Original protocol and amendments STOP-BPD study

In this document we have collected all versions of the STOP-BPS study protocol as submitted to the Ethics Committee of the Academic Medical Center in Amsterdam.

Version 1 is the original protocol submitted to the Ethics Committee

Version 2 is the revised version based on the comments of the Ethics Committee on the first submission.

Versions 3-5 contain small amendment changes that were submitted and accepted by the Ethics Committee.

All changes in the protocol versions are indicated by *Italic font*.

PROTOCOL

Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study

A multicenter randomised placebo controlled trial

Protocol ID	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
Short title	**SToP-BPD Study**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARR	Absolute Risk Reduction
BPD	BronchoPulmonary Dysplasia
BW	Birth Weight
CDP	Continuous Distension Pressure
CGA	Corrected Gestational Age
CP	Cerebral Palsy
DNRN	Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal Research Netwerk (NNRN)
DSMB	Data Safety Monitoring Board
ESEMC	External Safety and Efficacy Monitoring Committee
GA	Gestational Age
HFO	High Frequency Oscillation
IMP	Investigational Medicinal Product
IVH	IntraVentricular Haemorrhage
MAwP	Mean Airway Pressure
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie
MRI	Magnetic Resonance Imaging
NEC	Necrotising EnteroColitis
NICU	Neonatal Intensive Care Unit
NICHD	National Institutes for Child Health and Human Development
NNT	Number Needed to Treat
NVK	Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor Kindergeneeskunde
PDA	Persistent Ductus Arteriosus
PMA	PostMenstrual Age
PNA	PostNatal Age
PVL	PeriVentricular Leucomalacia
RCT	Randomised Controlled Trial
RI	Respiratory Index
SAE	Serious Adverse Event
SD	Standard Deviation
Sponsor	The sponsor is the party that commissions the organisation of performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
VLBW	Very Low Birth Weight
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Background: Randomised controlled trials (RCTs) have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Objective: To establish the efficacy of hydrocortisone given after one week of life to reduce the incidence of the combined outcome death or BPD in chronically ventilated preterm infants.

Study design: Randomised double blind placebo controlled multicenter study.

Study population: Very low birth weight infants (GA<30weeks and/or BW<1250grams), ventilator dependent at a postnatal age of 7 – 14 days.

Intervention: Administration of hydrocortisone or placebo during a 22 day tapering schedule.

Outcome parameters: Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age (CGA).

Burden, benefit and risks associated with participation; group relatedness:

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or in combination with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and will not be combined with other drugs that are known to increase the risk for these adverse effects. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

1. BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth[10-14] with life-long economic and social consequences.[15-18]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased the risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[27-29] Based on this concern, the American Academy of

Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.[27]

As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35] However, no placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]

In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids. Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that

remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the questions remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life. This questions seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate.

The NICU at the University Medical Center Utrecht, has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and has also been debated in the public press.[47] As a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed, an initiative that is also supported by the Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this

regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study.

Comparison of hydrocortisone to a placebo seems warranted because many NICUs nowadays try to avoid the use of glucocorticoids as much as possible. If patients do get treatment, this is usually late in the course of their disease. Although open label use of glucocorticoids is strongly discouraged in this study, its use is not prohibited.

Although based on the above, the *extra* risks for the patients in this study are probably limited, a data monitoring committee will closely monitor any possible adverse effects and risks, as also explained in paragraph 8.4.

2. OBJECTIVE

To investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study **does not** aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

3. STUDY DESIGN

Multicenter randomised double-blind placebo-controlled trial.

4. STUDY POPULATION

4.1 Population eligibility

Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4.2 Inclusion criteria

Preterm infants with:

- a gestational age < 30 wks and/or birth weight < 1250 g
- ventilator dependent at 7-14 days PNA
- a respiratory index (MAwP x FiO_2) of ≥ 3.5 for more than 12 h/day for at least 48 hours, ensuring normal oxygen saturation (86-94%) and pCO_2 values in premature infants (5.0-7.0 kPa).

4.3 Exclusion criteria

- chromosomal defects (e.g. trisomy 13, 18, 21)
- major congenital malformations that:
    - compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia)
    - result in chronic ventilation (e.g. Pierre Robin sequence)
    - increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations)

- Use of dexamethasone or hydrocortisone for the sole purpose of improving lung function and respiratory status

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses are know to be independent risk factors for developing BPD. Therefore, these diagnoses are not considered to be exclusion criteria. The following should be taken into consideration:

1. In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for inclusion.
2. It is strongly recommended to screen all ventilator-dependent preterm infants for a PDA at 5 days PNA. In case of a hemodynamic important PDA, medical intervention according to local protocols should be started as soon as possible. Ibuprofen or indomethacin treatment should not be combined with glucocorticoids, because it has been suggested that this combination will increase the risk of intestinal perforation. If, subsequently, the patient can't be extubated following medical treatment or requires surgical PDA closure, he/she should be included in the study - provided that all inclusion criteria are met.
3. If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

4.4 Sample size calculation

The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo.[24] However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials[26], we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

5. METHODS

5.1 Randomisation, blinding and treatment allocation

Written informed consent has to be obtained from either parents or care-givers prior to randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them

sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. The first dose of study medication should be administered within 72 hours after this decision. Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation.

Randomisation will be stratified per center and according to gestational age stratum (Stratum A: 24-26 weeks; Stratum B: 26-28 weeks; Stratum C: >28 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place.
The infants' parents and all members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Patient characteristics, including gestational age, birth weight and respiratory status, will be collected from all eligible infants that are not included in the study. In addition, we will collect data on why the patients were not included. With this information we will assess possible bias in patient inclusion.

5.2 Withdrawal of individual subjects

Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences. The investigator/attending physician can decide to withdraw a subject from the study in case of prespecified treatment failure (see section 6.1.2).

5.3 Replacement of individual subjects after withdrawal

The number of withdrawn patients not marked as prespecified treatment failure (see section 6.1.2) will be replaced.

5.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will be treated according to the standard of care, including neurodevelopmental outcome assessment at the outpatient clinic.

5.5 Premature termination of the trial

An independent *Data Safety Monitoring Board* will monitor the study on safety aspects (see section 8.4) and if necessary recommend termination of the study.

6. TREATMENT OF SUBJECTS

6.1. Therapeutic details

6.1.1 Preparation of the trial medication: Both hydrocortisone and placebo will be prepared according to GMP guidelines. In close collaboration with the AMC pharmacy (Dr. M. Kemper) we are currently investigating the best way of preparing and supplying the drugs to the participating centers. We will provide this information at a later date. The infants of the hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group.

Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule.

6.1.2 Stop criteria during study protocol medication (treatment failure): In case of life threatening deterioration of the pulmonary condition, the attending physician may decide to start open label corticosteroids therapy in an attempt to improve the pulmonary condition. At that point in time the study medication is stopped and the patient will be recorded as "treatment failure". In case of treatment failure the following data will be collected: timing of treatment failure, ventilatory support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

6.1.3 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label corticosteroids. Data on type of open label medication, the starting date, cumulative dose and duration of rescue therapy are collected.

6.1.4 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently) responding to first line treatment with intravascular volume expansion and inotropes (dopamine and/or dobutamine) the use of hydrocortisone. Treatment for hypotension will not be considered as treatment failure. Data on timing, dose and duration will be collected.

6.2. Use of co-intervention

All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first

week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and to treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria.

This trial will monitor the prognostically important co-interventions and conditions, as described in section 7.2.

6.3. Endpoints

6.3.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al.[21], since the severity of BPD has a high association with neurodevelopmental sequelae.[12] In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al.[21,49,50] should be preformed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life. For practical guidance on the use of the oxygen reduction test please go to appendix 2.

6.3.2. Secondary endpoints:

- treatment failure as defined in section 6.1.2
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- BPD at 28 days

- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
- incidence of hypertension, defined as systolic blood pressure > 2SD of standardized values used in the department
- hyperglycemia requiring the use of insulin therapy
- nosocomial infection, like sepsis, meningitis and pneumonia
- hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
- necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographyic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)
- gastrointestinal bleeding
- isolated gastrointestinal perforation diagnosed on abdominal radiography
- intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.[51]
- retinopathy of prematurity, including grading following international classification[52]
- weight gain, head circumference and length gain at 36 weeks PMA
- long-term health and neurodevelopmental sequelae, assessed at 2 years CGA:
    - readmissions since first discharge home
    - weight, length and head circumference at 24 months c.a.

- Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
- cerebral palsy and severity of cerebral palsy using gross motor function classification system
- hearing loss requiring hearing aids
- blindness
- behavioural problems (child behaviour checklist)

All primary and secondary endpoints are measured as part of standard usual care in the Netherlands and will be derived from the charts of the patients by the investigators.

7. DATA COLLECTION AND STATISTICAL ANALYSIS

7.1 Baseline characteristics

Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.

7.2 Co-interventions

Timing, dose and duration of all co-interventions, such as methylxanthines, diuretics, bronchodilators/inhalation corticosteroids and inhaled nitric oxide, as well as the ventilation mode with the ventilator settings will be recorded and analyzed.

7.3 Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student's *t* test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed. The effect of hydrocortisone on the primary outcome death or BPD will be assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at $p < 0.05$.

8. SAFETY REPORTING

8.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

In accordance to section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events (SAE)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject's parents or caregivers or observed by the

investigator or his staff will be recorded. A **serious adverse event** is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this trial);
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the Data Monitoring Committee and to the accredited METC that approved the protocol, according to the requirements of that METC.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The Steering Committee will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority.

The Steering Committee will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the Steering Committee has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the Steering Committee will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. All infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

8.4 Data Monitoring Committee (DMC)

An external Data Monitoring Committee (DMC) will conduct reviews of patient safety presented initially on hydrocortisone vs. placebo basis. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. Formal interim analyses will be conducted when approximately 25%, 50% and 75% of the anticipated outcome data are available. The DMC will have access to all safety data and will be in a position to make recommendations to the trial's Steering Committee - should a risk to the safety of participants arise. This safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes. The results of the

interim analyses will remain confidential – only the unblinded statistician will have access to the unblinded analyses. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 5 individuals with expertise and extensive experience in newborn ventilation, trial management or statistics. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. None of the members will be from institutions represented in the study. The DMC will report to the Steering Committee with whom the onus of early closure will ultimately reside. Both the DMC and the Steering Committee will be informed on the implications of recent information on premature stopping of trials.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[53] and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and informed consent

Patients will be recruited and their parents will be informed and asked for consent by the attending paediatricians. Informed written consent must be obtained from the parents prior to randomisation for the study. The patient information letter and informed consent are provided in section I of the study dossier. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment.

9.3 Benefits and risks assessment, group relatedness

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or in combination with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and will not be combined with other drugs that are known to increase the risk for these adverse effects. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with

the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.5 Incentives

Participants will not receive a financial compensation for participation as an incentive.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. Security is guaranteed with login names, login codes and encrypted data transfer. An experienced datamanager will maintain the database and check the information in the database for completeness, consistency and plausibility.

The data of all subjects will be coded and this coding will not be retraceable to the individual patient. The key to this coding is safeguarded by the investigator. A limited number of people have access to the source data. These are the principal investigator, investigating doctor and investigating personnel. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor, quality assurance auditor, employees from the METC and the Health Care Inspectorate of the Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have access to the source data. All are subject to the pledge of confidentiality. Data and human material will be stored for 15 years strictly confidential.

10.2 Amendments

Amendments are changes made to the trial after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the Steering Committee.

10.3 Annual progress report

If requested, an annual progress report of the progress of the trial will be provided to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the

investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.4 Public disclosure and publication policy

The study will be registered in the EUDRACT, the website of the Dutch National Competent Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial registry, part of the WHO registry. The results of the study will be published in peer-reviewed international medical journals. In addition, the results of the study will be used for development and implementation of a guideline on treatment of BPD, which will benefit future patients.

11. Organisation

Steering Committee

The Steering Committee is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsors, of the investigators of the participating centres and of the MCRN. The specific tasks of the Steering Committee are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager
- Approve study reports and papers for publication.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee . See Paragraph 8.4 for a description of the membership, tasks and responsibilities of the DMC.

Clinical Project Manager / Central Study Coordinator

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning. The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee

Study Monitoring

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in

compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

Quality Assurance Audits and Inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating this trial the investigator agree to this requirement.

The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

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APPENDIX 1

Afdeling Neonatologie

STUDIE MEDICATIE SCHEMA

voor: **[Klik hier en typ naam]**
geboren op: [Klik hier en typ geboortedatum]

Gewicht:		kg.					
startdatum:	1-jan-11						
	Frequentie	**mg/dosis**			**Frequentie**	**mg/dosis**	
1-jan-11	4 x	0	mg.	**13-jan-11**	2 x	0	mg.
2-jan-11	4 x	0	mg.	**14-jan-11**	2 x	0	mg.
3-jan-11	4 x	0	mg.	**15-jan-11**	2 x	0	mg.
4-jan-11	4 x	0	mg.	**16-jan-11**	2 x	0	mg.
5-jan-11	4 x	0	mg.	**17-jan-11**	2 x	0	mg.
6-jan-11	4 x	0	mg.	**18-jan-11**	1 x	0	mg.
7-jan-11	4 x	0	mg.	**19-jan-11**	1 x	0	mg.
8-jan-11	3 x	0	mg.	**20-jan-11**	1 x	0	mg.
9-jan-11	3 x	0	mg.	**21-jan-11**	1 x	0	mg.
10-jan-11	3 x	0	mg.	**22-jan-11**	1 x	0	mg.
11-jan-11	3 x	0	mg.				
12-jan-11	3 x	0	mg.				

Opmerkingen: [Klik hier en typ opmerkingen]

Naam arts: [Klik hier en typ naam arts]
sein: [Klik hier en typ seinnummer]

Paraaf: .....

APPENDIX 2

Oxygen reduction test

Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe depending on the amount and duration of supplemental oxygen and the level of respiratory support. If a patient has received supplemental oxygen for more than 28 d (FiO_2 > 0.21 for more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is between 0.21 and 0.30, BPD is classified as moderate and in case of a FiO_2 > 0.30 and/or receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
It is important to realize that the duration of supplemental oxygen is highly dependent on target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician to actively wean oxygen delivery.
To make sure that patients receive supplemental oxygen for pulmonary reasons and to standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al. developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% ***or*** if they receive a FiO_2> 0.30 resulting in a SpO2 > 96%. Patients supported with nasal cannulae (flow not nCPAP) without supplemental oxygen, and patients treated with nCPAP/mechanical ventilation or with a FiO_2 > 0.30 resulting in a SpO2 < 96% do not need additional testing, and are, respectively, classified as having mild and severe BPD.

The oxygen reduction test

Indications:

- FiO_2 > 0.21 and < 0.30 with oxygen saturation ranges between 90% and 96%

- FiO_2 > 0.30 with a oxygen saturation range above 96%

Methods:

The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The supplemental oxygen requirement will be gradually weaned to room air while monitoring SpO_2. The diagnosis moderate BPD can be rejected when the SpO_2 remain above ≥ 88% in room air during 1 hour without apnea or bradycardia.

The diagnosis moderate BPD is confirmed if the saturation goes below 80% during >1minute or remains between 80-87% during > 5 minutes. All occurrences of movement artifact (defined as visible motion of the infant together with loss of pleythsmograph signal from the monitor) are recorded and corresponding saturation values are to be deleted.

The test contains 4 phases

Phase 1: Baseline evaluation

For 15 minutes heart rate, respiratory rate, SpO_2, number of apnea (cessation of breathing > 20 seconds) and bradycardia (hartrate < 80/min during > 10 sec) will be collected.

Phase 2: Oxygen reduction

The supplemental oxygen will be weaned by 2% to room air, after which the flow will be weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but not removed from the face.

Phase 3: Observation period

For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87% for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

Phase 4: Back to situation before the test

The level of supplemental oxygen and flow will be reset to the status before the test.

PROTOCOL

Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study

A multicenter randomised placebo controlled trial

Protocol ID	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
Short title	**SToP-BPD Study**
Version	2
Date	05 January 2011
Principal investigator	**Anton van Kaam** Department of Neonatology (Room H3-228) Emma Children's Hospital AMC PO Box 22700, 1100 DD, Amsterdam, The Netherlands Tel: +31-20-5663971, Fax: +31-20-6965099 Email: a.h.vankaam@amc.uva.nl
Study Coördinator	Medicines for Children Research Network (MCRN)
	Martin Offringa Department of Pediatric Clinical Epidemiology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, the Netherlands **Anne De Jaegere** Department of Neonatology, Emma Children's Hospital, Academic Medical Center, Amsterdam, the Netherlands **Wes Onland**

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Sidarto Bambang Oetomo
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Department of Neonatology
Isala Medical Center
Zwolle, The Netherlands

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARR	Absolute Risk Reduction
BPD	BronchoPulmonary Dysplasia
BW	Birth Weight
CDP	Continuous Distension Pressure
CGA	Corrected Gestational Age
CP	Cerebral Palsy
DNRN	Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal Research Netwerk (NNRN)
DSMB	Data Safety Monitoring Board
ESEMC	External Safety and Efficacy Monitoring Committee
GA	Gestational Age
HFO	High Frequency Oscillation
IMP	Investigational Medicinal Product
IVH	IntraVentricular Haemorrhage
MAwP	Mean Airway Pressure
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie
MRI	Magnetic Resonance Imaging
NEC	Necrotising EnteroColitis
NICU	Neonatal Intensive Care Unit
NICHD	National Institutes for Child Health and Human Development
NNT	Number Needed to Treat
NVK	Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor Kindergeneeskunde
PDA	Persistent Ductus Arteriosus
PMA	PostMenstrual Age
PNA	PostNatal Age
PVL	PeriVentricular Leucomalacia
RCT	Randomised Controlled Trial
RI	Respiratory Index
SAE	Serious Adverse Event
SD	Standard Deviation
Sponsor	The sponsor is the party that commissions the organisation of performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
VLBW	Very Low Birth Weight
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Background: Randomised controlled trials (RCTs) have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Objective: To establish the efficacy of hydrocortisone given after one week of life to reduce the incidence of the combined outcome death or BPD in chronically ventilated preterm infants.

Study design: Randomised double blind placebo controlled multicenter study.

Study population: Very low birth weight infants (GA<30weeks and/or BW<1250grams), ventilator dependent at a postnatal age of 7 – 14 days.

Intervention: Administration of hydrocortisone or placebo during a 22 day tapering schedule.

Outcome parameters: Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age (CGA).

Burden, benefit and risks associated with participation; group relatedness:

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or in combination with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and will not be combined with other drugs that are known to increase the risk for these adverse effects. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

1. BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth[10-14] with life-long economic and social consequences.[15-18]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased the risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[27-29] Based on this concern, the American Academy of

Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.[27]

As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35] However, no placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]

In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids. Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that

remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the questions remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life. This questions seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate.

The NICU at the University Medical Center Utrecht, has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and has also been debated in the public press.[47] As a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed, an initiative that is also supported by the Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this

regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study.

Based on the current available evidence, the American Academy of Pediatrics has concluded that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended; (2) outside the context of a randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based on these recommendation ventilated preterm infants are no longer routinely treated with postnatal corticosteroids. Furthermore, in exceptional cases treatment is postponed until after the third week of life. Comparison of hydrocortisone to a placebo is therefore warranted because standard therapy in the second week of life (7-14 d after birth) is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances treatment with a (rescue) open label glucocorticoids is still possible in the current study.

Although based on the above, the *extra* risks for the patients in this study are probably limited, a data monitoring committee will closely monitor any possible adverse effects and risks, as also explained in paragraph 8.4.

2. OBJECTIVE

To investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study **does not** aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

3. STUDY DESIGN

Multicenter randomised double-blind placebo-controlled trial.

4. STUDY POPULATION

4.1 Population eligibility

Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4.2 Inclusion criteria

Preterm infants with:

- a gestational age < 30 wks and/or birth weight < 1250 g
- ventilator dependent at 7-14 days PNA
- a respiratory index (MAwP x FiO_2) of ≥ 3.5 for more than 12 h/day for at least 48 hours, ensuring normal oxygen saturation (86-94%) and pCO_2 values in premature infants (5.0-7.0 kPa).

4.3 Exclusion criteria

- chromosomal defects (e.g. trisomy 13, 18, 21)
- major congenital malformations that:
    - compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia)
    - result in chronic ventilation (e.g. Pierre Robin sequence)
    - increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations)
- Use of dexamethasone or hydrocortisone for the sole purpose of improving lung function and respiratory status

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses are know to be independent risk factors for developing BPD. Therefore, these diagnoses are not considered to be exclusion criteria. The following should be taken into consideration:

4. In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for inclusion.
5. It is strongly recommended to screen all ventilator-dependent preterm infants for a PDA at 5 days PNA. In case of a hemodynamic important PDA, medical intervention according to local protocols should be started as soon as possible. Ibuprofen or indomethacin treatment should not be combined with glucocorticoids, because it has been suggested that this combination will increase the risk of intestinal perforation. If, subsequently, the patient can't be extubated following medical treatment or

requires surgical PDA closure, he/she should be included in the study - provided that all inclusion criteria are met.

6. If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

4.4 Sample size calculation

The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo.[24] However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials[26], we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

5. METHODS

5.1 Randomisation, blinding and treatment allocation

Written informed consent has to be obtained from either parents or care-givers prior to randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. The first dose of study medication should be administered within 72 hours after this decision. Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation.

Randomisation will be stratified per center and according to gestational age stratum (Stratum A: 24-26 weeks; Stratum B: 26-28 weeks; Stratum C: >28 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place.

The infants' parents and all members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Patient characteristics, including gestational age, birth weight and respiratory status, will be collected from all eligible infants that are not included in the study. In addition, we will

collect data on why the patients were not included. With this information we will assess possible bias in patient inclusion.

5.2 Withdrawal of individual subjects

Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences. The investigator/attending physician can decide to withdraw a subject from the study in case of prespecified treatment failure (see section 6.1.2).

5.3 Replacement of individual subjects after withdrawal

The number of withdrawn patients not marked as prespecified treatment failure (see section 6.1.2) will be replaced.

5.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will be treated according to the standard of care, including neurodevelopmental outcome assessment at the outpatient clinic.

5.5 Premature termination of the trial

An independent *Data Safety Monitoring Board* will monitor the study on safety aspects (see section 8.4) and if necessary recommend termination of the study.

6. TREATMENT OF SUBJECTS

6.1. Therapeutic details

6.1.1 Preparation of the trial medication: Both hydrocortisone and placebo will be prepared according to GMP guidelines. In close collaboration with the AMC pharmacy (Dr. M. Kemper) we are currently investigating the best way of preparing and supplying the drugs to

the participating centers. We will provide this information at a later date. The infants of the hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule.

6.1.2 Stop criteria during study protocol medication (treatment failure): In case of life threatening deterioration of the pulmonary condition, the attending physician may decide to start open label corticosteroids therapy in an attempt to improve the pulmonary condition. At that point in time the study medication is stopped and the patient will be recorded as "treatment failure". In case of treatment failure the following data will be collected: timing of treatment failure, ventilatory support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

6.1.3 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label corticosteroids. Data on type of open label medication, the starting date, cumulative dose and duration of rescue therapy are collected.

6.1.4 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently) responding to first line treatment with intravascular volume expansion and inotropes

(dopamine and/or dobutamine) the use of hydrocortisone. Treatment for hypotension will not be considered as treatment failure. Data on timing, dose and duration will be collected.

6.2. Use of co-intervention

All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and to treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria.

This trial will monitor the prognostically important co-interventions and conditions, as described in section 7.2.

6.3. Endpoints

6.3.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al.[21], since the severity of BPD has a high association with neurodevelopmental sequelae.[12] In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al.[21,49,50] should be preformed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life. For practical guidance on the use of the oxygen reduction test please go to appendix 2.

6.3.2. Secondary endpoints:

- treatment failure as defined in section 6.1.2
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- BPD at 28 days
- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
- incidence of hypertension, defined as systolic blood pressure > 2SD of standardized values used in the department
- hyperglycemia requiring the use of insulin therapy
- nosocomial infection, like sepsis, meningitis and pneumonia
- hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
- necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographyic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)
- gastrointestinal bleeding
- isolated gastrointestinal perforation diagnosed on abdominal radiography
- intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.[51]
- retinopathy of prematurity, including grading following international classification[52]

- weight gain, head circumference and length gain at 36 weeks PMA
- long-term health and neurodevelopmental sequelae, assessed at 2 years CGA:
    - readmissions since first discharge home
    - weight, length and head circumference at 24 months c.a.
    - Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
    - cerebral palsy and severity of cerebral palsy using gross motor function classification system
    - hearing loss requiring hearing aids
    - blindness
    - behavioural problems (child behaviour checklist)

All primary and secondary endpoints are measured as part of standard usual care in the Netherlands and will be derived from the charts of the patients by the investigators.

7. DATA COLLECTION AND STATISTICAL ANALYSIS

7.1 Baseline characteristics

Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.

7.2 Co-interventions

Timing, dose and duration of all co-interventions, such as methylxanthines, diuretics, bronchodilators/inhalation corticosteroids and inhaled nitric oxide, as well as the ventilation mode with the ventilator settings will be recorded and analyzed.

7.3 Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student's *t* test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed. The effect of hydrocortisone on the primary outcome death or BPD will be assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at $p < 0.05$.

8. SAFETY REPORTING

8.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

In accordance to section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events (SAE)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject's parents or caregivers or observed by the investigator or his staff will be recorded. A **serious adverse event** is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this trial);
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the Data Monitoring Committee and to the accredited METC that approved the protocol, according to the requirements of that METC.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The Steering Committee will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority.

The Steering Committee will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the Steering Committee has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the Steering Committee will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. All infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

8.4 Data Monitoring Committee (DMC)

An external Data Monitoring Committee (DMC) will conduct reviews of patient safety presented initially on hydrocortisone vs. placebo basis. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. Formal interim analyses will be conducted when approximately 25%, 50% and 75% of the anticipated outcome data are available. The DMC will have access to all safety data and will be in a position to make recommendations to the trial's Steering Committee - should a risk to the safety of participants arise. This safety data will include, but not be restricted to, serious

adverse events and the safety outcomes listed as secondary outcomes. The results of the interim analyses will remain confidential – only the unblinded statistician will have access to the unblinded analyses. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 5 individuals with expertise and extensive experience in newborn ventilation, trial management or statistics. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. None of the members will be from institutions represented in the study. The DMC will report to the Steering Committee with whom the onus of early closure will ultimately reside. Both the DMC and the Steering Committee will be informed on the implications of recent information on premature stopping of trials.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[53] and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and informed consent

Patients will be recruited and their parents will be informed and asked for consent by the attending paediatricians. Informed written consent must be obtained from the parents prior to randomisation for the study. The patient information letter and informed consent are provided in section I of the study dossier. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment.

9.3 Benefits and risks assessment, group relatedness

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or in combination with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and will not be combined with other drugs that are known to increase the risk for these adverse effects. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.5 Incentives

Participants will not receive a financial compensation for participation as an incentive.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. Security is guaranteed with login names, login codes and encrypted data transfer. An experienced datamanager will maintain the database and check the information in the database for completeness, consistency and plausibility.

The data of all subjects will be coded and this coding will not be retraceable to the individual patient. The key to this coding is safeguarded by the investigator. A limited number of people have access to the source data. These are the principal investigator, investigating doctor and investigating personnel. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor, quality assurance auditor, employees from the METC and the Health Care Inspectorate of the Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have access to the source data. All are subject to the pledge of confidentiality. Data and human material will be stored for 15 years strictly confidential.

10.2 Amendments

Amendments are changes made to the trial after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the Steering Committee.

10.3 Annual progress report

If requested, an annual progress report of the progress of the trial will be provided to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the

investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.4 Public disclosure and publication policy

The study will be registered in the EUDRACT, the website of the Dutch National Competent Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial registry, part of the WHO registry. The results of the study will be published in peer-reviewed international medical journals. In addition, the results of the study will be used for development and implementation of a guideline on treatment of BPD, which will benefit future patients.

11. Organisation

Steering Committee

The Steering Committee is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsors, of the investigators of the participating centres and of the MCRN. The specific tasks of the Steering Committee are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager
- Approve study reports and papers for publication.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee . See Paragraph 8.4 for a description of the membership, tasks and responsibilities of the DMC.

Clinical Project Manager / Central Study Coordinator

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning. The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee

Study Monitoring

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in

compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

Quality Assurance Audits and Inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating this trial the investigator agree to this requirement.

The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

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APPENDIX 1

Afdeling Neonatologie

STUDIE MEDICATIE SCHEMA

voor: **[Klik hier en typ naam]**
geboren op: [Klik hier en typ geboortedatum]

Gewicht:		kg.							
startdatum:	3-jan-11								
	Dagdosis per lichaamsgewicht	**Frequentie**	**mg/dosis**			**Dagdosis per lichaamsgewicht**	**Frequentie**	**mg/dosis**	
3-jan-11	5 mg/kg/dg	4 x	0	mg.	**15-jan-11**	2.5 mg/kg/dg	2 x	0	mg.
4-jan-11	5 mg/kg/dg	4 x	0	mg.	**16-jan-11**	2.5 mg/kg/dg	2 x	0	mg.
5-jan-11	5 mg/kg/dg	4 x	0	mg.	**17-jan-11**	2.5 mg/kg/dg	2 x	0	mg.
6-jan-11	5 mg/kg/dg	4 x	0	mg.	**18-jan-11**	2.5 mg/kg/dg	2 x	0	mg.
7-jan-11	5 mg/kg/dg	4 x	0	mg.	**19-jan-11**	2.5 mg/kg/dg	2 x	0	mg.
8-jan-11	5 mg/kg/dg	4 x	0	mg.	**20-jan-11**	1.25 mg/kg/dg	1 x	0	mg.
9-jan-11	5 mg/kg/dg	4 x	0	mg.	**21-jan-11**	1.25 mg/kg/dg	1 x	0	mg.
10-jan-11	3.75 mg/kg/dg	3 x	0	mg.	**22-jan-11**	1.25 mg/kg/dg	1 x	0	mg.
11-jan-11	3.75 mg/kg/dg	3 x	0	mg.	**23-jan-11**	1.25 mg/kg/dg	1 x	0	mg.
12-jan-11	3.75 mg/kg/dg	3 x	0	mg.	**24-jan-11**	1.25 mg/kg/dg	1 x	0	mg.
13-jan-11	3.75 mg/kg/dg	3 x	0	mg.					
14-jan-11	3.75 mg/kg/dg	3 x	0	mg.					

Opmerkingen: [Klik hier en typ opmerkingen]

Naam arts: [Klik hier en typ naam arts]
sein: [Klik hier en typ seinnummer]

Paraaf: .....

APPENDIX 2

Oxygen reduction test

Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe depending on the amount and duration of supplemental oxygen and the level of respiratory support. If a patient has received supplemental oxygen for more than 28 d (FiO_2 > 0.21 for more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is between 0.21 and 0.30, BPD is classified as moderate and in case of a FiO_2 > 0.30 and/or receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
It is important to realize that the duration of supplemental oxygen is highly dependent on target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician to actively wean oxygen delivery.
To make sure that patients receive supplemental oxygen for pulmonary reasons and to standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al. developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% ***or*** if they receive a FiO_2> 0.30 resulting in a SpO2 > 96%. Patients supported with nasal cannulae (flow not nCPAP) without supplemental oxygen, and patients treated with nCPAP/mechanical ventilation or with a FiO_2 > 0.30 resulting in a SpO2 < 96% do not need additional testing, and are, respectively, classified as having mild and severe BPD.

The oxygen reduction test

Indications:

- FiO_2 > 0.21 and < 0.30 with oxygen saturation ranges between 90% and 96%

- FiO_2 > 0.30 with a oxygen saturation range above 96%

Methods:

The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The supplemental oxygen requirement will be gradually weaned to room air while monitoring SpO_2. The diagnosis moderate BPD can be rejected when the SpO_2 remain above ≥ 88% in room air during 1 hour without apnea or bradycardia.

The diagnosis moderate BPD is confirmed if the saturation goes below 80% during >1minute or remains between 80-87% during > 5 minutes. All occurrences of movement artifact (defined as visible motion of the infant together with loss of pleythsmograph signal from the monitor) are recorded and corresponding saturation values are to be deleted.

The test contains 4 phases

Phase 1: Baseline evaluation

For 15 minutes heart rate, respiratory rate, SpO_2, number of apnea (cessation of breathing > 20 seconds) and bradycardia (hartrate < 80/min during > 10 sec) will be collected.

Phase 2: Oxygen reduction

The supplemental oxygen will be weaned by 2% to room air, after which the flow will be weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but not removed from the face.

Phase 3: Observation period

For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87% for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

Phase 4: Back to situation before the test

The level of supplemental oxygen and flow will be reset to the status before the test.

PROTOCOL

Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study

A multicenter randomised placebo controlled trial

Protocol ID	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
Short title	**Hydrocortisone for bronchopulmonary dysplasia**
Version	3
Date	16 mei 2011
Principal investigator	**Dr. A.H.L.C. van Kaam** Department of Neonatology (Room H3-228) Emma Children's Hospital AMC PO Box 22700, 1100 DD, Amsterdam, The Netherlands Tel: +31-20-5663971, Fax: +31-20-6965099 Email: a.h.vankaam@amc.uva.nl
Sponsor	Academic Medical Center Meibergdreef 9 1105 AZ Amsterdam
Study Coördinator	Medicines for Children Research Network (MCRN)
Pharmacy	ACE Pharmaceuticals BV Schepenveld 41, NL-3891 ZK, Zeewolde
Co-investigators AMC	**Prof. Dr. M. Offringa** Department of Pediatric Clinical Epidemiology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam **Drs. A. P. De Jaegere** Department of Neonatology, Emma Children's Hospital, Academic Medical Center, Amsterdam

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARR	Absolute Risk Reduction
BPD	BronchoPulmonary Dysplasia
BW	Birth Weight
CDP	Continuous Distension Pressure
CGA	Corrected Gestational Age
CP	Cerebral Palsy
DNRN	Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal Research Netwerk (NNRN)
DMC	Data Monitoring & Safety Committee
ESEMC	External Safety and Efficacy Monitoring Committee
GA	Gestational Age
HFO	High Frequency Oscillation
IMP	Investigational Medicinal Product
IVH	IntraVentricular Haemorrhage
MAwP	Mean Airway Pressure
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie
MRI	Magnetic Resonance Imaging
NEC	Necrotising EnteroColitis
NICU	Neonatal Intensive Care Unit
NICHD	National Institutes for Child Health and Human Development
NNT	Number Needed to Treat
NVK	Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor Kindergeneeskunde
PDA	Persistent Ductus Arteriosus
PMA	PostMenstrual Age
PNA	PostNatal Age
PVL	PeriVentricular Leucomalacia
RCT	Randomised Controlled Trial
RI	Respiratory Index
SAE	Serious Adverse Event
SD	Standard Deviation
Sponsor	The sponsor is the party that commissions the organisation of performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
VLBW	Very Low Birth Weight
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Background: Randomised controlled trials (RCTs) have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Objective: To establish the efficacy of hydrocortisone given after one week of life to reduce the incidence of the combined outcome death or BPD in chronically ventilated preterm infants.

Study design: Randomised double blind placebo controlled multicenter study.

Study population: Very low birth weight infants (GA<30weeks and/or BW<1250grams), ventilator dependent at a postnatal age of 7 – 14 days.

Intervention: Administration of hydrocortisone or placebo during a 22 day tapering schedule.

Outcome parameters: Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age (CGA).

Burden, benefit and risks associated with participation; group relatedness:

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.
Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

1. BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth[10-14] with life-long economic and social consequences.[15-18]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased the risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[27-29] Based on this concern, the American Academy of

Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.[27]

As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35] However, no placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]

In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids. Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that

remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the question remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life. This question seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate.

The NICU at the University Medical Center Utrecht has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and has also been debated in the public press.[47] As a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed, an initiative that is also supported by the Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this

regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study.

Based on the current available evidence, the American Academy of Pediatrics has concluded that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended; (2) outside the context of a randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based on these recommendation ventilated preterm infants are no longer routinely treated with postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases, postponed until after the third week of life. Comparison of hydrocortisone to a placebo is therefore warranted because standard therapy in the second week of life (7-14 d after birth) is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances treatment with a (rescue) open label glucocorticoids is still possible in the current study. Although based on the above, the *extra* risks for the patients in this study are probably limited, a data monitoring committee will closely monitor any possible adverse effects and risks, as also explained in paragraph 9.4.

2. OBJECTIVE

To investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study **does not** aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

3. STUDY DESIGN

Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

4. STUDY POPULATION

4.1 Population eligibility

Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4.2 Inclusion criteria

Preterm infants with:

- a gestational age < 30 wks and/or birth weight < 1250 g
- ventilator dependency at 7-14 days PNA
- a respiratory index (RI = MAwP x FiO_2) of ≥ 3.5 for more than 12 h/day for at least 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO_2 values in premature infants (5.0-7.5 kPa).

Note: these targets are used to ensure homogeneous assessment of MAwP and FiO_2 for patient inclusion among participating centres. After inclusion of the patient in the study, physicians are free to use local targets for oxygenation and ventilation.

4.3 Exclusion criteria

- chromosomal defects (e.g. trisomy 13, 18, 21)
- major **congenital** malformations that:
    - compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia)
    - result in chronic ventilation (e.g. Pierre Robin sequence)
    - increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations)

      Note: intraventricular haemorrhages, periventricular leucomalacia and cerebral infarction are not considered **congenital** malformations and therefore are no exclusion criteria.
- Use of dexamethasone or hydrocortisone for the sole purpose of improving lung function and respiratory status prior to inclusion

Considerations

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses are know to be independent risk factors for developing BPD. Therefore, these diagnoses are **not** considered to be exclusion criteria. The following should be taken into consideration:

7. In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for inclusion.
8. *Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have shown that treatment with corticosteroids may increase the risk of intestinal perforation. Speculating on the pathogenesis of this adverse effect, it has been suggested that the synchronous use of indomethacin and corticosteroids might explain this finding. However, trials starting dexamethasone between 7-14 d after life have* ***not*** *reported an increased risk of intestinal perforation, despite the fact that some of these patients were also treated for hemodynamically significant PDA with indomethacin. In other words, the evidence for a possible adverse effect of the combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason the combined use of corticosteroids and indomethacin/ibuprofen is* ***NOT*** *prohibited within the STOP-BPD trial. However, where possible in the time window of 7-14 days, we do encourage physicians to treat a hemodynamically significant PDA before randomizing the patient for the study. To make this feasible physicians are strongly encouraged to determine the presence of a hemodynamically significant PDA at day 7 of life. This way the patient can, if necessary according to the local protocol, still be treated with 2 courses of indomethacin / ibuprofen before day 14 of life.*
   If there is an indication to treat a hemodynamically significant PDA with indomethacin/ibuprofen after randomization, study medication is ***NOT*** *stopped. Yet, any synchronous use of indomethacin/ibuprofen and study medication or the occurrence of an intestinal perforation recorded in the case record form, will*

*automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert Procedure**. This will allow for a close and individual monitoring of possible adverse effects.*

9. If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

4.4 Sample size calculation The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo.[24] However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials[26], we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should

be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

5. TREATMENT OF SUBJECTS

5.1. Therapeutic details

5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule.

5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on corticosteroids use in the second week of life (mainly dexamethasone) have reported that the following transient short term side-effects: hyperglycaemia, increased risk of infection, and hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of preterm birth and its treatment. There is extensive experience in treating these morbidities with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or infection will be closely monitored (secondary endpoints), in case of an event, the study medication should ***NOT*** *be adjusted.*

Hypertension is a much less common morbidity after preterm delivery and antihypertensive drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually treated and resolved by reducing the dose. So, in case of hypertension, the study medication is

*lowered according to appendix 1 if no other treatable cause of hypertension can be identified. Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90 mmHg for infants 26-28 wks, and > 100 mmHg for infants ≥ 28 wks. Data on the time, reason and dose adjustment will be collected. The presence of hypertension leading to adjustment of study medication will be reported via the **Alert Procedure** (see paragraph 9.4).*

*5.1.3 Stop criteria during study protocol medication (treatment failure): In general, the use of open label hydrocortisone during the 22 day treatment course is strongly discouraged. Open label hydrocortisone use **may be considered** in the following conditions:*

1. *The pulmonary condition is progressively deteriorating and the respiratory index (MAwP x FiO_2) is >10 for more than 6 consecutive hours.*
2. *The pulmonary condition of the patient is stable (RI < 10) but not improving over time. In these circumstances open label hydrocortisone **may be considered** if the following conditions are met:*
    a. *Extubation was attempted (extubation trial) within 24 hours before considering open label treatment and this attempt failed.*
    b. *The patient is on study medication for **at least** 10 days (but preferably at a later time).*

The open label hydrocortisone dosage schedule is similar to that used in the study. At that point in time the study medication is stopped and the patient will be recorded as "treatment failure". In case of treatment failure the following data will be collected: timing of treatment failure, ventilator support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

The use of open label hydrocortisone will be reported via the Alert Procedure *(see paragraph 9.4)***.**

5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label hydrocortisone. *In such cases the physician should first attempt extubation before considering open label use. The open label hydrocortisone dosage schedule is similar to that used in the study (see appendix 1).* Data on the starting date, cumulative dose and duration of rescue therapy are collected.

5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently) responding to first line treatment with intravascular volume expansion and inotropes (dopamine and/or dobutamine) *the use of hydrocortisone is allowed in a dose of 3 mg/kg/day for 5 days.* Treatment for hypotension will not be considered as treatment failure. Data on timing, dose and duration will be collected.

5.1.6 Inhalation corticosteroids: There is currently insufficient evidence that inhaled corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is not an exclusion criterion. Data on timing, dose and duration will be collected.

5.2. Use of co-intervention

All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and

treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria.

This trial will monitor the prognostic important co-interventions and conditions, as described in section 8.2.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product

In this multicenter study the investigational medicinal product is hydrocortisone. A detailed description of hydrocortisone can be found in the summary of product characteristics (SPC) which is added to this protocol as a separate document.

6.2 Summary of findings from non-clinical studies

More details on both hydrocortisone and the placebo used in this study can be found in, respectively, the summary of product characteristics (SPC) and investigational medicinal product dossier (IMPD) both added to this protocol as separate documents. In addition to this information, animal studies have shown that hydrocortisone, in contrast to dexamethasone, did not increase the risk of adverse effects on the brain when compared to a placebo.[35]

6.3 Summary of findings from clinical studies

Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm infants, hydrocortisone is used for the following indications: 1) primary or secondary deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in

developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first indication is authorized. The fact that hydrocortisone is used for other unauthorized indications is not exceptional, because off-label use of medication is more the rule than the exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory properties on the lungs of preterm infants at high risk for BPD ventilated in the second week of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] Use of hydrocortisone after the first week of life with a higher dose has been the standard of care in 4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in an identical treatment schedule as this study for several decades. Several historical cohort studies have shown that hydrocortisone use for this indication (reduction of BPD) did not increase the risk of adverse neurodevelopmental outcome.[44-46]

6.4 Summary of known and potential risks and benefits

As studies with hydrocortisone are limited, the assessment of risks and benefits are based on data obtained from previous RCTs investigating other corticosteroids (mainly dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies, hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal

perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

6.5 Description and justification of route of administration and dosage

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study. More details on the dose regiment and the route of administration can be found in paragraph 5.1.

6.6 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone (Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the placebo will be manufactured by ACE Pharmaceuticals BV (Zeewolde, the Netherlands). The

SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In addition, we have added an example of labels for the vials and boxes as separate documents.

6.7 Drug accountability

Drug accountability will be according to current GMP guidelines. The "kenniscentrum geneesmiddelen onderzoek" of the AMC pharmacy will take full responsibility and supervision of the drug accountability process.

7. METHODS

7.1 Randomisation, blinding and treatment allocation

Written informed consent has to be obtained from either parents or care-givers prior to randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. *Following inclusion and randomization, the first dose of study medication should be administered within 24 hours.* Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation.

Randomisation will be per center and stratified according to gestational age stratum (Stratum A: < 27 weeks; Stratum B: ≥ 27 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or

caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place.
The infants' parents and all members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Patient characteristics, including gestational age, birth weight and respiratory status, will be collected from all eligible infants that are not included in the study. In addition, we will collect data on why the patients were not included. With this information we will assess possible bias in patient inclusion.

7.2 Withdrawal of individual subjects

Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences.
Note: patients who are considered to have "treatment failure" based on the prespecified criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.

7.3 Replacement of individual subjects after withdrawal

The number of withdrawn patients not marked as prespecified treatment failure (see section 7.2) will be replaced.

7.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will be treated according to the standard of care, including neurodevelopmental outcome assessment at the outpatient clinic.

7.5 Premature termination of the trial

An independent *Data Monitoring Committee (DMC)* will monitor the study on safety aspects (see section 9.4) and if necessary recommend termination of the study.

7.6 Breaking the randomization code

Unblinding is only performed in emergency situations where knowledge of the identity of the study drug is considered absolutely necessary for the clinical management of the subject. If local investigator or attending physician decides unblinding is essential, (s)he will make every effort to contact the PI before unblinding to discuss options. For this purpose a 24/7 reachable telephone service will be installed. Details of the unblinding procedure will be defined in the study specific working instructions.

7.7. Endpoints

7.7.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al.[21], since the severity of BPD has a high association with neurodevelopmental sequelae.[12] In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al.[21,49,50] should be preformed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life. For practical guidance on the use of the oxygen reduction test please go to appendix 2.

7.7.2. Secondary endpoints:

- treatment failure as defined in section 5.1.3

- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- BPD at 28 days
- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
- incidence of hypertension, as defined in paragraph 5.1.2
- hyperglycaemia requiring the use of insulin therapy
- nosocomial infection, like sepsis, meningitis and pneumonia
- pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
- necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)
- gastrointestinal bleeding
- isolated gastrointestinal perforation diagnosed on abdominal radiography
- intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.[51]
- retinopathy of prematurity, including grading following international classification[52]
- weight, head circumference and length at 36 weeks PMA
- long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:

- readmissions since first discharge home
- weight, length and head circumference at 24 months c.a.
- Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
- cerebral palsy and severity of cerebral palsy using gross motor function classification system
- hearing loss requiring hearing aids
- blindness
- behavioural problems (child behaviour checklist)

All primary and secondary endpoints are measured as part of standard usual care in the Netherlands and Belgium, and will be derived from the charts of the patients by the investigators.

8. DATA COLLECTION AND STATISTICAL ANALYSIS

8.1 Baseline characteristics

Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.

8.2 Co-interventions

Apart from the study medication all patients will receive standard care, including co-medication such as surfactant, inhaled nitric oxide. methylxanthines, vitamin A, antibiotics, antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled corticosteroids. These co-medications are prescribed on the basis of (inter)national guidelines and/or local protocols. Since the route of administration (e.g. oral or IV), the dose and frequency may vary continuously depending on the weight and the clinical condition of the patients, only name, start and stop date are recorded in the CRF. For all other drugs used during the admission data will be recorded according to GCP guidelines.
Also the ventilation mode with the ventilator settings will be recorded and analyzed.

8.3 Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student's *t* test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed. The effect of hydrocortisone on the primary outcome death or BPD will be assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at $p < 0.05$.

9. SAFETY REPORTING

9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research

proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will ensure that all subjects' parents or caregivers are kept informed.

9.2 Adverse and serious adverse events (SAE)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events observed by the investigator or his staff will be recorded. A **serious adverse event** is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this trial);
- *other important events that may jeopardize the safety of the subject or may require intervention to prevent one of the outcomes listed above.*

All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data Monitoring Committee (DMC) and to the accredited METC that approved the protocol, according to the requirements of that METC.

<u>9.2.1 Context-specific SAE reporting</u>

This study population (critically ill preterm infants) has a high risk of serious complications (so-called "context-specific SAE's"), which are inherent to their vulnerable condition and unrelated to the intervention which is under evaluation in this trial.

These complications are included in the primary and secondary outcomes of this study and are recorded in the Case Report Form. This documentation will include the date of diagnosis, classification/gradation of the complication, type of action taken if appropriate (with some complications a wait and see approach is warranted). Since these complications are highly interrelated and of longitudinal character, it is impossible to indicate an exact date for the resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the complication will be classified as ongoing.

In light of the above, immediate and individual reporting of all these condition related complications will not enhance the safety of study. [1,2] This is also in accordance with CCMO regulations (http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178)

The context-specific SAEs that will be identified include the events listed under paragraph 7.7.2, on page 27 and 28 of the protocol.

Once a year, an overview of the aforementioned complications for each treatment arm and ordered by organ system will be presented to the DMC and METC. This overview will consist of the following information: name of the complication, date of diagnosis, classification/gradation of the complication, type of action taken, date of discharge or ongoing.[53,54]

9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (see SPC/IMPD) or the context-specific SAEs listed in paragraph 9.2.1.

*Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the study coordinator via the study website (**Alert Procedure,** see paragraph 9.4). The PI will report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent authority, Medicine Evaluation Board as well as to the competent authorities in other Member States, according to the requirements of the Member States.*
The expedited reporting will occur not later than 15 days after the PI has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.2.3 Annual safety report

In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout the clinical trial, a safety report to the DMC, accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States as well as the investigators of all participating centers.
This safety report consists of:

- *a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions*
- *a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.*

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated. According to the standard of care, all infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

9.4 Data Monitoring Committee (DMC), the Alert Procedure

An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes and will provide the trial's Steering Committee with recommendations regarding continuing or stopping the trial (for all patients or subgroups of patients) when approximately 25% (safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated outcome data are available. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. The safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes. The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the data manager will be stand-by to reveal the allocation labels if the DMC thinks this is

necessary. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician who has experience with trials, and some experience on previous DMCs and a pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in neonates. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. Identification and circulation of external evidence (e.g., from other trials/systematic reviews) is not the responsibility of the DMC members. It is the responsibility of the PI to provide any such information to the DMC.

To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been added to the CRF and the website (SUSAR), "The Alert Procedure". This tool is used to monitor special conditions and acute situations that need the direct attention of the principle investigator and the study coordinator. If necessary the Steering Committee can decide to alert the DMC. Furthermore, the Steering Committee will provide a summary report after every 10 alerts to the DMC.

*There are 5 situations when the **Alert Procedure** must be used:*

1. *Any synchronous use of indomethacin/ibuprofen and study medication*
2. *Any intestinal perforation occurring during or after the study medication treatment course*
3. *Occurrence of hypertension as defined*
4. *Any use of open label hydrocortisone*
5. *Occurrence of a SUSAR*

The "Alert Procedure" will run in the background for the first 4 conditions. CRF data will be linked automatically and an email will be send to principal investigator and the study coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local investigator can alert the principal investigator and the study coordinator via a SUSAR email button on the trial website.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[55] and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and informed consent

Patients will be recruited and their parents will be informed and asked for consent by the attending paediatricians. Informed written consent must be obtained from the parents prior to randomisation for the study. The patient information letter and informed consent are provided in section I of the study dossier. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment.

10.3 Benefits and risks assessment, group relatedness

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients since intravenous access will be necessary for other clinical reasons. If this is no longer the

case, study medication may be administered via the oral route. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia, hypertension and systemic infection. Although the increased risk of gastrointestinal perforation has up to now only been reported during the early (within the first 96 hours of life) administration of corticosteroids, the risk may also be increased when administering hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use of dexamethasone has been associated with an increase risk for neurodevelopmental sequelae. Historical cohort studies investigating the use of hydrocortisone after the first week of life have found no evidence to support this. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding

Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives

Participants will not receive a financial compensation for participation as an incentive.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. Security is guaranteed with login names, login codes and encrypted data transfer. An experienced datamanager will maintain the database and check the information in the database for completeness, consistency and plausibility.

The data of all subjects will be coded and this coding will not be retraceable to the individual patient. The key to this coding is safeguarded by the investigator. A limited number of

people have access to the source data. These are the principal investigator, investigating doctor and investigating personnel. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor, quality assurance auditor, employees from the METC and the Health Care Inspectorate of the Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have access to the source data. All are subject to the pledge of confidentiality. Data and human material will be stored for 15 years strictly confidential.

11.2 Amendments

Amendments are changes made to the trial after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the Steering Committee.

11.3 Annual progress report

If requested, an annual progress report of the progress of the trial will be provided to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.4 Public disclosure and publication policy

The study will be registered in the EUDRACT, the website of the Dutch National Competent Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial registry, part of the WHO registry. The results of the study will be published in peer-reviewed international medical journals. In addition, the results of the study will be used for development and implementation of a guideline on treatment of BPD, which will benefit future patients.

12. ORGANISATION

12.1 Steering Committee

The Steering Committee is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsor, of the investigators of the participating centres and of the MCRN. The specific tasks of the Steering Committee are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager
- Approve study reports and papers for publication.

12.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a description of the membership, tasks and responsibilities of the DMC.

12.3 Clinical Project Manager / Central Study Coordinator

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning. The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee

12.4 Study Monitoring

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in

compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

12.5 Quality Assurance Audits and Inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating this trial the investigator agrees to this requirement.

The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

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APPENDIX 1 STUDIE MEDICATIE SCHEMA

Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.	Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm	Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatticaly skip the next dose and commence the following dose with a lower daily frequency.	Step 4: For print out of study medication list, press: Print

Study identification
Name
Date of birth
Weight gram

First administration
Date/time
Lowering dosage regimen
Date/time

Day in regimen	Time	Times per day	mg/dose		Daily dose/kg
Day 1	0-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	0-01-00 6:00				
	0-01-00 12:00				
	0-01-00 18:00				
Day 2	1-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	1-01-00 6:00				
	1-01-00 12:00				
	1-01-00 18:00				
Day 3	2-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	2-01-00 6:00				
	2-01-00 12:00				
	2-01-00 18:00				
Day 4	3-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	3-01-00 6:00				
	3-01-00 12:00				
	3-01-00 18:00				
Day 5	4-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	4-01-00 6:00				
	4-01-00 12:00				
	4-01-00 18:00				
Day 6	5-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	5-01-00 6:00				
	5-01-00 12:00				
	5-01-00 18:00				
Day 7	6-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	6-01-00 6:00				
	6-01-00 12:00				
	6-01-00 18:00				

Day in regimen	Time	Times per day	mg/dose		Daily dose/kg
Day 8	7-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	7-01-00 8:00				
	7-01-00 16:00				
Day 9	8-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	8-01-00 8:00				
	8-01-00 16:00				
Day 10	9-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	9-01-00 8:00				
	9-01-00 16:00				
Day 11	10-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	10-01-00 8:00				
	10-01-00 16:00				
Day 12	11-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	11-01-00 8:00				
	11-01-00 16:00				
Day 13	12-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	12-01-00 12:00				
Day 14	13-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	13-01-00 12:00				
Day 15	14-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	14-01-00 12:00				
Day 16	15-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	15-01-00 12:00				
Day 17	16-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	16-01-00 12:00				
Day 18	17-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 19	18-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 20	19-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 21	20-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 22	21-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d

APPENDIX 2

Oxygen reduction test

Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe depending on the amount and duration of supplemental oxygen and the level of respiratory support. If a patient has received supplemental oxygen for more than 28 d (FiO_2 > 0.21 for more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is between 0.21 and 0.30, BPD is classified as moderate and in case of a FiO_2 > 0.30 and/or receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
It is important to realize that the duration of supplemental oxygen is highly dependent on target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician to actively wean oxygen delivery.
To make sure that patients receive supplemental oxygen for pulmonary reasons and to standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al. developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% ***or*** if they receive a FiO_2> 0.30 resulting in a SpO2 > 96%. Patients supported with nasal cannulae (flow not nCPAP) without supplemental oxygen, and patients treated with nCPAP/mechanical ventilation or with a FiO_2 > 0.30 resulting in a SpO2 < 96% do not need additional testing, and are, respectively, classified as having mild and severe BPD.

The oxygen reduction test

Indications:

- FiO_2 > 0.21 and < 0.30 with oxygen saturation ranges between 90% and 96%

- FiO_2 > 0.30 with a oxygen saturation range above 96%

Methods:

The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The supplemental oxygen requirement will be gradually weaned to room air while monitoring SpO_2. The diagnosis moderate BPD can be rejected when the SpO_2 remain above ≥ 88% in room air during 1 hour without apnea or bradycardia.

The diagnosis moderate BPD is confirmed if the saturation goes below 80% during >1minute or remains between 80-87% during > 5 minutes. All occurrences of movement artifact (defined as visible motion of the infant together with loss of pleythsmograph signal from the monitor) are recorded and corresponding saturation values are to be deleted.

The test contains 4 phases

Phase 1: Baseline evaluation

For 15 minutes heart rate, respiratory rate, SpO_2, number of apnea (cessation of breathing > 20 seconds) and bradycardia (hartrate < 80/min during > 10 sec) will be collected.

Phase 2: Oxygen reduction

The supplemental oxygen will be weaned by 2% to room air, after which the flow will be weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but not removed from the face.

Phase 3: Observation period

For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87% for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

Phase 4: Back to situation before the test

The level of supplemental oxygen and flow will be reset to the status before the test.

PROTOCOL

Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study

A multicenter randomised placebo controlled trial

Protocol ID	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
Short title	**Hydrocortisone for bronchopulmonary dysplasia**
Version	*4*
Date	*25 April 2012*
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARR	Absolute Risk Reduction
BPD	BronchoPulmonary Dysplasia
BW	Birth Weight
CDP	Continuous Distension Pressure
CGA	Corrected Gestational Age
CP	Cerebral Palsy
DNRN	Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal Research Netwerk (NNRN)
DMC	Data Monitoring & Safety Committee
ESEMC	External Safety and Efficacy Monitoring Committee
GA	Gestational Age
HFO	High Frequency Oscillation
IMP	Investigational Medicinal Product
IVH	IntraVentricular Haemorrhage
MAwP	Mean Airway Pressure
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie
MRI	Magnetic Resonance Imaging
NEC	Necrotising EnteroColitis
NICU	Neonatal Intensive Care Unit
NICHD	National Institutes for Child Health and Human Development
NNT	Number Needed to Treat
NVK	Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor Kindergeneeskunde
PDA	Persistent Ductus Arteriosus
PMA	PostMenstrual Age
PNA	PostNatal Age
PVL	PeriVentricular Leucomalacia
RCT	Randomised Controlled Trial
RI	Respiratory Index
SAE	Serious Adverse Event
SD	Standard Deviation
Sponsor	The sponsor is the party that commissions the organisation of performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
VLBW	Very Low Birth Weight
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Background: Randomised controlled trials (RCTs) have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Objective: To establish the efficacy of hydrocortisone given after one week of life to reduce the incidence of the combined outcome death or BPD in chronically ventilated preterm infants.

Study design: Randomised double blind placebo controlled multicenter study.

Study population: Very low birth weight infants (GA<30weeks and/or BW<1250grams), ventilator dependent at a postnatal age of 7 – 14 days.

Intervention: Administration of hydrocortisone or placebo during a 22 day tapering schedule.

Outcome parameters: Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age (CGA).

Burden, benefit and risks associated with participation; group relatedness:

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.
Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

1. BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth[10-14] with life-long economic and social consequences.[15-18]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased the risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[27-29] Based on this concern, the American Academy of

Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.[27]

As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35] However, no placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]

In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids. Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that

remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the question remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life. This question seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate.

The NICU at the University Medical Center Utrecht has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and has also been debated in the public press.[47] As a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed, an initiative that is also supported by the Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this

regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study.

Based on the current available evidence, the American Academy of Pediatrics has concluded that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended; (2) outside the context of a randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based on these recommendation ventilated preterm infants are no longer routinely treated with postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases, postponed until after the third week of life. Comparison of hydrocortisone to a placebo is therefore warranted because standard therapy in the second week of life (7-14 d after birth) is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances treatment with a (rescue) open label glucocorticoids is still possible in the current study. Although based on the above, the *extra* risks for the patients in this study are probably limited, a data monitoring committee will closely monitor any possible adverse effects and risks, as also explained in paragraph 9.4.

2. OBJECTIVE

To investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study **does not** aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

3. STUDY DESIGN

Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

4. STUDY POPULATION

4.1 Population eligibility

Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4.2 Inclusion criteria

Preterm infants *with an increased risk of BPD* and:

- a gestational age < 30 wks and/or birth weight < 1250 g
- ventilator dependency at 7-14 days PNA
- *a respiratory index (RI = MAwP x FiO_2) of ≥ 3.0* for more than 12 h/day for at least 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO_2 values in premature infants (5.0-7.5 kPa).

Note: these targets are used to ensure homogeneous assessment of MAwP and FiO_2 for patient inclusion among participating centres. *For the same reason, clinician are encouraged to aim for the median value of these targets when assessing the RI.* After inclusion of the patient in the study, physicians are free to use local targets for oxygenation and ventilation.

4.3 Exclusion criteria

- chromosomal defects (e.g. trisomy 13, 18, 21)
- major **congenital** malformations that:
    - compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia)
    - result in chronic ventilation (e.g. Pierre Robin sequence)
    - increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations)

      Note: intraventricular haemorrhages, periventricular leucomalacia and cerebral infarction are not considered **congenital** malformations and therefore are no exclusion criteria.
- Use of dexamethasone or hydrocortisone for the sole purpose of improving lung function and respiratory status prior to inclusion

Considerations

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

are know to be independent risk factors for developing BPD. Therefore, these diagnoses are **not** considered to be exclusion criteria. The following should be taken into consideration:

10. In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for inclusion.
11. Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have shown that treatment with corticosteroids may increase the risk of intestinal perforation. Speculating on the pathogenesis of this adverse effect, it has been suggested that the synchronous use of indomethacin and corticosteroids might explain this finding. However, trials starting dexamethasone between 7-14 d after life have **not** reported an increased risk of intestinal perforation, despite the fact that some of these patients were also treated for hemodynamically significant PDA with indomethacin. In other words, the evidence for a possible adverse effect of the combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason the combined use of corticosteroids and indomethacin/ibuprofen is **NOT** prohibited within the STOP-BPD trial. However, where possible in the time window of 7-14 days, we do encourage physicians to treat a hemodynamically significant PDA before randomizing the patient for the study. To make this feasible physicians are strongly encouraged to determine the presence of a hemodynamically significant PDA at day 7 of life. This way the patient can, if necessary according to the local protocol, still be treated with 2 courses of indomethacin / ibuprofen before day 14 of life.

    If there is an indication to treat a hemodynamically significant PDA with indomethacin/ibuprofen after randomization, study medication is **NOT** stopped. Yet,

any synchronous use of indomethacin/ibuprofen and study medication or the occurrence of an intestinal perforation recorded in the case record form, will automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert Procedure**. This will allow for a close and individual monitoring of possible adverse effects.

12. If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

4.4 Sample size calculation The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo.[24] However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials[26], we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch

NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

5. TREATMENT OF SUBJECTS

5.1. Therapeutic details

5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule. *Clinicians are encouraged to administer the study medication intravenously as long as this route of access is required for other reasons. If intravenous access is no longer required for the standard treatment, the study medication can be administered orally using the same solution and dose.*

5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on corticosteroids use in the second week of life (mainly dexamethasone) have reported that the following transient short term side-effects: hyperglycaemia, increased risk of infection, and hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of preterm birth and its treatment. There is extensive experience in treating these morbidities with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or

infection will be closely monitored (secondary endpoints), in case of an event, the study medication should **NOT** be adjusted.

Hypertension is a much less common morbidity after preterm delivery and antihypertensive drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually treated and resolved by reducing the dose. So, in case of hypertension, the study medication is lowered according to appendix 1 if no other treatable cause of hypertension can be identified. Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90 mmHg for infants 26-28 wks, and > 100 mmHg for infants ≥ 28 wks. Data on the time, reason and dose adjustment will be collected. The presence of hypertension leading to adjustment of study medication will be reported via the **Alert Procedure** (see paragraph 9.4).

5.1.3 Stop criteria during study protocol medication (treatment failure): In general, the use of open label hydrocortisone during the 22 day treatment course is strongly discouraged. Open label hydrocortisone use **may be considered** in the following conditions:

3. The pulmonary condition is progressively deteriorating and the respiratory index (MAwP x FiO_2) is >10 for more than 6 consecutive hours.
4. The pulmonary condition of the patient is stable (RI < 10) but not improving over time. In these circumstances open label hydrocortisone **may be considered** if the following conditions are met:
    a. Extubation was attempted (extubation trial) within 24 hours before considering open label treatment and this attempt failed.
    b. The patient is on study medication for **at least** 10 days (but preferably at a later time).

The open label hydrocortisone dosage schedule is similar to that used in the study. At that point in time the study medication is stopped and the patient will be recorded as “treatment

failure". In case of treatment failure the following data will be collected: timing of treatment failure, ventilator support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

The use of open label hydrocortisone will be reported via the Alert Procedure (see paragraph 9.4)**.**

5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label hydrocortisone. In such cases the physician should first attempt extubation before considering open label use. The open label hydrocortisone dosage schedule is similar to that used in the study (see appendix 1). Data on the starting date, cumulative dose and duration of rescue therapy are collected.

5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently) responding to first line treatment with intravascular volume expansion and inotropes (dopamine and/or dobutamine) the use of hydrocortisone is allowed in a dose of 3 mg/kg/day for 5 days. Treatment for hypotension will not be considered as treatment failure. Data on timing, dose and duration will be collected.

5.1.6 Stress dosing during and after study medication: Infants treated for a longer period of time with corticosteroids might experience inadequate adrenal response to stress (i.e. surgery or sepsis) for several months after stopping treatment. For this reason corticosteroids treatment is almost always tempered over time, as this minimizes the risk of adrenal insufficiency. Some NICUs consider this risk to be so low, that they will only treat patients

*with corticosteroids if they show signs of adrenal insufficiency (hypotension, hypoglycaemia), while other NICUs will start **preventive** treatment with corticosteroids in case of stressful events such as surgery. This study will also allow for a **preventive** stress dose treatment if this is deemed necessary according to the local protocol of the participating NICU. In other words, **preventive** treatment with a stress dose is **NOT** mandatory.*

It is clear that only the patients receiving hydrocortisone, and not those allocated to placebo treatment, will potentially benefit from a stress dose of hydrocortisone. For this reason patients will receive a stress dose identical to their study medication. A separate, second (stress) randomization procedure will make sure that allocation occurs in a blinded fashion. When the event occurs after completion of study medication, the prescribed dosing schedule is 5 mg/kg Q.I.D. on the day the event occurs, subsequently lowering the frequency by one dose every day. This leads to a total duration of stress dosing therapy of 5 days and a cumulative dose of 15 mg/kg study medication. In case the stress event occurs during study treatment, a stress dose is only started after the first week of treatment. In that case the actual dose is increased to 5 mg/kg Q.I.D. and subsequently lowered according to the aforementioned stress schedule until the actual dose of study medication is once again reached. From that point onwards the original regimen of study medication will be followed again.

*It is important to emphasize that the above mentioned procedure only applies to **preventive** treatment in case of a stressful event. If a patients shows signs of adrenal insufficiency at any time during a stressful events, he or she should be treated with open label hydrocortisone according to the dosing schedule mentioned in this paragraph.*

Data on number of courses, timing and dose will be collected.

5.1.7 Inhalation corticosteroids: There is currently insufficient evidence that inhaled corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled

corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is not an exclusion criterion. Data on timing, dose and duration will be collected.

5.2. Use of co-intervention

All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria.

This trial will monitor the prognostic important co-interventions and conditions, as described in section 8.2.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product

In this multicenter study the investigational medicinal product is hydrocortisone. A detailed description of hydrocortisone can be found in the summary of product characteristics (SPC) which is added to this protocol as a separate document.

6.2 Summary of findings from non-clinical studies

More details on both hydrocortisone and the placebo used in this study can be found in, respectively, the summary of product characteristics (SPC) and investigational medicinal product dossier (IMPD) both added to this protocol as separate documents. In addition to

this information, animal studies have shown that hydrocortisone, in contrast to dexamethasone, did not increase the risk of adverse effects on the brain when compared to a placebo.[35]

6.3 Summary of findings from clinical studies

Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm infants, hydrocortisone is used for the following indications: 1) primary or secondary deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first indication is authorized. The fact that hydrocortisone is used for other unauthorized indications is not exceptional, because off-label use of medication is more the rule than the exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory properties on the lungs of preterm infants at high risk for BPD ventilated in the second week of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] Use of hydrocortisone after the first week of life with a higher dose has been the standard of care in 4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in an identical treatment schedule as this study for several decades. Several historical cohort studies have shown that hydrocortisone use for this indication (reduction of BPD) did not increase the risk of adverse neurodevelopmental outcome.[44-46]

6.4 Summary of known and potential risks and benefits

As studies with hydrocortisone are limited, the assessment of risks and benefits are based on data obtained from previous RCTs investigating other corticosteroids (mainly dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies, hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

6.5 Description and justification of route of administration and dosage

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48]

Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study. More details on the dose regiment and the route of administration can be found in paragraph 5.1.

6.6 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone (Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the placebo will be manufactured by ACE Pharmaceuticals BV (Zeewolde, the Netherlands). The SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In addition, we have added an example of labels for the vials and boxes as separate documents.

6.7 Drug accountability

Drug accountability will be according to current GMP guidelines. The “kenniscentrum geneesmiddelen onderzoek” of the AMC pharmacy will take full responsibility and supervision of the drug accountability process.

7. METHODS

7.1 Randomisation, blinding and treatment allocation

Written informed consent has to be obtained from either parents or care-givers prior to randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. Following inclusion and randomization, the first

dose of study medication should be administered within 24 hours. Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation.

Randomisation will be per center and stratified according to gestational age stratum (Stratum A: < 27 weeks; Stratum B: ≥ 27 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place.
The infants' parents and all members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Patient characteristics, including gestational age, birth weight and respiratory status, will be collected from all eligible infants that are not included in the study. In addition, we will collect data on why the patients were not included. With this information we will assess possible bias in patient inclusion.

7.2 Withdrawal of individual subjects

Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences.
Note: patients who are considered to have "treatment failure" based on the prespecified criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.

7.3 Replacement of individual subjects after withdrawal

The number of withdrawn patients not marked as prespecified treatment failure (see section 7.2) will be replaced.

7.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will be treated according to the standard of care, including neurodevelopmental outcome assessment at the outpatient clinic.

7.5 Premature termination of the trial

An independent *Data Monitoring Committee (DMC)* will monitor the study on safety aspects (see section 9.4) and if necessary recommend termination of the study.

7.6 Breaking the randomization code

Unblinding is only performed in emergency situations where knowledge of the identity of the study drug is considered absolutely necessary for the clinical management of the subject. If local investigator or attending physician decides unblinding is essential, (s)he will make every effort to contact the PI before unblinding to discuss options. For this purpose a 24/7 reachable telephone service will be installed. Details of the unblinding procedure will be defined in the study specific working instructions.

7.7. Endpoints

7.7.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al.[21], since the severity of BPD has a high association with neurodevelopmental

sequelae.[12] In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al.[21,49,50] should be preformed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life. For practical guidance on the use of the oxygen reduction test please go to appendix 2.

7.7.2. Secondary endpoints:

- treatment failure as defined in section 5.1.3
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- BPD at 28 days
- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
- incidence of hypertension, as defined in paragraph 5.1.2
- hyperglycaemia requiring the use of insulin therapy
- nosocomial infection, like sepsis, meningitis and pneumonia
- pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
- necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)

- gastrointestinal bleeding
- isolated gastrointestinal perforation diagnosed on abdominal radiography
- intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.[51]
- retinopathy of prematurity, including grading following international classification[52]
- weight, head circumference and length at 36 weeks PMA
- long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:
    - readmissions since first discharge home
    - weight, length and head circumference at 24 months c.a.
    - Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
    - cerebral palsy and severity of cerebral palsy using gross motor function classification system
    - hearing loss requiring hearing aids
    - blindness
    - behavioural problems (child behaviour checklist)

All primary and secondary endpoints are measured as part of standard usual care in the Netherlands and Belgium, and will be derived from the charts of the patients by the investigators.

8. DATA COLLECTION AND STATISTICAL ANALYSIS

8.1 Baseline characteristics

Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.

8.2 Co-interventions

Apart from the study medication all patients will receive standard care, including co-medication such as surfactant, inhaled nitric oxide. methylxanthines, vitamin A, antibiotics, antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled corticosteroids. These co-medications are prescribed on the basis of (inter)national guidelines and/or local protocols. Since the route of administration (e.g. oral or IV), the dose and frequency may vary continuously depending on the weight and the clinical condition of the patients, only name, start and stop date are recorded in the CRF. For all other drugs used during the admission data will be recorded according to GCP guidelines.
Also the ventilation mode with the ventilator settings will be recorded and analyzed.

8.3 Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student's *t* test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed. The effect of hydrocortisone on the primary outcome death or BPD will be

assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at $p < 0.05$.

9. SAFETY REPORTING

9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will ensure that all subjects' parents or caregivers are kept informed.

9.2 Adverse and serious adverse events (SAE)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events observed by the investigator or his staff will be recorded. A **serious adverse event** is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this trial);
- other important events that may jeopardize the safety of the subject or may require intervention to prevent one of the outcomes listed above.

All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data Monitoring Committee (DMC) and to the accredited METC that approved the protocol, according to the requirements of that METC.

9.2.1 Context-specific SAE reporting

This study population (critically ill preterm infants) has a high risk of serious complications (so-called "context-specific SAE's"), which are inherent to their vulnerable condition and unrelated to the intervention which is under evaluation in this trial.

These complications are included in the primary and secondary outcomes of this study and are recorded in the Case Report Form. This documentation will include the date of diagnosis, classification/gradation of the complication, type of action taken if appropriate (with some complications a wait and see approach is warranted). Since these complications are highly interrelated and of longitudinal character, it is impossible to indicate an exact date for the resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the complication will be classified as ongoing.

In light of the above, immediate and individual reporting of all these condition related complications will not enhance the safety of study. [1,2] This is also in accordance with CCMO regulations (http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178)

The context-specific SAEs that will be identified include the events listed under paragraph 7.7.2, on page 27 and 28 of the protocol.

Once a year, an overview of the aforementioned complications for each treatment arm and ordered by organ system will be presented to the DMC and METC. This overview will consist of the following information: name of the complication, date of diagnosis, classification/gradation of the complication, type of action taken, date of discharge or ongoing.[53,54]

9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (see SPC/IMPD) or the context-specific SAEs listed in paragraph 9.2.1.

Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the study coordinator via the study website (**Alert Procedure,** see paragraph 9.4). The PI will report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent authority, Medicine Evaluation Board as well as to the competent authorities in other Member States, according to the requirements of the Member States.
The expedited reporting will occur not later than 15 days after the PI has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.2.3 Annual safety report

In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout the clinical trial, a safety report to the DMC, accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States as well as the investigators of all participating centers.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated. According to the standard of care, all infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

9.4 Data Monitoring Committee (DMC), the Alert Procedure

An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes and will provide the trial's Steering Committee with recommendations regarding continuing or stopping the trial (for all patients or subgroups of patients) when approximately 25% (safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated

outcome data are available. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. The safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes. The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the data manager will be stand-by to reveal the allocation labels if the DMC thinks this is necessary. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician who has experience with trials, and some experience on previous DMCs and a pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in neonates. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. Identification and circulation of external evidence (e.g., from other trials/systematic reviews) is not the responsibility of the DMC members. It is the responsibility of the PI to provide any such information to the DMC.

To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been added to the CRF and the website (SUSAR), “The Alert Procedure”. This tool is used to monitor special conditions and acute situations that need the direct attention of the principle investigator and the study coordinator. If necessary the Steering Committee can decide to alert the DMC. Furthermore, the Steering Committee will provide a summary report after every 10 alerts to the DMC.

There are 5 situations when the **Alert Procedure** must be used:

6. Any synchronous use of indomethacin/ibuprofen and study medication

7. Any intestinal perforation occurring during or after the study medication treatment course
8. Occurrence of hypertension as defined
9. Any use of open label hydrocortisone
10. Occurrence of a SUSAR

The “Alert Procedure” will run in the background for the first 4 conditions. CRF data will be linked automatically and an email will be send to principal investigator and the study coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local investigator can alert the principal investigator and the study coordinator via a SUSAR email button on the trial website.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[55] and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and informed consent

Patients will be recruited and their parents will be informed and asked for consent by the attending paediatricians. Informed written consent must be obtained from the parents prior to randomisation for the study. The patient information letter and informed consent are provided in section I of the study dossier. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment.

10.3 Benefits and risks assessment, group relatedness

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients since intravenous access will be necessary for other clinical reasons. If this is no longer the case, study medication may be administered via the oral route. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia, hypertension and systemic infection. Although the increased risk of gastrointestinal perforation has up to now only been reported during the early (within the first 96 hours of life) administration of corticosteroids, the risk may also be increased when administering hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use of dexamethasone has been associated with an increase risk for neurodevelopmental sequelae. Historical cohort studies investigating the use of hydrocortisone after the first week of life have found no evidence to support this. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives

Participants will not receive a financial compensation for participation as an incentive.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. Security is guaranteed with login names, login

codes and encrypted data transfer. An experienced datamanager will maintain the database and check the information in the database for completeness, consistency and plausibility.

The data of all subjects will be coded and this coding will not be retraceable to the individual patient. The key to this coding is safeguarded by the investigator. A limited number of people have access to the source data. These are the principal investigator, investigating doctor and investigating personnel. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor, quality assurance auditor, employees from the METC and the Health Care Inspectorate of the Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have access to the source data. All are subject to the pledge of confidentiality. Data and human material will be stored for 15 years strictly confidential.

11.2 Amendments

Amendments are changes made to the trial after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the Steering Committee.

11.3 Annual progress report

If requested, an annual progress report of the progress of the trial will be provided to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. In case the study

is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.4 Public disclosure and publication policy

The study will be registered in the EUDRACT, the website of the Dutch National Competent Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial registry, part of the WHO registry. The results of the study will be published in peer-reviewed international medical journals. In addition, the results of the study will be used for development and implementation of a guideline on treatment of BPD, which will benefit future patients.

12. ORGANISATION

12.1 Steering Committee

The Steering Committee is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsor, of the investigators of the participating centres and of the MCRN. The specific tasks of the Steering Committee are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager

- Approve study reports and papers for publication.

12.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a description of the membership, tasks and responsibilities of the DMC.

12.3 Clinical Project Manager / Central Study Coordinator

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning. The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee

12.4 Study Monitoring

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

12.5 Quality Assurance Audits and Inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating this trial the investigator agrees to this requirement.

The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

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APPENDIX 1 STUDIE MEDICATIE SCHEMA

Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.	Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm	Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatticaly skip the next dose and commence the following dose with a lower daily frequency.	Step 4: For print out of study medication list, press: Print

Study identification
Name
Date of birth
Weight gram

First administration
Date/time
Lowering dosage regimen
Date/time

Day in regimen	Time	Times per day	mg/dose	Daily dose/kg
Day 1	0-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	0-01-00 6:00			
	0-01-00 12:00			
	0-01-00 18:00			
Day 2	1-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	1-01-00 6:00			
	1-01-00 12:00			
	1-01-00 18:00			
Day 3	2-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	2-01-00 6:00			
	2-01-00 12:00			
	2-01-00 18:00			
Day 4	3-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	3-01-00 6:00			
	3-01-00 12:00			
	3-01-00 18:00			
Day 5	4-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	4-01-00 6:00			
	4-01-00 12:00			
	4-01-00 18:00			
Day 6	5-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	5-01-00 6:00			
	5-01-00 12:00			
	5-01-00 18:00			
Day 7	6-01-00 0:00	4 x	0.00 mg.	5 mg/kg/d
	6-01-00 6:00			
	6-01-00 12:00			
	6-01-00 18:00			

Day in regimen	Time	Times per day	mg/dose	Daily dose/kg
Day 8	7-01-00 0:00	3 x	0.00 mg.	3.75 mg/kg/d
	7-01-00 8:00			
	7-01-00 16:00			
Day 9	8-01-00 0:00	3 x	0.00 mg.	3.75 mg/kg/d
	8-01-00 8:00			
	8-01-00 16:00			
Day 10	9-01-00 0:00	3 x	0.00 mg.	3.75 mg/kg/d
	9-01-00 8:00			
	9-01-00 16:00			
Day 11	10-01-00 0:00	3 x	0.00 mg.	3.75 mg/kg/d
	10-01-00 8:00			
	10-01-00 16:00			
Day 12	11-01-00 0:00	3 x	0.00 mg.	3.75 mg/kg/d
	11-01-00 8:00			
	11-01-00 16:00			
Day 13	12-01-00 0:00	2 x	0.00 mg.	2.5 mg/kg/d
	12-01-00 12:00			
Day 14	13-01-00 0:00	2 x	0.00 mg.	2.5 mg/kg/d
	13-01-00 12:00			
Day 15	14-01-00 0:00	2 x	0.00 mg.	2.5 mg/kg/d
	14-01-00 12:00			
Day 16	15-01-00 0:00	2 x	0.00 mg.	2.5 mg/kg/d
	15-01-00 12:00			
Day 17	16-01-00 0:00	2 x	0.00 mg.	2.5 mg/kg/d
	16-01-00 12:00			
Day 18	17-01-00 0:00	1 x	0.00 mg.	1.25 mg/kg/d
Day 19	18-01-00 0:00	1 x	0.00 mg.	1.25 mg/kg/d
Day 20	19-01-00 0:00	1 x	0.00 mg.	1.25 mg/kg/d
Day 21	20-01-00 0:00	1 x	0.00 mg.	1.25 mg/kg/d
Day 22	21-01-00 0:00	1 x	0.00 mg.	1.25 mg/kg/d

APPENDIX 2

Oxygen reduction test

Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe depending on the amount and duration of supplemental oxygen and the level of respiratory support. If a patient has received supplemental oxygen for more than 28 d (FiO_2 > 0.21 for more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is between 0.21 and 0.30, BPD is classified as moderate and in case of a FiO_2 > 0.30 and/or receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
It is important to realize that the duration of supplemental oxygen is highly dependent on target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician to actively wean oxygen delivery.
To make sure that patients receive supplemental oxygen for pulmonary reasons and to standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al. developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% ***or*** if they receive a FiO_2> 0.30 resulting in a SpO2 > 96%. Patients supported with nasal cannulae (flow not nCPAP) without supplemental oxygen, and patients treated with nCPAP/mechanical ventilation or with a FiO_2 > 0.30 resulting in a SpO2 < 96% do not need additional testing, and are, respectively, classified as having mild and severe BPD.

The oxygen reduction test

Indications:

- FiO_2 > 0.21 and < 0.30 with oxygen saturation ranges between 90% and 96%

- FiO_2 > 0.30 with a oxygen saturation range above 96%

Methods:

The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The supplemental oxygen requirement will be gradually weaned to room air while monitoring SpO_2. The diagnosis moderate BPD can be rejected when the SpO_2 remain above ≥ 88% in room air during 1 hour without apnea or bradycardia.

The diagnosis moderate BPD is confirmed if the saturation goes below 80% during >1minute or remains between 80-87% during > 5 minutes. All occurrences of movement artifact (defined as visible motion of the infant together with loss of pleythsmograph signal from the monitor) are recorded and corresponding saturation values are to be deleted.

The test contains 4 phases

Phase 1: Baseline evaluation

For 15 minutes heart rate, respiratory rate, SpO_2, number of apnea (cessation of breathing > 20 seconds) and bradycardia (hartrate < 80/min during > 10 sec) will be collected.

Phase 2: Oxygen reduction

The supplemental oxygen will be weaned by 2% to room air, after which the flow will be weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but not removed from the face.

Phase 3: Observation period

For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87% for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

Phase 4: Back to situation before the test

The level of supplemental oxygen and flow will be reset to the status before the test.

PROTOCOL

Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study

A multicenter randomised placebo controlled trial

Protocol ID	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
Short title	**Hydrocortisone for bronchopulmonary dysplasia**
Version	5
Date	11 November 2012
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARR	Absolute Risk Reduction
BPD	BronchoPulmonary Dysplasia
BW	Birth Weight
CDP	Continuous Distension Pressure
CGA	Corrected Gestational Age
CP	Cerebral Palsy
DNRN	Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal Research Netwerk (NNRN)
DMC	Data Monitoring & Safety Committee
ESEMC	External Safety and Efficacy Monitoring Committee
GA	Gestational Age
HFO	High Frequency Oscillation
IMP	Investigational Medicinal Product
IVH	IntraVentricular Haemorrhage
MAwP	Mean Airway Pressure
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie
MRI	Magnetic Resonance Imaging
NEC	Necrotising EnteroColitis
NICU	Neonatal Intensive Care Unit
NICHD	National Institutes for Child Health and Human Development
NNT	Number Needed to Treat
NVK	Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor Kindergeneeskunde
PDA	Persistent Ductus Arteriosus
PMA	PostMenstrual Age
PNA	PostNatal Age
PVL	PeriVentricular Leucomalacia
RCT	Randomised Controlled Trial
RI	Respiratory Index
SAE	Serious Adverse Event
SD	Standard Deviation
Sponsor	The sponsor is the party that commissions the organisation of performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
VLBW	Very Low Birth Weight
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Background: Randomised controlled trials (RCTs) have shown that treatment of chronically ventilated preterm infants after the first week of life with dexamethasone reduces the incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been suggested as an alternative therapy. So far no RCT has investigated its efficacy when administered after the first week of life to ventilated preterm infants.

Objective: To establish the efficacy of hydrocortisone given after one week of life to reduce the incidence of the combined outcome death or BPD in chronically ventilated preterm infants.

Study design: Randomised double blind placebo controlled multicenter study.

Study population: Very low birth weight infants (GA<30weeks and/or BW<1250grams), ventilator dependent at a postnatal age of 7 – 14 days.

Intervention: Administration of hydrocortisone or placebo during a 22 day tapering schedule.

Outcome parameters: Primary outcome measure is survival free of BPD at 36 weeks postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary condition, adverse effects during hospitalization, and long-term neurodevelopmental sequelae assessed at 2 years corrected gestational age (CGA).

Burden, benefit and risks associated with participation; group relatedness:

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.
Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

1. BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth, with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory distress, the need for prolonged respiratory support, an increased risk of recurrent pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions and utilization of health services resulting in tremendous societal costs compared to children without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse neurodevelopmental outcome after premature birth[10-14] with life-long economic and social consequences.[15-18]

In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity, pulmonary inflammation has been identified as an important mediator in the development of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24] Furthermore, systemic glucocorticoids seem to be most effective when administered in a time frame of 7 to 14 days postnatal age, the so-called moderately early treatment onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be associated with an increased the risk of cerebral palsy (CP). Although this complication has not been reported by RCTs investigating dexamethasone treatment initiated after the first week of life, these alarming reports have resulted in a general concern on the use of dexamethasone in preterm infants.[27-29] Based on this concern, the American Academy of

Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine have stated that clinical trials should be performed to investigate the use of alternative anti-inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]

Despite the ongoing concerns on their use, systemic glucocorticoids are still used in approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the most widely used glucocorticoid drug, but its dose has been significantly reduced and administration is often postponed until the 3rd or 4th week of life.[27]

As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35] However, no placebo controlled RCT has investigated the use of hydrocortisone after the first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These findings are supported by several historical cohort studies, showing no increased risk of adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]

In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-dependent in the second week of life are no longer treated with glucocorticoids. Infants are kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes supported by other interventions, such as diuretics and inhalation therapy. With this approach, some infants can be successfully weaned and extubated. Only those infants that

remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the primary objective to wean and extubate.

Although this approach will undoubtedly result in successful extubation of most infants with the lowest possible use of glucocorticoids, the question remains if this is also the best strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life. This question seems justified and relevant because BPD, and not failure to extubate, is associated with adverse medium- and long-term outcome. This is the main reason why the primary outcome of this study is death or BPD and not failure to extubate.

The NICU at the University Medical Center Utrecht has historically used hydrocortisone for chronically ventilated preterm infants. Retrospective studies seem to indicate that hydrocortisone is effective in reducing BPD, without causing serious adverse effects. However, these findings need to be confirmed or refuted by a large randomized placebo controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between NICUs is undesirable and has also been debated in the public press.[47] As a first step to resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing hydrocortisone with placebo is urgently needed, an initiative that is also supported by the Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this

regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study.

Based on the current available evidence, the American Academy of Pediatrics has concluded that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended; (2) outside the context of a randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based on these recommendation ventilated preterm infants are no longer routinely treated with postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases, postponed until after the third week of life. Comparison of hydrocortisone to a placebo is therefore warranted because standard therapy in the second week of life (7-14 d after birth) is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances treatment with a (rescue) open label glucocorticoids is still possible in the current study. Although based on the above, the *extra* risks for the patients in this study are probably limited, a data monitoring committee will closely monitor any possible adverse effects and risks, as also explained in paragraph 9.4.

2. OBJECTIVE

To investigate if hydrocortisone is safe and effective in reducing the incidence of the combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants, as compared to placebo. This study **does not** aim to successfully extubate ventilator-dependent preterm infants with the lowest possible use of glucocorticoids (i.e. hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this point of view the treatment strategy is fundamentally different from what is currently used in daily clinical practice.

3. STUDY DESIGN

Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

4. STUDY POPULATION

4.1 Population eligibility

Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4.2 Inclusion criteria

Preterm infants with an increased risk of BPD and:

- a gestational age < 30 wks and/or birth weight < 1250 g
- ventilator dependency at 7-14 days PNA
- *a respiratory index (RI = MAwP x FiO_2) of ≥ 2.5* for more than 12 h/day for at least 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO_2 values in premature infants (5.0-7.5 kPa).

Note: these targets are used to ensure homogeneous assessment of MAwP and FiO_2 for patient inclusion among participating centres. For the same reason, clinician are encouraged to aim for the median value of these targets when assessing the RI. After inclusion of the patient in the study, physicians are free to use local targets for oxygenation and ventilation.

4.3 Exclusion criteria

- chromosomal defects (e.g. trisomy 13, 18, 21)
- major **congenital** malformations that:
    - compromise lung function (e.g. surfactant protein deficiencies, congenital diaphragmatic hernia)
    - result in chronic ventilation (e.g. Pierre Robin sequence)
    - increase the risk of death or adverse neurodevelopmental outcome (congenital cerebral malformations)

      Note: intraventricular haemorrhages, periventricular leucomalacia and cerebral infarction are not considered **congenital** malformations and therefore are no exclusion criteria.
- Use of dexamethasone or hydrocortisone for the sole purpose of improving lung function and respiratory status prior to inclusion

Considerations

Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

are know to be independent risk factors for developing BPD. Therefore, these diagnoses are **not** considered to be exclusion criteria. The following should be taken into consideration:

13. In ventilator-dependent cases of sepsis and pneumonia the attending physician may start antibiotics and await the effect on respiratory drive/ pulmonary status for 48 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for inclusion.
14. Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have shown that treatment with corticosteroids may increase the risk of intestinal perforation. Speculating on the pathogenesis of this adverse effect, it has been suggested that the synchronous use of indomethacin and corticosteroids might explain this finding. However, trials starting dexamethasone between 7-14 d after life have **not** reported an increased risk of intestinal perforation, despite the fact that some of these patients were also treated for hemodynamically significant PDA with indomethacin. In other words, the evidence for a possible adverse effect of the combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason the combined use of corticosteroids and indomethacin/ibuprofen is **NOT** prohibited within the STOP-BPD trial. However, where possible in the time window of 7-14 days, we do encourage physicians to treat a hemodynamically significant PDA before randomizing the patient for the study. To make this feasible physicians are strongly encouraged to determine the presence of a hemodynamically significant PDA at day 7 of life. This way the patient can, if necessary according to the local protocol, still be treated with 2 courses of indomethacin / ibuprofen before day 14 of life.

    If there is an indication to treat a hemodynamically significant PDA with indomethacin/ibuprofen after randomization, study medication is **NOT** stopped. Yet,

any synchronous use of indomethacin/ibuprofen and study medication or the occurrence of an intestinal perforation recorded in the case record form, will automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert Procedure**. This will allow for a close and individual monitoring of possible adverse effects.

15. If the physician considers extubation not an option because of the general condition of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal distension) inclusion in the study can be postponed until the maximum of 14 days PNA.

4.4 Sample size calculation The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4) compared with placebo.[24] However, there are no data currently available on the efficacy of hydrocortisone and the suggested cumulative dose in the present study is considerably lower compared to previously used dexamethasone doses. Since the shown efficacy of dexamethasone is dependent on the used doses in these trials[26], we would propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With an estimated a priori risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2 tailed) and a power of 80% the number of patients to be included in each treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients need to be included in each treatment arm (total 400). Based on a retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch

NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should be included in the study. For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

5. TREATMENT OF SUBJECTS

5.1. Therapeutic details

5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone schedules will be calculated according to weight on the day of randomisation and not adjusted to the actual weight during the tapering schedule. Clinicians are encouraged to administer the study medication intravenously as long as this route of access is required for other reasons. If intravenous access is no longer required for the standard treatment, the study medication can be administered orally using the same solution and dose.

5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on corticosteroids use in the second week of life (mainly dexamethasone) have reported that the following transient short term side-effects: hyperglycaemia, increased risk of infection, and hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of preterm birth and its treatment. There is extensive experience in treating these morbidities with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or

infection will be closely monitored (secondary endpoints), in case of an event, the study medication should **NOT** be adjusted.

Hypertension is a much less common morbidity after preterm delivery and antihypertensive drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually treated and resolved by reducing the dose. So, in case of hypertension, the study medication is lowered according to appendix 1 if no other treatable cause of hypertension can be identified. Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90 mmHg for infants 26-28 wks, and > 100 mmHg for infants ≥ 28 wks. Data on the time, reason and dose adjustment will be collected. The presence of hypertension leading to adjustment of study medication will be reported via the **Alert Procedure** (see paragraph 9.4).

5.1.3 Stop criteria during study protocol medication (treatment failure): In general, the use of open label hydrocortisone during the 22 day treatment course is strongly discouraged. Open label hydrocortisone use **may be considered** in the following conditions:

5. The pulmonary condition is progressively deteriorating and the respiratory index (MAwP x FiO_2) is >10 for more than 6 consecutive hours.
6. The pulmonary condition of the patient is stable (RI < 10) but not improving over time. In these circumstances open label hydrocortisone **may be considered** if the following conditions are met:
    a. Extubation was attempted (extubation trial) within 24 hours before considering open label treatment and this attempt failed.
    b. The patient is on study medication for **at least** 10 days (but preferably at a later time).

The open label hydrocortisone dosage schedule is similar to that used in the study. At that point in time the study medication is stopped and the patient will be recorded as “treatment

failure". In case of treatment failure the following data will be collected: timing of treatment failure, ventilator support and settings, type of open label medication, starting date, cumulative dose and duration of rescue therapy. The patients will be followed as all other patients until the clinical endpoints occur or until end of follow up.

The use of open label hydrocortisone will be reported via the Alert Procedure (see paragraph 9.4)**.**

5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on mechanical ventilation after completion of the study medication, i.e. day 22, may be treated with open label hydrocortisone. In such cases the physician should first attempt extubation before considering open label use. The open label hydrocortisone dosage schedule is similar to that used in the study (see appendix 1). Data on the starting date, cumulative dose and duration of rescue therapy are collected.

5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently) responding to first line treatment with intravascular volume expansion and inotropes (dopamine and/or dobutamine) the use of hydrocortisone is allowed in a dose of 3 mg/kg/day for 5 days. Treatment for hypotension will not be considered as treatment failure. Data on timing, dose and duration will be collected.

5.1.6 Stress dosing during and after study medication: Infants treated for a longer period of time with corticosteroids might experience inadequate adrenal response to stress (i.e. surgery or sepsis) for several months after stopping treatment. For this reason corticosteroids treatment is almost always tempered over time, as this minimizes the risk of adrenal insufficiency. Some NICUs consider this risk to be so low, that they will only treat patients

with corticosteroids if they show signs of adrenal insufficiency (hypotension, hypoglycaemia), while other NICUs will start **preventive** treatment with corticosteroids in case of stressful events such as surgery. This study will also allow for a **preventive** stress dose treatment if this is deemed necessary according to the local protocol of the participating NICU. In other words, **preventive** treatment with a stress dose is **NOT** mandatory.

It is clear that only the patients receiving hydrocortisone, and not those allocated to placebo treatment, will potentially benefit from a stress dose of hydrocortisone. For this reason patients will receive a stress dose identical to their study medication. A separate, second (stress) randomization procedure will make sure that allocation occurs in a blinded fashion. When the event occurs after completion of study medication, the prescribed dosing schedule is 5 mg/kg Q.I.D. on the day the event occurs, subsequently lowering the frequency by one dose every day. This leads to a total duration of stress dosing therapy of 5 days and a cumulative dose of 15 mg/kg study medication. In case the stress event occurs during study treatment, a stress dose is only started after the first week of treatment. In that case the actual dose is increased to 5 mg/kg Q.I.D. and subsequently lowered according to the aforementioned stress schedule until the actual dose of study medication is once again reached. From that point onwards the original regimen of study medication will be followed again.

It is important to emphasize that the above mentioned procedure only applies to **preventive** treatment in case of a stressful event. If a patients shows signs of adrenal insufficiency at any time during a stressful events, he or she should be treated with open label hydrocortisone according to the dosing schedule mentioned in this paragraph.

Data on number of courses, timing and dose will be collected.

5.1.7 Inhalation corticosteroids: There is currently insufficient evidence that inhaled corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is not an exclusion criterion. Data on timing, dose and duration will be collected.

5.2. Use of co-intervention

All randomized patients will be treated according to the guidelines of the individual NICUs. All participating NICUs explore treatable causes of ventilator dependency during the first week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and treat these according to the department protocol. Although all of these conditions can be an alternative cause of respiratory failure, they are known risk factors for developing BPD and therefore are not considered exclusion criteria.

This trial will monitor the prognostic important co-interventions and conditions, as described in section 8.2.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product

In this multicenter study the investigational medicinal product is hydrocortisone. A detailed description of hydrocortisone can be found in the summary of product characteristics (SPC) which is added to this protocol as a separate document.

6.2 Summary of findings from non-clinical studies

More details on both hydrocortisone and the placebo used in this study can be found in, respectively, the summary of product characteristics (SPC) and investigational medicinal product dossier (IMPD) both added to this protocol as separate documents. In addition to this information, animal studies have shown that hydrocortisone, in contrast to dexamethasone, did not increase the risk of adverse effects on the brain when compared to a placebo.[35]

6.3 Summary of findings from clinical studies

Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm infants, hydrocortisone is used for the following indications: 1) primary or secondary deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first indication is authorized. The fact that hydrocortisone is used for other unauthorized indications is not exceptional, because off-label use of medication is more the rule than the exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory properties on the lungs of preterm infants at high risk for BPD ventilated in the second week

of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] Use of hydrocortisone after the first week of life with a higher dose has been the standard of care in 4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in an identical treatment schedule as this study for several decades. Several historical cohort studies have shown that hydrocortisone use for this indication (reduction of BPD) did not increase the risk of adverse neurodevelopmental outcome.[44-46]

6.4 Summary of known and potential risks and benefits

As studies with hydrocortisone are limited, the assessment of risks and benefits are based on data obtained from previous RCTs investigating other corticosteroids (mainly dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies, hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal perforation and delayed neurodevelopment have only been reported in studies administering corticosteroids in the first week of life and/or during combinations with other medication. In this study the risk of gastrointestinal perforation and delayed neurodevelopment may be reduced because hydrocortisone will be administered after the first week of life and combinations with other drugs will be avoided as much as possible.

Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

6.5 Description and justification of route of administration and dosage

The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has been using a fixed hydrocortisone treatment regimen for several decades now and this regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective studies strongly suggest that this is a safe dose, because it was not associated with an increased risk of adverse neurological outcome.[45,48] Comparing hydrocortisone treated patients with dexamethasone treated patients in other NICUs showed no difference in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.[48] Based on these findings and current clinical practice, we decided to adopt the dosing regimen from Utrecht for this study. More details on the dose regiment and the route of administration can be found in paragraph 5.1.

6.6 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone (Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the placebo will be manufactured by ACE Pharmaceuticals BV (Zeewolde, the Netherlands). The SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In addition, we have added an example of labels for the vials and boxes as separate documents.

6.7 Drug accountability

Drug accountability will be according to current GMP guidelines. The “kenniscentrum geneesmiddelen onderzoek” of the AMC pharmacy will take full responsibility and supervision of the drug accountability process.

7. METHODS

7.1 Randomisation, blinding and treatment allocation

Written informed consent has to be obtained from either parents or care-givers prior to randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis of developing BPD, parents receive the study information as soon as possible allowing them sufficient time to consider participation. The actual decision to include the patient in the trial should be made between day 7 and 14 PNA. Following inclusion and randomization, the first dose of study medication should be administered within 24 hours. Randomization will be centrally controlled and web-based using a computer program designed for this study. This trial will be protected from selection bias by using concealed, stratified and blocked randomisation.

Randomisation will be per center and stratified according to gestational age stratum (Stratum A: < 27 weeks; Stratum B: ≥ 27 weeks), in order to achieve an equal distribution in both treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block sizes. Multiple birth infants will be randomised independently, unless the parents or caretakers explicitly demand that the siblings should be treated according to the same treatment arm. An automated mechanism to perform twin randomisation is in place.

The infants' parents and all members of the medical team, including investigators, remain blinded to group assignment throughout the study.

Patient characteristics, including gestational age, birth weight and respiratory status, will be collected from all eligible infants that are not included in the study. In addition, we will collect data on why the patients were not included. With this information we will assess possible bias in patient inclusion.

7.2 Withdrawal of individual subjects

Parents or caregivers can leave the study at any time for any reason if they wish to do so without any consequences.

Note: patients who are considered to have "treatment failure" based on the prespecified criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.

7.3 Replacement of individual subjects after withdrawal

The number of withdrawn patients not marked as prespecified treatment failure (see section 7.2) will be replaced.

7.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will be treated according to the standard of care, including neurodevelopmental outcome assessment at the outpatient clinic.

7.5 Premature termination of the trial

An independent Data Monitoring Committee (DMC) will monitor the study on safety aspects (see section 9.4) and if necessary recommend termination of the study.

7.6 Breaking the randomization code

Unblinding is only performed in emergency situations where knowledge of the identity of the study drug is considered absolutely necessary for the clinical management of the subject. If local investigator or attending physician decides unblinding is essential, (s)he will make every effort to contact the PI before unblinding to discuss options. For this purpose a 24/7 reachable telephone service will be installed. Details of the unblinding procedure will be defined in the study specific working instructions.

7.7. Endpoints

7.7.1. Primary endpoint: the dichotomous variable BPD free survival at 36 weeks PMA. BPD at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed by Jobe et.al.[21], since the severity of BPD has a high association with neurodevelopmental sequelae.[12] In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks PMA, the oxygen reduction test as described by Walsh et.al.[21,49,50] should be preformed. A positive oxygen reduction test has a high correlation with the risk on discharge home with oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission during the first year of life. For practical guidance on the use of the oxygen reduction test please go to appendix 2.

7.7.2. Secondary endpoints:

- treatment failure as defined in section 5.1.3
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge

- BPD at 28 days
- failure to extubate 3, 7, 14 and 21 days after initiating therapy
- duration of mechanical ventilation
- use of “rescue treatment” with hydrocortisone outside the study protocol
- total time on supplemental oxygen
- length of hospital stay
- incidence of hypertension, as defined in paragraph 5.1.2
- hyperglycaemia requiring the use of insulin therapy
- nosocomial infection, like sepsis, meningitis and pneumonia
- pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- hemodynamic significant patent ductus arteriosus for which medical intervention or surgical ligation is needed
- necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic finding of pneumotosis intestinalis or hepatobiliary gas (Bell stage II)
- gastrointestinal bleeding
- isolated gastrointestinal perforation diagnosed on abdominal radiography
- intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL), including grading on cerebral ultrasonography according to protocol defined by Ment et.al.[51]
- retinopathy of prematurity, including grading following international classification[52]
- weight, head circumference and length at 36 weeks PMA
- long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:
    - readmissions since first discharge home
    - weight, length and head circumference at 24 months c.a.

- Bayley Scales of Infant Development III, Mental Developmental Index and Psychomotor Developmental Index
- cerebral palsy and severity of cerebral palsy using gross motor function classification system
- hearing loss requiring hearing aids
- blindness
- behavioural problems (child behaviour checklist)

All primary and secondary endpoints are measured as part of standard usual care in the Netherlands and Belgium, and will be derived from the charts of the patients by the investigators.

8. DATA COLLECTION AND STATISTICAL ANALYSIS

8.1 Baseline characteristics

Baseline characteristics are collected prior to inclusion and randomization with respect to the following baseline characteristics: demographic details and patient characteristics, such as gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be collected on day of randomization.

8.2 Co-interventions

Apart from the study medication all patients will receive standard care, including co-medication such as surfactant, inhaled nitric oxide. methylxanthines, vitamin A, antibiotics, antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled corticosteroids. These co-medications are prescribed on the basis of (inter)national guidelines

and/or local protocols. Since the route of administration (e.g. oral or IV), the dose and frequency may vary continuously depending on the weight and the clinical condition of the patients, only name, start and stop date are recorded in the CRF. For all other drugs used during the admission data will be recorded according to GCP guidelines.
Also the ventilation mode with the ventilator settings will be recorded and analyzed.

8.3 Statistical analysis

Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians and (interquartile) ranges. Categorical data will be analysed using the Chi-square test. Continuous data will be analysed using the Student's *t* test or Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be employed. The effect of hydrocortisone on the primary outcome death or BPD will be assessed by multi-variable logistic regression analysis including possible confounders. Statistical significance is set at $p < 0.05$.

9. SAFETY REPORTING

9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will ensure that all subjects' parents or caregivers are kept informed.

9.2 Adverse and serious adverse events (SAE)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events observed by the investigator or his staff will be recorded. A **serious adverse event** is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect (not applicable in this trial);
- other important events that may jeopardize the safety of the subject or may require intervention to prevent one of the outcomes listed above.

All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data Monitoring Committee (DMC) and to the accredited METC that approved the protocol, according to the requirements of that METC.

9.2.1 Context-specific SAE reporting

This study population (critically ill preterm infants) has a high risk of serious complications (so-called "context-specific SAE's"), which are inherent to their vulnerable condition and unrelated to the intervention which is under evaluation in this trial.

These complications are included in the primary and secondary outcomes of this study and are recorded in the Case Report Form. This documentation will include the date of diagnosis, classification/gradation of the complication, type of action taken if appropriate (with some

complications a wait and see approach is warranted). Since these complications are highly interrelated and of longitudinal character, it is impossible to indicate an exact date for the resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the complication will be classified as ongoing.

In light of the above, immediate and individual reporting of all these condition related complications will not enhance the safety of study. [1,2] This is also in accordance with CCMO regulations (http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178)
The context-specific SAEs that will be identified include the events listed under paragraph 7.7.2, on page 27 and 28 of the protocol.

Once a year, an overview of the aforementioned complications for each treatment arm and ordered by organ system will be presented to the DMC and METC. This overview will consist of the following information: name of the complication, date of diagnosis, classification/gradation of the complication, type of action taken, date of discharge or ongoing.[53,54]

9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (see SPC/IMPD) or the context-specific SAEs listed in paragraph 9.2.1.

Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the study coordinator via the study website (**Alert Procedure,** see paragraph 9.4). The PI will report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent authority, Medicine Evaluation Board as well as to the competent authorities in other Member States, according to the requirements of the Member States.
The expedited reporting will occur not later than 15 days after the PI has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.2.3 Annual safety report

In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout the clinical trial, a safety report to the DMC, accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States as well as the investigators of all participating centers.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated. According to the standard of care, all infants will participate in the usual NICU follow-up program. This program is targeted at evaluating and coordinating diagnostic procedures and treatment of all prematurity related problems, in close cooperation with regional and local pediatricians.

9.4 Data Monitoring Committee (DMC), the Alert Procedure

An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes and will provide the trial's Steering Committee with recommendations regarding continuing or stopping the trial (for all patients or subgroups of patients) when approximately 25% (safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated outcome data are available. Data summaries for the DMC will be prepared by a statistician who is not a member of the investigating team. The safety data will include, but not be restricted to, serious adverse events and the safety outcomes listed as secondary outcomes. The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the data manager will be stand-by to reveal the allocation labels if the DMC thinks this is necessary. If the DMC recommends modification or cessation of the study protocol, this will be discussed with the Steering Committee, who will make the decision. The DMC will be composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician who has experience with trials, and some experience on previous DMCs and a pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in neonates. The Steering Committee will propose a detailed mandate and review this with the DMC, from the outset. Identification and circulation of external evidence (e.g., from other

trials/systematic reviews) is not the responsibility of the DMC members. It is the responsibility of the PI to provide any such information to the DMC.

To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been added to the CRF and the website (SUSAR), “The Alert Procedure”. This tool is used to monitor special conditions and acute situations that need the direct attention of the principle investigator and the study coordinator. If necessary the Steering Committee can decide to alert the DMC. Furthermore, the Steering Committee will provide a summary report after every 10 alerts to the DMC.

There are 5 situations when the **Alert Procedure** must be used:

11. Any synchronous use of indomethacin/ibuprofen and study medication
12. Any intestinal perforation occurring during or after the study medication treatment course
13. Occurrence of hypertension as defined
14. Any use of open label hydrocortisone
15. Occurrence of a SUSAR

The “Alert Procedure” will run in the background for the first 4 conditions. CRF data will be linked automatically and an email will be send to principal investigator and the study coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local investigator can alert the principal investigator and the study coordinator via a SUSAR email button on the trial website.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[55] and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and informed consent

Patients will be recruited and their parents will be informed and asked for consent by the attending paediatricians. Informed written consent must be obtained from the parents prior to randomisation for the study. The patient information letter and informed consent are provided in section I of the study dossier. The right of a parent or patient to refuse participation without giving reasons will be respected. The parents will remain free to withdraw their child at any time from the study without consequences for further treatment.

10.3 Benefits and risks assessment, group relatedness

Burden: All infants participating in (either treatment arm of) the study are subjected to routine neonatal intensive care. The administration of the study intervention itself (hydrocortisone or placebo administration) does not pose an extra burden on the patients since intravenous access will be necessary for other clinical reasons. If this is no longer the case, study medication may be administered via the oral route. This study does not require extra investigations or interventions.

Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia, hypertension and systemic infection. Although the increased risk of gastrointestinal

perforation has up to now only been reported during the early (within the first 96 hours of life) administration of corticosteroids, the risk may also be increased when administering hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use of dexamethasone has been associated with an increase risk for neurodevelopmental sequelae. Historical cohort studies investigating the use of hydrocortisone after the first week of life have found no evidence to support this. Infants assigned to the placebo group will not benefit from the aforementioned possible beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any intervention aiming to reduce the risk of this complication therefore needs to be studied in this specific population at risk.

10.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives

Participants will not receive a financial compensation for participation as an incentive.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines. Patient data will be entered by way of an eCRF in a central GCP proof internet based database to facilitate on-site data-entry. Security is guaranteed with login names, login codes and encrypted data transfer. An experienced datamanager will maintain the database and check the information in the database for completeness, consistency and plausibility.

The data of all subjects will be coded and this coding will not be retraceable to the individual patient. The key to this coding is safeguarded by the investigator. A limited number of people have access to the source data. These are the principal investigator, investigating doctor and investigating personnel. Personal data are only processed by the researchers or by those who fall directly under their authority. In addition, the study monitor, quality assurance auditor, employees from the METC and the Health Care Inspectorate of the Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have access to the source data. All are subject to the pledge of confidentiality. Data and human material will be stored for 15 years strictly confidential.

11.2 Amendments

Amendments are changes made to the trial after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the Steering Committee.

11.3 Annual progress report

If requested, an annual progress report of the progress of the trial will be provided to the accredited METC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.4 Public disclosure and publication policy

The study will be registered in the EUDRACT, the website of the Dutch National Competent Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial registry, part of the WHO registry. The results of the study will be published in peer-reviewed international medical journals. In addition, the results of the study will be used for development and implementation of a guideline on treatment of BPD, which will benefit future patients.

12. ORGANISATION

12.1 Steering Committee

The Steering Committee is the main policy and decision making committee of the study and has final responsibility for the scientific conduct of the study. It will be composed of representatives of the sponsor, of the investigators of the participating centres and of the MCRN. The specific tasks of the Steering Committee are:

- Approve the study protocol
- Approve necessary changes in the protocol based on considerations of feasibility
- Act upon recommendations of the Data Monitoring Committee
- Review performance reports of the study sites
- Resolve operational problems brought before it by the project manager
- Approve study reports and papers for publication.

12.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be created specifically for this trial. The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a description of the membership, tasks and responsibilities of the DMC.

12.3 Clinical Project Manager / Central Study Coordinator

An experienced clinical project manager (CPM) from MCRN will manage the quality of the study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring process, and verify the quality of conduct of all study personnel. The CPM and/or clinical research associate (CRA) will arrange that the study personnel is adequately trained in GCP

and study protocol, where needed. The CPM meets regularly with the CRA, data managers, the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and all other relevant parties to assure study progress, quality and financials are according to planning. The CPM will coordinate regulatory authority and ethics committee submissions. The CPM provides regularly an overall study status report to the Steering Committee

12.4 Study Monitoring

The study will be monitored by an experienced monitor from MCRN throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence).

Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and wellbeing of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

12.5 Quality Assurance Audits and Inspections

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating this trial the investigator agrees to this requirement.

The clinical study may also be subject to inspection by regulatory authorities as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

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APPENDIX 1 STUDIE MEDICATIE SCHEMA

Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.	Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm	Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatticaly skip the next dose and commence the following dose with a lower daily frequency.	Step 4: For print out of study medication list, press: Print

Study identification
Name
Date of birth
Weight gram

First administration
Date/time
Lowering dosage regimen
Date/time

Day in regimen	Time	Times per day	mg/dose		Daily dose/kg
Day 1	0-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	0-01-00 6:00				
	0-01-00 12:00				
	0-01-00 18:00				
Day 2	1-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	1-01-00 6:00				
	1-01-00 12:00				
	1-01-00 18:00				
Day 3	2-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	2-01-00 6:00				
	2-01-00 12:00				
	2-01-00 18:00				
Day 4	3-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	3-01-00 6:00				
	3-01-00 12:00				
	3-01-00 18:00				
Day 5	4-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	4-01-00 6:00				
	4-01-00 12:00				
	4-01-00 18:00				
Day 6	5-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	5-01-00 6:00				
	5-01-00 12:00				
	5-01-00 18:00				
Day 7	6-01-00 0:00	4 x	0.00	mg.	5 mg/kg/d
	6-01-00 6:00				
	6-01-00 12:00				
	6-01-00 18:00				

Day in regimen	Time	Times per day	mg/dose		Daily dose/kg
Day 8	7-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	7-01-00 8:00				
	7-01-00 16:00				
Day 9	8-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	8-01-00 8:00				
	8-01-00 16:00				
Day 10	9-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	9-01-00 8:00				
	9-01-00 16:00				
Day 11	10-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	10-01-00 8:00				
	10-01-00 16:00				
Day 12	11-01-00 0:00	3 x	0.00	mg.	3.75 mg/kg/d
	11-01-00 8:00				
	11-01-00 16:00				
Day 13	12-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	12-01-00 12:00				
Day 14	13-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	13-01-00 12:00				
Day 15	14-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	14-01-00 12:00				
Day 16	15-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	15-01-00 12:00				
Day 17	16-01-00 0:00	2 x	0.00	mg.	2.5 mg/kg/d
	16-01-00 12:00				
Day 18	17-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 19	18-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 20	19-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 21	20-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d
Day 22	21-01-00 0:00	1 x	0.00	mg.	1.25 mg/kg/d

APPENDIX 2

Oxygen reduction test

Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe depending on the amount and duration of supplemental oxygen and the level of respiratory support. If a patient has received supplemental oxygen for more than 28 d (FiO_2 > 0.21 for more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is between 0.21 and 0.30, BPD is classified as moderate and in case of a FiO_2 > 0.30 and/or receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
It is important to realize that the duration of supplemental oxygen is highly dependent on target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician to actively wean oxygen delivery.
To make sure that patients receive supplemental oxygen for pulmonary reasons and to standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al. developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% ***or*** if they receive a FiO_2> 0.30 resulting in a SpO2 > 96%. Patients supported with nasal cannulae (flow not nCPAP) without supplemental oxygen, and patients treated with nCPAP/mechanical ventilation or with a FiO_2 > 0.30 resulting in a SpO2 < 96% do not need additional testing, and are, respectively, classified as having mild and severe BPD.

The oxygen reduction test

Indications:

- FiO_2 > 0.21 and < 0.30 with oxygen saturation ranges between 90% and 96%

- FiO_2 > 0.30 with a oxygen saturation range above 96%

Methods:

The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The supplemental oxygen requirement will be gradually weaned to room air while monitoring SpO_2. The diagnosis moderate BPD can be rejected when the SpO_2 remain above ≥ 88% in room air during 1 hour without apnea or bradycardia.

The diagnosis moderate BPD is confirmed if the saturation goes below 80% during >1minute or remains between 80-87% during > 5 minutes. All occurrences of movement artifact (defined as visible motion of the infant together with loss of pleythsmograph signal from the monitor) are recorded and corresponding saturation values are to be deleted.

The test contains 4 phases

Phase 1: Baseline evaluation

For 15 minutes heart rate, respiratory rate, SpO_2, number of apnea (cessation of breathing > 20 seconds) and bradycardia (hartrate < 80/min during > 10 sec) will be collected.

Phase 2: Oxygen reduction

The supplemental oxygen will be weaned by 2% to room air, after which the flow will be weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but not removed from the face.

Phase 3: Observation period

For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87% for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

Phase 4: Back to situation before the test

The level of supplemental oxygen and flow will be reset to the status before the test.