a balance between rates of procedure events, quality conditions of surfactant administration and neonatal comfort, in favor of the Propofol strategy, without affecting significantly the respiratory primary endpoint, i.e. rate of MV within 72h.

## 14.2 LIMITATIONS OF HYPOTHESIS AND SAMPLE SIZE CALCULATION

In this controlled double-blind trial aimed at comparing the LISA procedure with sedation versus the same procedure with placebo, our hypothesis is that while neonatal comfort and procedure conditions will be improved, there might be an increase from 30 to 48% in MV within 72 hours of life. We acknowledge that this margin might be considered as high, in particular because lower thresholds are usually used in non-inferiority drug efficacy trials. Nevertheless, our main objective is focused on a short-term tolerance of sedation and corresponds to an intermediate respiratory criterion. This 18% margin was chosen because it was considered as clinically acceptable.

## 14.3 BLINDING

Due to Propofol's pharmacological properties, and despite indistinguishable containers, neonatologists are likely to identify sedated babies allocated in the intervention arm following the first injection. In case of bradycardia, or apnea, this might influence their decision to implement mechanical ventilation, and lead in the end to rejection of the non-inferiority hypothesis. Nevertheless, should blinding be compromised other considerations are that: firstly the rate of cardio-respiratory depression in the control group might also be consequent in the absence of sedation; secondly, indications for MV have been rigorously defined to avoid any subjective decision.

## 14.4 RECRUITMENT AND FEASIBILITY

Preterm babies ≤32wGA represent 1.5% of all births, and are the target of many interventional studies evaluating survival, as well as infectious, respiratory, and neurological outcomes at short, middle and long term. Newborns cannot be enrolled in several interventional projects, as concomitant trials could compromise the feasibility of PROLISA. Nevertheless the participating NICUs are part of large University Neonatology Departments, used to having several trials running at the same time with a variety of case-mixes. Furthermore, our target population concerns the majority of newborns <32wGA as 85% of them will present a respiratory distress syndrome at birth. Many other trials are focused on highly specific small subgroups of preterm babies.

The acquired experience and high reputation of the neonatal team at Grenoble Alps University Hospital is another reassuring element for the feasibility of this trial. Pr T Debillon is the principal investigator of a national prospective cohort LyTONEPAL (Long term prognostic of neonatal hypoxic ischemic encephalopathy in the era of neuroprotective treatment with hypothermia). All French regions, except one, have joined this project funded by a PHRC in 2013. This cohort has successfully included 800 infants with moderate or severe hypoxic-ischemic encephalopathy in 2015-2017, with 3 years follow-up initiated in the spring of 2017. Pr T Debillon and Dr A Ego are also on the regional steering committee of the EPIPAGE2 cohort (Epidémiologie des petits Ages Gestationnels), as well as http://www.inserm.fr/ Unit 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team, including all very preterm births in the Rhône-Alpes region in 2011. More than 400 infants are currently followed to the age of 5 years.

## 14.5 DEVELOPMENT OF THE WIDESPREAD APPROPRIATE USE OF THE LISA PROCEDURE

Currently, the absence of guidelines on sedation is a major barrier to adopting less invasive surfactant administration for preterm babies presenting RDS, and there is a lack of well-conducted studies defining the best way to perform this procedure. With this trial, we hope to demonstrate the non-inferiority of LISA preceded by sedation in terms of respiratory outcomes. The expected benefit for participating babies in our trial relies essentially on improving the comfort and success of the procedure with equal rates of mechanical ventilation. If so,

proposing a less painful procedure for administration of surfactant will be a strong argument towards convincing all NICUs to adopt the LISA strategy for surfactant administration with a high degree of safety. LISA should subsequently benefit a larger number of neonates, previously exposed to tracheal intubation, who might represent half of the target population. This will be a step forward in neonatal care with the reduction of BDP at 36wGA which is a main public health concern for preterm newborns.

Moreover, this study is timely, and will enable us to draw up clear recommendations on the use of one of the sedative drugs currently used by neonatologists. At present Propofol is used anyway, but at the discretion of the clinicians and without enough scientific justification. This study should lead to the better management of pain. Painful events during the hospitalization of neonates contribute to the occurrence of adverse complications in preterm infants and as much as possible must be done to minimize stressful procedures. The short-term outcomes will be complemented by an evaluation of in-hospital morbidity and outcomes at two years. Initiating this first trial on sedation versus placebo will allow the development of other trials comparing sedative strategies in the preterm population.

# 15 STUDY COMMITTEES AND TEAM EXPERIENCE

## 15.1 STEERING COMMITTEE

The steering committee will meet twice a year to monitor the project as it advances.

The committee will be composed of:

- The principal investigator (Grenoble): Pr Marie Chevallier
- The Coordinator of the CIC (INSERM Clinical Research Center) (Grenoble): Pr Alexandre Moreau-Gaudry
- A Clinical Research Assistant designated by the CIC (Grenoble)
- The methodologist from the CIC: Dr Anne Ego
- The biostatisticians of the data management and biostatistics department :

Minutes of the meetings will be transmitted to the sponsor for information.

### 15.2 SCIENTIFIC COMMITTEE

The members of the scientific committee will bring their knowledge and experience in neonatal care and health research in perinatal epidemiology. It is composed of all the principal investigators of the study

## 16 RIGHTS OF ACCESS TO DATA AND SOURCE DOCUMENTS

### 16.1 ACCESS TO DATA

The sponsor is responsible for obtaining the agreement of all parties involved in the research to ensure direct access to all places in which the research is performed, to source data, to source documents and to reports for quality control and auditing by the sponsor.
The investigators must make the documents and individual data necessary for monitoring, quality control and auditing of the research available to persons who require access to these documents in accordance with legislative and regulatory provisions (Articles R.5121-13 and L.1121-3 of the Code of Public Health).

### 16.2 SOURCE DATA

Any original document or object proving the existence or the accuracy of a value or fact recorded during the research is defined as a source document:

- Medical file
- Laboratory results
- Scale and questionnaire
- Imaging results
- Video recordings, conditioned by the specific consent of parents

### 16.3 CONFIDENTIALITY OF DATA

In accordance with the existing legislation (Articles L.1121-3 and R.5121-13 of the French code of public health), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to experimental drugs, research and people who participate, in particular with regard to their identity and the results obtained. These people, along with the investigators themselves are subject to professional secrecy.
During the clinical research or after its termination, the collected data on persons who participate will be made anonymous before being communicated to the sponsor by the

investigators (or any other specialized person). In no case should the names or addresses of the persons concerned appear.

Only the first letter of the first name and of the surname of the subject will be recorded, along with an encrypted number unique to the study indicating the center and the order of inclusion of the subject.

The sponsor will ensure that each person participating in the research has given written consent for access to personal data relating to him and necessary for the quality control of the research.

# 17 QUALITY CONTROL AND INSURANCE

## 17.1 INSTRUCTIONS FOR DATA COLLECTION

Erroneous data collected in electronic case report forms will be corrected and new data will be entered. An audit trail of the eCRF records the initials, date and possibly a justification by the investigator or authorized persons who made the correction.

## 17.2 QUALITY CONTROL

A clinical research assistant mandated by the sponsor will regularly visit the study sites centers: while the study is being set-up, one or more times during the course of the research depending on the rate of inclusions and at the end of the research. The elements to be reviewed during these visits and the frequency of these visits will be defined prior to the start of the study in collaboration with the investigative team and according to the assessment of the risk level of the study.

All visits will be the object of a written report. A copy will be forwarded to the Principal Investigator.

## 17.3 DATA MANAGEMENT

The organization “Data-Stat” will be responsible for the data management of the study. The e-CRF data will be entered in a data management system, which is fully validated and compliant to 21 CFR, part 11. Data entry will be done on site (electronic CRF).

Data validation checks will be performed at regular intervals and may result in data queries. The resolved queries are to be confirmed and updates subsequently made in the database by the investigator.

When all data have been received, all data problems are solved and all data checks and quality control have been performed, a data review meeting has been held, the study database is considered clean and can be locked.

Details regarding data management will be described in a specific Data management plan.

### 17.4 AUDIT AND INSPECTION

An audit conducted at the request of the sponsor or an inspection conducted by the health authorities may be carried out at any time by persons independent of those performing the research. It aims to ensure the quality of research, the validity of its results and compliance with the law and regulations.

The auditors / inspectors should have direct access to all sources and medical data and any document related to the conduct of the clinical study.

Data confidentiality and anonymity of the subjects will be respected.

Investigators must agree to comply with the requirements of the sponsor and the competent authorities regarding an audit or inspection of the research.

An audit may be requested at all stages of the research, from the writing of the protocol to the publication of results and classification of the data generated or used as part of the research.

## 18 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with Regulation (EU) 536/2014 of April 16, 2014 on clinical trials of medicinal products for human use, the Declaration of Helsinki (as amended in 2013 in Fortaleza, for full version see http://www.wma.net ), the recommendations for Good Clinical Practice (GCP, ICHE6) and any other regulations applicable locally.

The research will be performed in accordance with this protocol. The investigator(s) agree to comply with the protocol in all respects especially regarding obtaining consent and reporting and monitoring serious adverse events.

Grenoble Alps University Hospital, the sponsor of this research, has subscribed to an insurance policy for civil liability in accordance with Article L1121-10 of the French Code of Public Health.

The study will not start until the receipt of approval from the Ethics Committee (Comité de Protection des Personnes CPP) and health authorities (National Agency for Safety of Drugs and Health Products, ANSM).

The data recorded during this research are subject to computer processing by the clinical research center, Grenoble Alps University Hospital in accordance with Law No. 78-17 of 6 January 1978 on computers, files and freedoms amended by Law 2004-801 of August 6, 2004. This research comes under the "Reference Methodology" (MR-001) category under the provisions of Article 54 paragraph 5 of the Act of 6 January 1978 relating to information, files and freedoms. This change was approved on 5 January 2006. Grenoble Alps University Hospital has signed a commitment to comply with the "Reference Methodology". - This research is registered on the site http://clinicaltrials.gov/.

Protocol amendments

Any substantial change, ie. any changes likely to have a significant impact on the protection of persons, the conditions of validity and the results of the research, on the quality and safety of the products tested, on the interpretation of the scientific papers that support the conduct of the research or on the conditions in which it is undertaken, will be the subject to a written amendment that is submitted to the sponsor, who must obtain, prior to its implementation, a favorable opinion of the ethics committee (CPP) and authorization by the health authorities (ANSM).

All amendments must be approved by the sponsor, and all the stakeholders in the research who are affected by the change, before submission to the ethics committee (CPP) and the health authorities (ANSM).

All amendments to the protocol should be made available to all investigators involved in the research. The investigators agree to respect the content.

Any amendment which modifies the treatment of the subjects or the benefits, risks and limitations of the research must be the subject of a new patient information document and a new consent form

Summary of clinical trial results

Whatever the results of a clinical trial, a summary of the clinical trial results will be transmitted by the sponsor to the Union database at the end of the statistical analysis:

Normally, the regulatory deadline is one year from the end of the clinical trial in all member states concerned.

# 19 ARCHIVING

The following documents concerning for this research are to be archived in accordance with Good Clinical Practices:

By the investigating physicians:

**- For a period of 25 years following the end of the research**

- The Protocol and any amendments to the Protocol
- The case report forms
- The source documents of participants who signed consent
- All other documents and correspondence relating to the research
- The original copy of the signed informed consent of participants

All these documents are the responsibility of the investigator for the prescribed archiving period.

By the sponsor:

**- For a period of 25 years following the end of the research**

- The Protocol and any amendments to the Protocol
- All other documents and correspondence relating to the research
- A copy of the signed informed consent of participants
- Documents concerning serious adverse events

All these documents are the responsibility of the sponsor for the prescribed archiving period.

No transfer or destruction can be made without the agreement of the sponsor. After the regulatory archival period the sponsor will be consulted concerning destruction. All data, and all documents and reports may be subject to audit or inspection

# 20 PUBLICATIONS

## 20.1 SCIENTIFIC COMMUNICATIONS

Data analysis will be carried out by the biostatisticians of the data management and biostatistics department, Grenoble Alps University Hospital. This analysis will result in a written report that

will be submitted to the sponsor, which will submit it to the ethics committee (CPP) and the health authorities (ANSM).

Any written or oral communication of research results must receive the prior approval of the principal/coordinating investigator and, of any committee established for the research. The publication of the main results must indicate in the acknowledgements the name of the sponsor, and investigators, methodologists, biostatisticians and data managers who substantially participated in the research, and possibly members of the committee(s) formed for the research and the name of the funding source. The name of any person contributing to writing or editing the manuscript, if not already in the author list, should also be given in the acknowledgements. Account will be taken of international standards of writing and publishing (The Uniform Requirements for Manuscripts of the ICMJE, April 2010) including the conditions for authorship.

Communication of the results to the subjects

According to the law n ° 2002-303 of March 4, 2002, the parents of participating subjects can be informed, at their request, of the overall results of the research.

## 20.2 COMMUNICATION OF RESULTS TO SUBJECTS

The subject is informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a lay person will be made available in the Union database, in accordance with Article 37(4), regardless of the outcome of the clinical trial and, as far as possible, when the summaries are available.

## 20.3 CESSATION OF THE DATABASE

Data collection and data management are provided by the associated services. The terms of sale of all or part of the research database are decided by the sponsor who owns the research data and will be subject to a written contract.

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