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Identifying effect modifiers of systemic hydrocortisone treatment initiated 7–14 days after birth in ventilated very preterm infants on long-term outcome: secondary analysis of a randomised controlled trial

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ABSTRACT

Objective To explore clinical effect modifiers of systemic hydrocortisone in ventilated very preterm infants for survival and neurodevelopmental outcome at 2 years' corrected age (CA).

Design Secondary analysis of a randomised placebo-controlled trial.

Setting Dutch and Belgian neonatal intensive care units.

Patients Infants born <30 weeks' gestational age (GA), ventilator-dependent in the second week of postnatal life.

Intervention Infants were randomly assigned to systemic hydrocortisone (cumulative dose 72.5 mg/kg; n=182) or placebo (n=190).

Main outcome measures The composite of death or neurodevelopmental impairment (NDI) at 2 years' CA and its components. Candidate effect modifiers (GA, small for GA, respiratory index, sex, multiple births, risk of moderate/severe bronchopulmonary dysplasia or death) were analysed using regression models with interaction terms and subpopulation treatment effect pattern plots.

Results The composite outcome was available in 356 (96.0%) of 371 patients (one consent withdrawn). For this outcome, treatment effect heterogeneity was seen across GA subgroups (<27 weeks: hydrocortisone (n=141) vs placebo (n=156), 54.6% vs 66.2%; OR 0.61 (95% CI 0.38 to 0.98); ≥27 weeks: hydrocortisone (n=30) vs placebo (n=31), 66.7% vs 45.2%; OR 2.43 (95% CI 0.86 to 6.85); p=0.02 for interaction). This effect was also found for the component death (<27 weeks: 20.1% vs 32.1%; OR 0.53 (95% CI 0.32 to 0.90); ≥27 weeks: 28.1% vs 16.1%; OR 2.04 (95% CI 0.60 to 6.95); p=0.049 for interaction) but not for the component NDI. No differential treatment effects were observed across other subgroups.

Conclusion This secondary analysis suggests that in infants <27 weeks' GA, systemic hydrocortisone may improve the outcome death or NDI, mainly driven by its

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study showed no difference in the primary composite outcome death or bronchopulmonary dysplasia and long-term composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age between both allocation groups in the total study population of infants born <30 weeks' gestation or with a birth weight <1250 g.

⇒ Previous subgroup analysis of the SToP-BPD Study at 36 weeks' postmenstrual age suggested a reduced death rate in favour of hydrocortisone in the gestational age subgroup below 27 weeks.

⇒ Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance.

WHAT THIS STUDY ADDS

⇒ This secondary analysis of the SToP-BPD trial suggests a potential beneficial systemic hydrocortisone treatment effect in the subgroup of ventilated preterm infants born before 27 weeks' gestation on the long-term composite outcome death or NDI, mainly driven by its component death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study provide further guidance for larger future clinical trials on postnatal corticosteroids to prevent bronchopulmonary dysplasia in patients with certain risk factors.

component death. There was insufficient evidence for other selected candidate effect modifiers.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) remains the most common morbidity of extreme prematurity.[1 2] Its pathogenesis is multifactorial, but pulmonary inflammation is considered an important risk factor.[3] Because of their anti-inflammatory effects, corticosteroids have been studied for the prevention and treatment of BPD.[4 5] The corticosteroid dexamethasone reduces the risk of BPD,[4] but has also been associated with an increased incidence of neurodevelopmental impairment (NDI).[6–8] The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study investigated if systemic hydrocortisone, started in the second week after birth in ventilator-dependent very preterm infants, would be an effective and safe alternative. It showed that hydrocortisone did not reduce the risk of death or BPD at 36 weeks' postmenstrual age (PMA),[9] and did not increase the risk of death or NDI at 2 years' corrected age (CA).[10]

The estimated overall treatment effect of the SToP-BPD Study reflects the average effect for the total study population. Yet, it is conceivable that infants with different characteristics may respond differently to the same intervention. Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance. Previous subgroup analysis of the SToP-BPD Study at 36 weeks' PMA for preselected patient characteristics suggested a differential treatment effect for the primary outcome component death across gestational age (GA) subgroups.[9] This illustrates that the treatment effect of hydrocortisone may vary across subpopulations of infants. It is unclear if effect modification also applies to the long-term outcome. Therefore, the objective of the current study was to explore potential clinical effect modifiers of hydrocortisone treatment on long-term survival and neurodevelopmental outcome at 2 years' CA of infants included in the SToP-BPD Study.

METHODS

Study population

The SToP-BPD Study is a double-blind, placebo-controlled, randomised trial, which was performed between November 2011 and December 2016 in 16 neonatal intensive care units in the Netherlands and Belgium.[9 11] It included infants born with a GA less than 30 weeks and/or with a birth weight below 1250 g who were ventilator dependent in the second week of life. Infants were randomly assigned to receive either a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg) or placebo.

Key long-term composite outcome and its individual components

Follow-up assessment at 2 years' CA was performed between April 2014 and June 2019. The key long-term outcome concerned the composite of death or NDI at 2 years' CA and its individual components. The estimated overall treatment effect on these outcomes was published previously.[10] NDI was defined as presence of one or more of the following: cognitive and/or motor composite score less than 85 on the Bayley Scales of Infant and Toddler Development Third Edition, Dutch version; cerebral palsy greater than level II on the Gross Motor Function Classification System; hearing or visual impairment. More details on definitions can be found in the online supplemental file 2.

Candidate treatment effect modifiers

Candidate treatment effect modifiers included the preselected risk factors GA, small for GA (SGA) (<10th percentile Fenton growth chart), respiratory index (mean airway pressure×fraction of inspired oxygen (FiO_2)) at randomisation, sex and multiple pregnancies (online supplemental file 2).[12] Information on the preselected risk factors parental education and multilingual environment was missing for the deceased infants; therefore, these were not included. The included candidate treatment effect modifiers are postulated, biologically plausible risk factors for BPD and death.[11 13] BPD is considered an important modifier of long-term outcome and is associated with neurodevelopmental delay.[14]

To evaluate whether the a priori risk of BPD would modulate the effect of hydrocortisone on survival and neurodevelopmental outcome, the Neonatal BPD Outcome Estimator, developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network was post hoc selected as a candidate effect modifier.[15] This composite risk score considers the simultaneous impact of GA, birth weight, race/ethnicity, sex, respiratory support and FiO_2 on the outcome death or BPD. Combination of individual risk factors in a composite risk score predicts more accurately the underlying individual infants' BPD risk and facilitates analysis across different risk distributions.[16] Since we had only access to the equation for postnatal day 1 and day 3, we used the model at postnatal day 3 and the respiratory settings at randomisation to calculate the individual predicted probability of moderate/severe BPD or death of each individual infant.

Statistical analysis

Data analyses were performed in the intention-to-treat population, including all randomised patients regardless of protocol deviations or use of open-label corticosteroids. Subgroups were categorised using prespecified cut-off points: GA groups (<27, ≥27 weeks), SGA (yes, no), respiratory index (≤median, >median of the total study population), sex (male, female) and multiple pregnancies (multiple births, singleton).[12] Crude relative and absolute treatment effect estimates within subgroups were calculated with the corresponding 95% CI. Treatment effect heterogeneity across subgroups was statistically tested through the corresponding (treatment×subgroup) interaction effect in a logistic regression model and generalised linear model including treatment, subgroup and (treatment×subgroup) interaction term (online supplemental file 3).[12] Within-subgroup treatment effects are estimated independent of whether the test of the specific interaction term is statistically significant.

Since dichotomising continuous variables may obscure important information that is contained across the full continuum of values, we explored post hoc treatment effect heterogeneity according to the candidate effect modifiers across their full spectrum of values, using subpopulation treatment effect pattern plots (STEPP).[17] STEPP is a non-parametric, graphical approach which constructs overlapping patient subpopulations along the continuum of the covariate, that is, a 'sliding-window' pattern of subpopulations. STEPP analysis improves the precision of the estimated treatment effects within the subgroups by plotting treatment effect estimates against the median values of the specific covariate in the subpopulations to provide a graphical presentation of the heterogeneity of treatment effects. STEPP

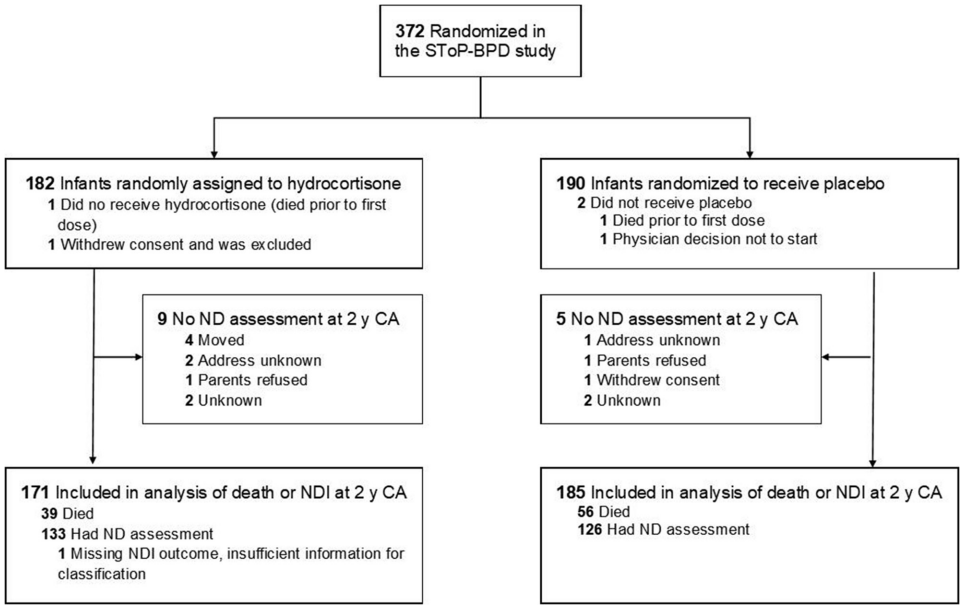

Figure 1 Consolidated Standards of Reporting Trials flow diagram. CA, corrected age; ND=neurodevelopmental; NDI, neurodevelopmental impairment; SToP-BPD, Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants.

makes no prior assumptions regarding the pattern of interaction and thus has the potential to highlight complex associations.[18] The STEPP analyses were performed according to the general guidelines as described by Yip *et al*.[17] Subpopulations were chosen using two window smoothing parameters r2 and r1, that is, a sample size of 100 infants per subset (r2) and an overlap of 50 infants (r1) between subsequent subsets, to create a minimum of four to five subgroups with 50% overlap. For a formal interaction test, the p value for interaction from a supremum test statistic is reported. To assess the consistency of the results, sensitivity analyses with varying sample size (r2) and varying overlap (r1) were performed.

All analyses were performed using two-sided tests and $p<0.05$ was regarded as statistically significant; as the analyses were hypothesis generating only, we did not adjust for multiple testing. Statistical analysis was performed in SPSS Statistics for Windows, V.28.0 (IBM Corp), R V.4.1.3 for Windows (R-package stepp and lattice; R Foundation for Statistical Computing) and RStudio.

RESULTS

The composite outcome death or NDI at 2 years' CA was available in 356 (96.0%) of 371 infants; 95 infants died before 2 years' follow-up, and neurodevelopment assessment was performed in 262 infants (one infant had a missing NDI outcome) (figure 1). Baseline characteristics of both treatment groups were similar, except for more multiple births in the hydrocortisone group (table 1).

Subgroup analyses showed a differential treatment effect across the dichotomised GA subgroups for the composite outcome of death or NDI at 2 years' CA, with a reduced rate in infants born before 27 weeks' gestation in the hydrocortisone group compared with the placebo group (<27 weeks: hydrocortisone (n=141) vs placebo (n=156), 54.6% vs 66.2%, crude absolute risk difference (ARD) −11.6% (95% CI −22.4% to −0.5%), crude OR 0.61 (95% CI 0.38 to 0.98); and ≥27 weeks: hydrocortisone (n=30) vs placebo (n=31), 66.7% vs 45.2%, crude ARD 21.5% (95% CI −3.2% to 42.8%), crude OR 2.43 (95% CI 0.86 to 6.85); p=0.02 for interaction tests) (figure 2A and online supplemental tables S1 and S2). This was also found for the component death (hydrocortisone vs placebo: <27 weeks, 20.1% vs 32.1%, crude ARD −11.9% (95% CI −21.4% to −2.1%); ≥27 weeks, 28.1% vs 16.1%; crude ARD 12.0% (95% CI −8.8% to 31.5%), p=0.04 for interaction test; crude OR <27 weeks, 0.53 (95% CI 0.32 to 0.90); crude OR ≥27 weeks, 2.04 (95% CI 0.60 to 6.95), p=0.049 for interaction test), but not for the NDI component (figure 2B,C and online supplemental tables S1 and S2). No differential treatment effects were observed across the subgroups of other preselected categorical candidate effect modifiers (figure 2A–C and online supplemental tables S1 and S2).

In line with the dichotomised GA subgroup analysis, STEPP suggested treatment effect heterogeneity for the composite outcome death or NDI and its component death, with benefit of

Table 1 Clinical characteristics at birth and at randomisation of infants with a composite outcome death or neurodevelopmental impairment at 2 years' corrected age

	Hydrocortisone (n=171)	Placebo (n=185)
Infant characteristics		
Gestational age, median (IQR), weeks	25.4 (24.9–26.4)	25.6 (24.7–26.4)
Birth weight, median (IQR), g	777 (640–865)	710 (628–810)
Male sex, n (%)	89 (52.0)	105 (56.8)
Small for gestational age, n (%)*	24 (14.0)	37 (20.0)
Multiple births, n (%)	66 (38.6)	51 (27.6)
Respiratory settings at randomisation		
High-frequency oscillatory ventilation, n (%)	95 (55.6)	86 (46.5)
Fraction of inspired oxygen, median (IQR)	0.35 (0.30–0.45)	0.34 (0.29–0.40)
Respiratory index, median (IQR)†	4.3 (3.3–5.4)	3.9 (3.1–5.0)
Predicted probability of moderate/severe BPD or death, median (IQR), %‡	88.7 (83.1–93.0)	90.2 (85.1–93.4)

*Small for gestational age was defined as birth weight less than the 10th percentile on the Fenton growth chart.
†Respiratory index was defined as mean airway pressure×fraction of inspired oxygen.
‡Predicted probability of moderate/severe BPD was calculated using the NICHD Neonatal BPD Outcome Estimator.
BPD, bronchopulmonary dysplasia; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

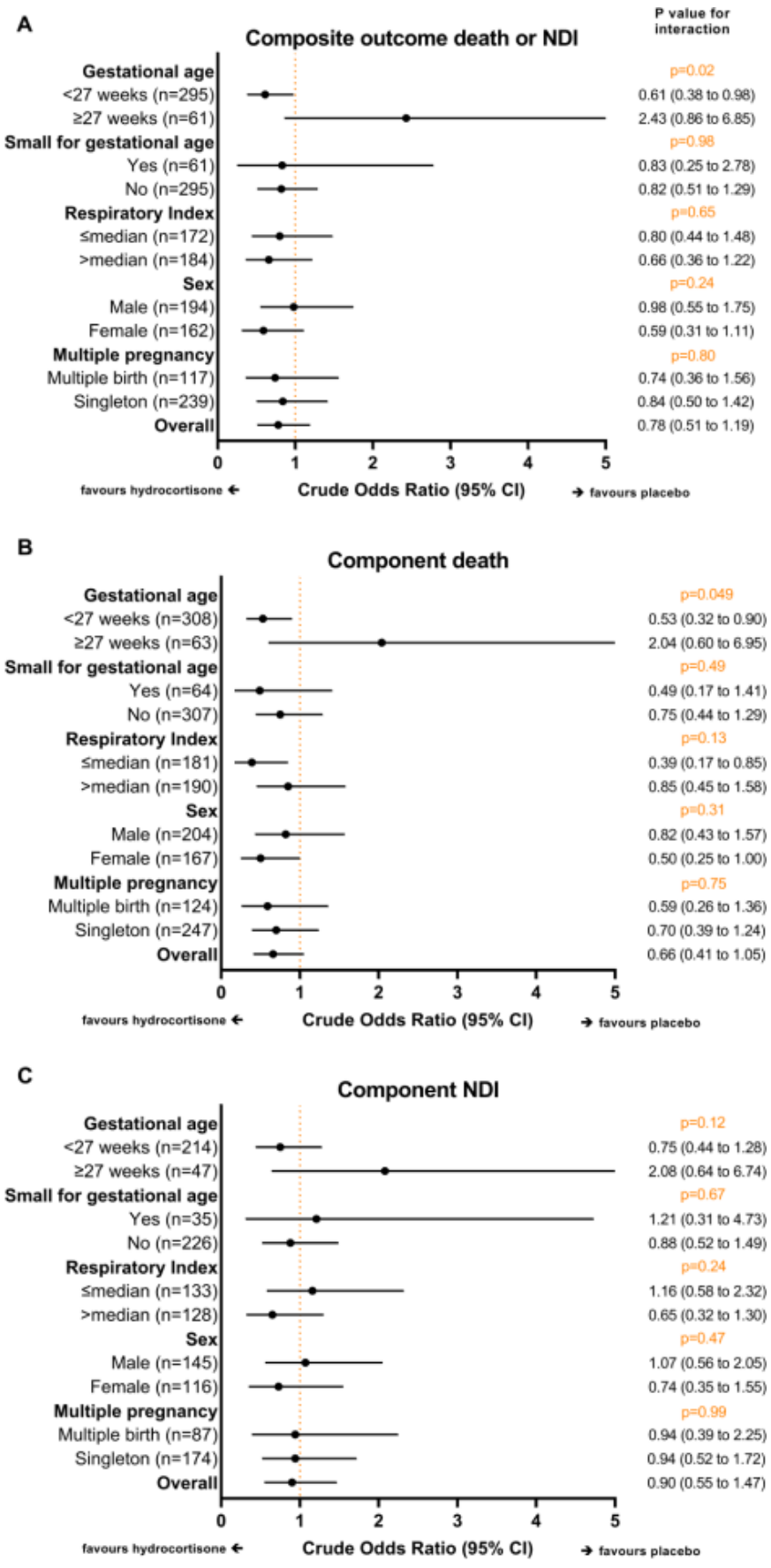

Figure 2 Forest plot of the subgroup analyses of the composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age (A) and its individual components (B,C) at 2 years' corrected age.[a] [a]Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in logistic regression models. P value for interaction is reported.

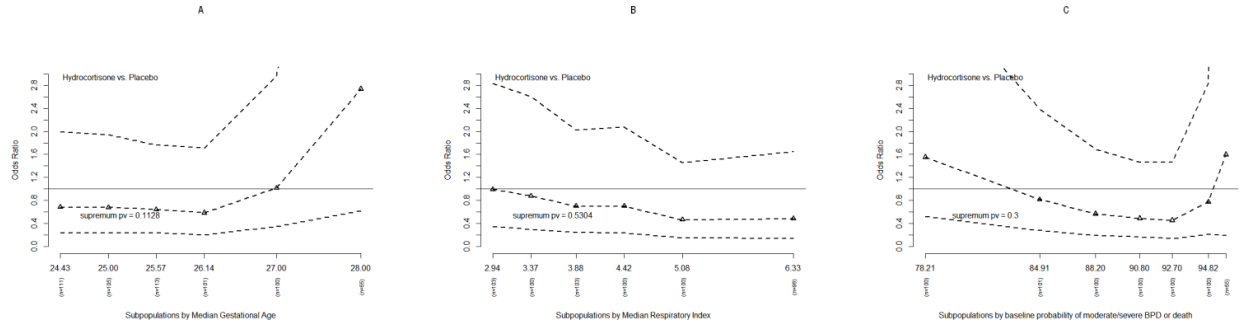

Figure 3 STEPP of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term outcome death or neurodevelopmental impairment at 2 years' corrected age, based on crude OR estimates.[a] [a]Subpopulations were chosen with sample size r2 of 100 infants per subset and overlap r1 of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% CIs of the OR per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction p values derived from permutation tests with 2500 resampling steps. An OR <1 indicates that hydrocortisone is the preferred strategy. BPD, bronchopulmonary dysplasia; STEPP, subpopulation treatment effect pattern plots.

hydrocortisone treatment across the GA range below 27 weeks, although this did not yield statistical significance (figure 3A and online supplemental figures 1A and 2A). Exploration of patterns of treatment effects for varying levels of respiratory index and probability of moderate/severe BPD or death following the NICHD Neonatal BPD Outcome Estimator suggested no clear treatment heterogeneity across subpopulations for the composite outcome and its individual components (figure 3B,C and online supplemental figures 2 and 3). Sensitivity STEPP analyses yielded results (online supplemental table 3).

DISCUSSION

This prespecified secondary analysis of the SToP-BPD trial is to our knowledge the first study exploring potential clinical effect modifiers of hydrocortisone treatment initiated in the second week after birth in ventilated very preterm infants for long-term survival and neurodevelopmental outcome. We observed a modifying treatment effect of GA; infants born before 27 weeks' gestation had a significantly reduced rate of the composite outcome death or NDI at 2 years' CA in favour of hydrocortisone, mainly driven by a reduction in death. No other selected candidate treatment effect modifiers showed sufficient evidence of a differential hydrocortisone treatment effect.

Lower GA is an important risk factor for neonatal morbidities, including an inverse relation with impaired neurodevelopmental outcome.[19 20] Consequently, it is conceivable that the most immature infants may have a different risk profile than more mature infants and may respond differently to hydrocortisone treatment. An exploratory analysis of the PREMILOC Study, a randomised trial involving prophylactic hydrocortisone treatment, suggested a differential hydrocortisone effect in GA subgroups for neurodevelopmental outcome. The authors reported a significant improvement in neurodevelopmental outcomes following hydrocortisone treatment in the subgroup of infants born at 24–25 weeks' gestation, which was not the case in the subgroup of infants born at 26–27 weeks' gestation.[21] This improvement in neurodevelopment in the specific subgroup of infants born at 24–25 weeks of gestation was not observed in our STEPP for GA. Important differences between the two studies in patient characteristics, dosage and timing of hydrocortisone treatment may explain this discrepancy.

In the initial SToP-BPD Study, subgroup analyses were performed for the primary outcome death or BPD at 36 weeks' PMA and its components.[9] Across categorical GA subgroups (<27 or ≥27 weeks), a differential treatment effect was found for the component death, with a reduced rate in favour of hydrocortisone in the GA subgroup below 27 weeks. Consistent with this earlier finding at 36 weeks' PMA, the current study also observed a statistically significant and clinically relevant reduction in mortality at 2 years' CA in favour of hydrocortisone in infants born below 27 weeks' gestation. Importantly, our results suggest that this improved survival was not associated with an increased risk of NDI. The small size of the GA subgroup ≥27 weeks and the consequently wide CI provide too little information for inference about the treatment effect in this subgroup.

For further inspection, we used post hoc STEPP analysis to explore the effect of hydrocortisone along the continuum of GA, respiratory index and the probability of moderate/severe BPD or death. STEPP has the advantage over the more conventional approach of categorisation of a continuous covariate, that it provides more insight into the effect along the range of covariate values, and where treatment may be particularly beneficial (or detrimental). STEPP is an exploratory tool, not intended to set specific cut-off points for subgroups, but rather to provide some indication on ranges of values where the treatment effect might have a particular behaviour.[17 18] Hence, it facilitates hypothesis generation and provides guidance for future research. The STEPP of treatment effect heterogeneity for GA supported the results of the prespecified dichotomised subgroup analysis, though not statistically significant. Additional analyses of treatment effect heterogeneity for GA should be considered in other studies of hydrocortisone treatment.

In daily practice, the decision to start postnatal corticosteroids is often guided by the severity of the patients' respiratory condition and the presumed risk of BPD. This is probably based on a meta-regression analysis of randomised controlled trials investigating dexamethasone that suggests that the effect of postnatal corticosteroids on the combined outcome death or cerebral palsy varies with the underlying baseline risk of BPD. Infants at higher risk of BPD seem to benefit from postnatal dexamethasone treatment, while treating infants at low risk of BPD might be harmful.[16] We found no clear treatment effect heterogeneity for the key long-term composite outcome and its components across the range of probabilities for moderate/severe BPD or death, calculated with the NICHD Neonatal BPD Outcome Estimator.[15] This lack of treatment effect heterogeneity may partly be explained by the fact that the SToP-BPD Study included ventilator-dependent very preterm infants with a respiratory index above 2.5. These criteria resulted in a narrow distribution of the probabilities of moderate/severe BPD or death as almost

all infants in our study were classified as high risk. Furthermore, the NICHD Neonatal BPD Outcome Estimator is based on the US population and is not yet validated in the Dutch/Belgian population, so it remains unclear how it will perform in the SToP-BPD Study population. Additional analyses for heterogeneity of the hydrocortisone treatment effect are needed in other clinical studies to gain more insight.

Our study has some limitations. First, the SToP-BPD Study was only powered for the overall treatment effect on the primary composite outcome death or BPD at 36 weeks' PMA.[9] Due to the small numbers within various subgroups, there is limited statistical power to identify subgroups that might have a differential effect of hydrocortisone treatment. Also, except for the randomisation stratification factor GA, interpretation of the other subgroups is hampered by potential confounder imbalance. Therefore, this secondary analysis of the SToP-BPD Study should be regarded as exploratory and hypothesis generating only. Second, STEPP analysis is sensitive to the choices of subgroup sample size (r2) and overlap between subsequent subgroups (r1).[17 18] However, our sensitivity analyses with varying r1 and r2 showed similar patterns of heterogeneity. Third, a relatively high proportion of infants in the placebo group (56.8%) was treated with open-label hydrocortisone, particularly those with a GA below 27 weeks. Although no firm conclusions can be drawn, it is unlikely that this impacted the subgroup analyses, as a previous published meta-regression analysis showed no modulating effect of open-label steroids on long-term outcomes.[22]

CONCLUSIONS

This secondary analysis of the SToP-BPD trial suggests that in the subgroup of ventilated preterm infants born before 27 weeks' gestation, systemic hydrocortisone initiated in the second week after birth may improve the composite outcome death or NDI, mainly driven by its component death. There was insufficient evidence for the other selected candidate treatment effect modifiers. The findings of this study require confirmation in larger future trials.

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Contributors MS, RMS, CK-E, MvS, SM-dT, RNGBT, TM, EB, KS, BWK, AD, MMvW, YM, HG, KP, MO and AGvW-L are local investigators at the participating centres, and made substantial contributions to the concept and design of the study, and interpretation of data. NMH performed the statistical analyses, prepared the data tables, drafted the initial manuscript and revised the manuscript. MPM participated in the statistical analyses, and critically reviewed and revised the manuscript for important intellectual content. WO and AHvK are local investigators who made substantial contributions to the concept and design of the study, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted. AHvK is the guarantor.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010_297) and the local Ethics Committee of each participating hospital. Written informed consent was obtained from both parents before randomisation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocol, the statistical analysis plan and the analytical code. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Professor Anton van Kaam (email: a.h.vankaam@amsterdamumc.nl).

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Online supplementary content

eTable 1. Absolute risk differences for subgroup analyses of the composite outcome and its components at two years' corrected age.

eTable 2. Effect sizes of the differences in treatment effects between subgroups (i.e. treatment-by-subgroup interaction effect): ratio of odds ratios and difference of absolute risk differences, hydrocortisone vs. placebo, with corresponding confidence intervals and P value.

eTable 3. Sensitivity analysis: impact of *r1* and *r2* on the key long term composite outcome (death or neurodevelopmental impairment at two years' corrected age.

eFigure 1. STEPP plots of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term composite outcome death or neurodevelopmental impairment (NDI) at two years' corrected age based on crude absolute risk difference estimates.

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Original protocol and amendments SToP-BPD study

Supplement to Statistical Analysis Plan – SAP for the long-term outcomes at two years' corrected age of the SToP-BPD study

Halbmeijer NM, *et al. Arch Dis Child Fetal Neonatal Ed* 2023;0:1–7. doi: 10.1136/archdischild-2023-325558

eTable 1. Absolute risk differences for subgroup analyses of the composite outcome and its components at two years' corrected age.

	Hydrocortisone	Placebo	Difference, % (95% CI)	P value for interaction test[a]
Composite outcome death or NDI				
Overall	97/171 (56.7)	116/185 (62.7)	-6.0 (-16.0 to 4.2)	NA
Subgroups				
Gestational age < 27 weeks	77/141 (54.6)	102/154 (66.2)	-11.6 (-22.4 to -0.5)	0.02
Gestational age ≥ 27 weeks	20/30 (66.7)	14/31 (45.2)	21.5 (-3.2 to 42.8)	
Small for gestational age: yes	18/24 (75.0)	29/37 (78.4)	-3.4 (-25.8 to 16.9)	0.89
Small for gestational age: no	79/147 (53.7)	87/148 (58.8)	-5.0 (-16.1 to 6.2)	
Respiratory index: ≤ median	36/70 (51.4)	58/102 (56.9)	-5.4 (-20.1 to 9.5)	0.70
Respiratory index: > median	61/101 (60.4)	58/83 (69.9)	-9.5 (-22.6 to 4.4)	
Male	53/89 (59.6)	63/105 (60.0)	-0.4 (-14.1 to 13.1)	0.24
Female	44/82 (53.7)	53/80 (66.3)	-12.6 (-26.8 to 2.5)	
Multiple birth	34/66 (51.5)	30/51 (58.8)	-7.3 (-24.4 to 10.6)	0.78
Singleton	63/105 (60.0)	86/134 (64.2)	-4.2 (-16.4 to 8.0)	
Component death at 2 years' CA				
Overall	39/181 (21.5)	56/190 (29.5)	-7.9 (-16.6 to 1.0)	NA
Subgroups				
Gestational age < 27 weeks	30/149 (20.1)	51/159 (32.1)	-11.9 (-21.4 to -2.1)	0.04
Gestational age ≥ 27 weeks	9/32 (28.1)	5/31 (16.1)	12.0 (-8.8 to 31.5)	
Small for gestational age: yes	8/26 (30.8)	18/38 (47.4)	-16.6 (-37.6 to 7.7)	0.37
Small for gestational age: no	31/155 (20.0)	38/152 (25.0)	-5.0 (-14.3 to 4.4)	
Respiratory index: ≤ median	10/77 (13.0)	29/104 (27.9)	-14.9 (-25.8 to -2.8)	0.20
Respiratory index: > median	29/104 (27.9)	27/86 (31.4)	-3.5 (-16.5 to 9.3)	
Male	21/95 (22.1)	28/109 (25.7)	-3.6 (-15.0 to 8.3)	0.27
Female	18/86 (20.9)	28/81 (34.6)	-13.6 (-26.7 to -0.07)	
Multiple birth	14/70 (20.0)	16/54 (29.6)	-9.6 (-24.9 to 5.4)	0.78
Singleton	25/111 (22.5)	40/136 (29.4)	-6.9 (-17.5 to 4.2)	
Component NDI at 2 years' CA				
Overall	58/132 (43.9)	60/129 (46.5)	-2.6 (-14.4 to 9.4)	NA
Subgroups				
Gestational age < 27 weeks	47/111 (42.3)	51/103 (49.5)	-7.2 (-20.1 to 6.1)	0.12
Gestational age ≥ 27 weeks	11/21 (52.4)	9/26 (34.6)	17.8 (-9.9 to 42.3)	
Small for gestational age: yes	10/16 (62.5)	11/19 (57.9)	4.6 (-25.9 to 33.4)	0.66
Small for gestational age: no	48/116 (41.4)	49/110 (44.5)	-3.2 (-15.8 to 9.6)	
Respiratory index: ≤ median	26/60 (43.3)	29/73 (39.7)	3.6 (-12.8 to 19.9)	0.24
Respiratory index: > median	32/72 (44.4)	31/56 (55.4)	-10.9 (-27.3 to 6.4)	
Male	32/68 (47.1)	35/77 (45.5)	1.6 (-14.3 to 17.4)	0.47
Female	26/64 (40.6)	25/52 (48.1)	-7.5 (-24.8 to 10.4)	
Multiple birth	20/52 (38.5)	14/35 (40.0)	-1.5 (-21.9 to 18.3)	0.99
Singleton	38/80 (47.5)	46/94 (48.9)	-1.4 (-16.0 to 13.2)	

Data are n (%) unless stated differently. CI=confidence interval, NA=not applicable, NDI=neurodevelopmental impairment, CA=corrected age.

[a] Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in Generalized Linear Models with identity link function and binomial distribution, P-value for interaction is reported.

eTable 2. Effect sizes of the differences in treatment effects between subgroups (i.e. treatment-by-subgroup interaction effect): ratio of odds ratios and difference of absolute risk differences, hydrocortisone vs. placebo, with corresponding confidence intervals and P value.

	Ratio of odds ratio's, (95% CI)	**P value for interaction test[a]**	**Difference of absolute risk differences, % (95% CI)**	**P value for interaction test[b]**
Composite outcome death or NDI				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.25 (0.08 to 0.79)	0.02	-33.1 (-59.9 to -6.4)	0.02
Small for gestational age (yes vs. no)	1.02 (0.28 to 3.71)	0.98	1.7 (-22.9 to 26.2)	0.89
Respiratory index (≤ vs. > median)	1.22 (0.52 to 2.91)	0.65	4.0 (-16.4 to 24.5)	0.70
Sex (female vs. male)	0.60 (0.26 to 1.42)	0.24	-12.1 (-32.5 to 8.2)	0.24
Multiple pregnancy (singleton vs. multiple birth)	1.13 (0.46 to 2.79)	0.80	3.1 (-18.8 to 25.1)	0.78
Component death at 2 years' CA				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.26 (0.07 to 0.997)	0.049	-23.9 (-46.4 to -1.5)	0.04
Small for gestational age (yes vs. no)	0.66 (0.20 to 2.14)	0.49	-11.6 (-37.2 to 14.0)	0.37
Respiratory index (≤ vs. > median)	0.46 (0.17 to 1.25)	0.13	-11.4 (-28.7 to 6.0)	0.20
Sex (female vs. male)	0.61 (0.24 to 1.58)	0.31	-10.1 (-27.9 to 7.8)	0.27
Multiple pregnancy (singleton vs. multiple birth)	1.18 (0.43 to 3.22)	0.75	2.7 (-16.1 to 21.6)	0.78
Component NDI at 2 years' CA				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.36 (0.10 to 1.32)	0.12	-24.9 (-56.1 to 6.2)	0.12
Small for gestational age (yes vs. no)	1.38 (0.32 to 5.94)	0.67	7.8 (-27.2 to 42.7)	0.66
Respiratory index (≤ vs. > median)	1.80 (0.67 to 4.83)	0.24	14.5 (-9.7 to 38.7)	0.24
Sex (female vs. male)	0.69 (0.26 to 1.86)	0.47	-9.1 (-33.4 to 15.3)	0.47
Multiple pregnancy (singleton vs. multiple birth)	1.01 (0.35 to 2.91)	0.99	0.1 (-25.6 to 25.8)	0.99

CA=corrected age, CI=confidence interval, NDI=neurodevelopmental impairment

[a] Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in logistic regression models, P-value for interaction is reported.

[b] Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in Generalized Linear Models with identity link function and binomial distribution, P-value for interaction is reported.

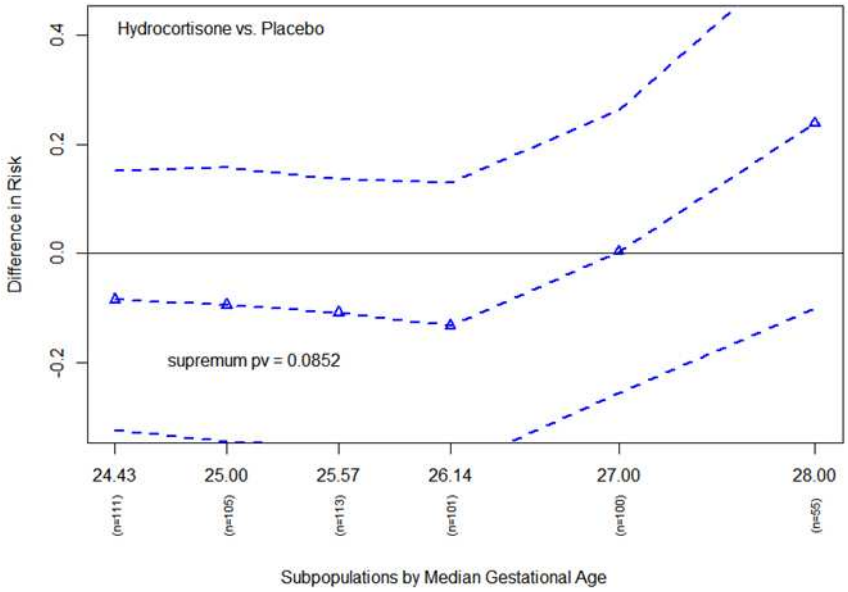
eTable 3. Sensitivity analysis: impact of *r1* and *r2* on the key long term composite outcome (death or neurodevelopmental impairment at two years' corrected age.

Candidate treatment effect modifier	*r2*	*r1*	*r1/r2*	# of subpopulations	Supremum P-value based on odds ratio estimates	Supremum P-value based on absolute risk difference estimates
Gestational age						
	100	30	30%	5	0.632	0.422
		50	50%	6	0.113	0.085
		70	70%	8	0.445	0.386
	80	24	30%	5	0.248	0.208
		40	50%	7	0.346	0.309
		56	70%	9	0.327	0.251
Respiratory index						
	100	30	30%	5	0.194	0.227
		50	50%	6	0.534	0.605
		70	70%	9	0.044	0.175
	80	24	30%	6	0.087	0.212
		40	50%	8	0.253	0.506
		56	70%	12	0.129	0.263
Predicted probability of moderate/severe BPD or death						
	100	30	30%	5	0.256	0.215
		50	50%	7	0.300	0.241
		70	70%	10	0.108	0.126
	80	24	30%	6	0.147	0.104
		40	50%	8	0.161	0.114
		56	70%	13	0.238	0.173

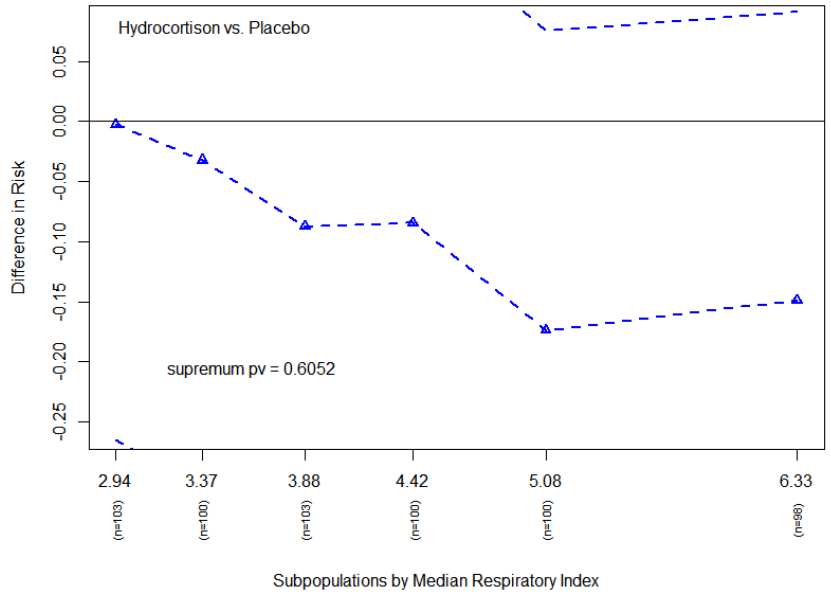
BPD=bronchopulmonary dysplasia.

eFigure 1. STEPP plots of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term composite outcome death or neurodevelopmental impairment (NDI) at two years' corrected age based on crude absolute risk difference estimates.

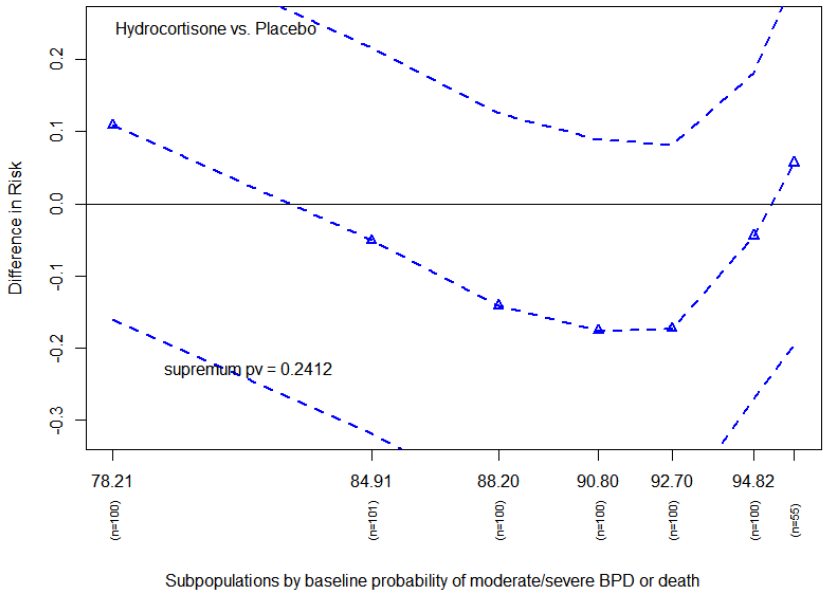
A. Composite outcome death or NDI by gestational age.



B. Composite outcome death or NDI by respiratory index.



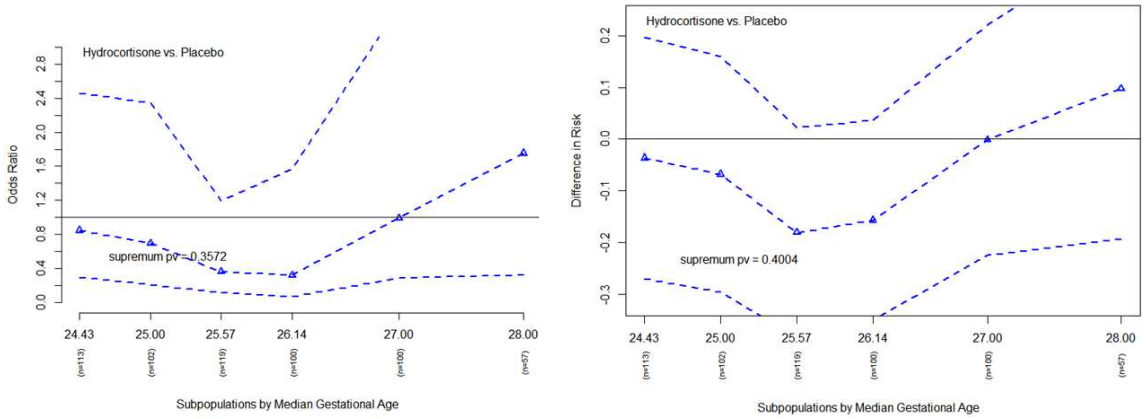
C. Composite outcome death or NDI by predicted probability of moderate/severe BPD or death.



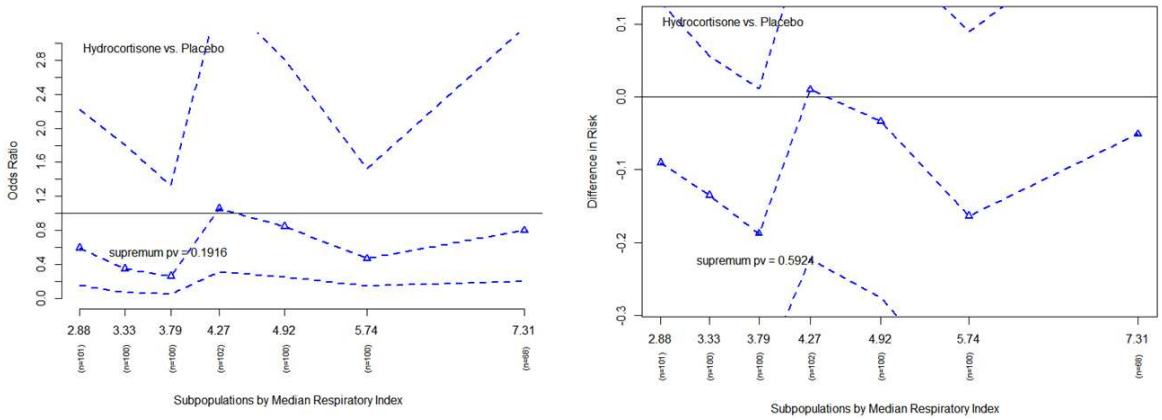
Subpopulations were chosen with sample size *r2* of 100 infants per subset and overlap *r1* of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction *p* values derived from permutations tests with 2500 resampling steps. A risk difference < 0 indicates that hydrocortisone is the preferred strategy.

eFigure 2. STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component death at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

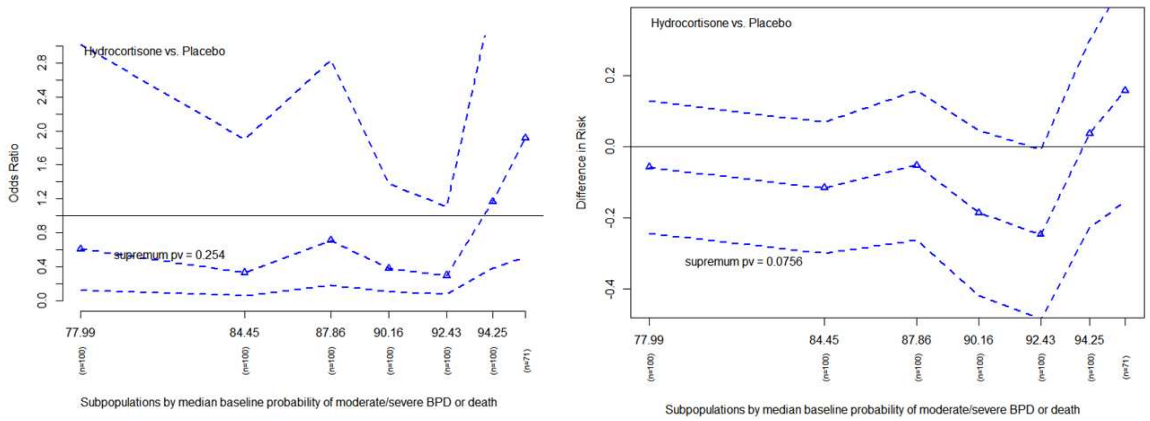
A. Component death by gestational age.



B. Component death by respiratory index.



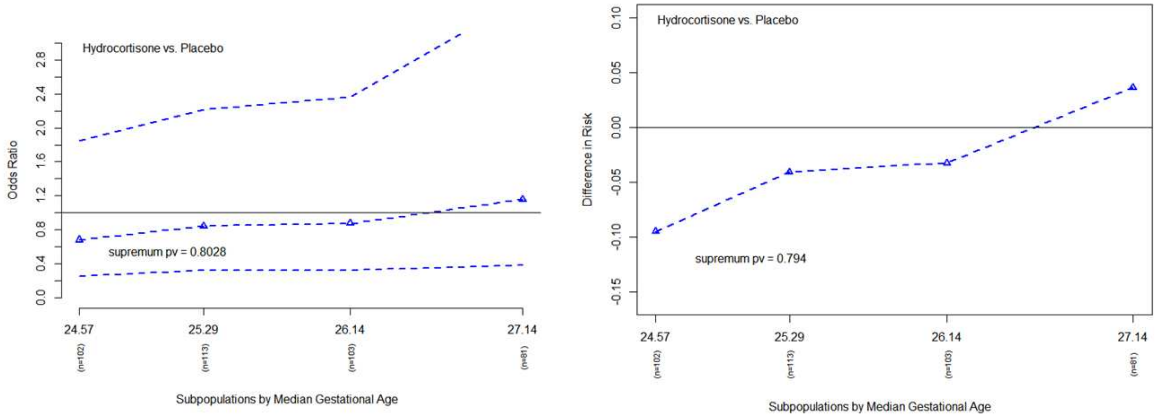
C. Component death by predicted probability of moderate/severe BPD or death.



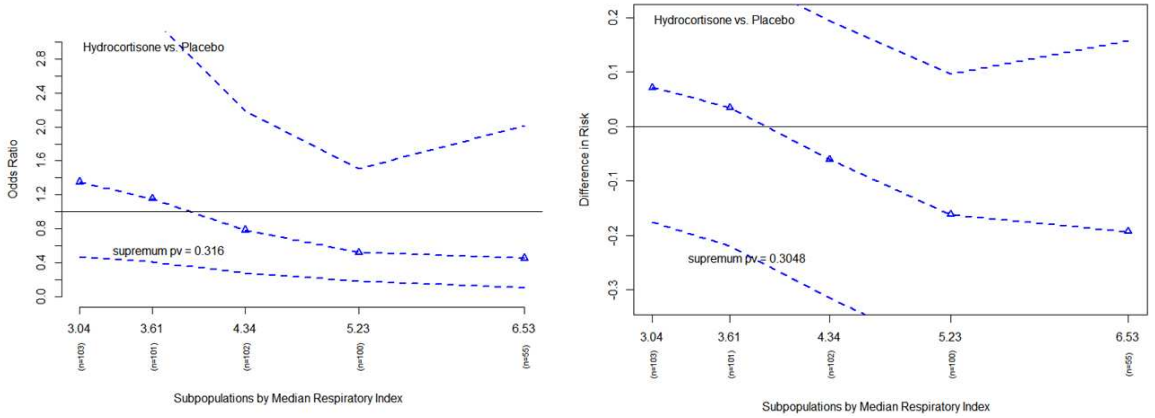
Subpopulations were chosen with sample size *r2* of 100 infants per subset and overlap *r1* of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the odds ratio and absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction *p* values derived from permutations tests with 2500 resampling steps. An odds ratio < 1 indicates that hydrocortisone is the preferred strategy; an absolute risk difference < 0 indicates that hydrocortisone is the preferred strategy.

eFigure 3. STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component neurodevelopmental impairment (NDI) at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

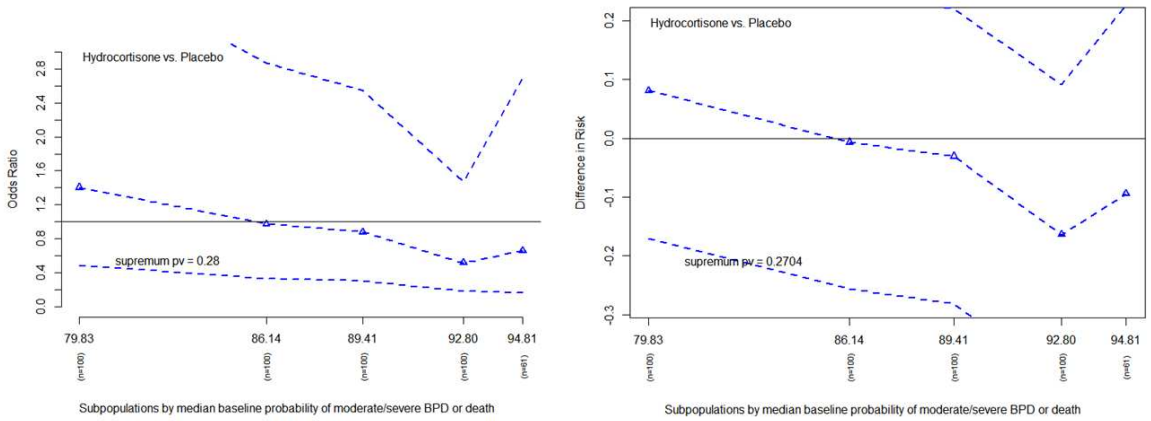
A. Component NDI by gestational age.



B. Component NDI by respiratory index.



C. Component NDI by predicted probability of moderate/severe BPD or death.



Subpopulations were chosen with sample size *r2* of 100 infants per subset and overlap *r1* of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the odds ratio and absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction *p* values derived from permutations tests with 2500 resampling steps. An odds ratio < 1 indicates that hydrocortisone is the preferred strategy; an absolute risk difference < 0 indicates that hydrocortisone is the preferred strategy.

Original protocol and amendments STOP-BPD study

In this document we have collected all versions of the STOP-BPD 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*.

Halbmeijer NM, *et al. Arch Dis Child Fetal Neonatal Ed* 2023;0:1–7. doi: 10.1136/archdischild-2023-325558

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	1
Date	18 november 2010
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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.

196 **1. BACKGROUND**

197 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
198 with a reported incidence of 8% to 35%.[1,2] BPD is characterized by chronic respiratory
199 distress, the need for prolonged respiratory support, an increased risk of recurrent
200 pulmonary infections, airway hyperreactivity during the first years of life[3] and life-long
201 alterations in lung function.[4-6] Patients with established BPD have high rates of readmissions
202 and utilization of health services resulting in tremendous societal costs compared to children
203 without BPD.[7-9] Furthermore, BPD is considered an important risk factor for adverse
204 neurodevelopmental outcome after premature birth[10-14] with life-long economic and social
205 consequences.[15-18]
206
207 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
208 pulmonary inflammation has been identified as an important mediator in the development
209 of BPD.[19-21] This is the rationale for treating patients with glucocorticoids, a well known anti-
210 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
211 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
212 the risk of the combined outcome death or BPD in ventilated preterm infants.[22-24]
213 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
214 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
215 onset.[25,26] However, initiating dexamethasone treatment in the first days of life seems to be
216 associated with an increased the risk of cerebral palsy (CP). Although this complication has
217 not been reported by RCTs investigating dexamethasone treatment initiated after the first
218 week of life, these alarming reports have resulted in a general concern on the use of
219 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)

316 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung
317 function and respiratory status
318
319 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and
320 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses
321 are know to be independent risk factors for developing BPD. Therefore, these diagnoses are
322 not considered to be exclusion criteria. The following should be taken into consideration:
323 1. In ventilator-dependent cases of sepsis and pneumonia the attending physician may
324 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48
325 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for
326 inclusion.
327 2. It is strongly recommended to screen all ventilator-dependent preterm infants for a
328 PDA at 5 days PNA. In case of a hemodynamic important PDA, medical intervention
329 according to local protocols should be started as soon as possible. Ibuprofen or
330 indomethacin treatment should not be combined with glucocorticoids, because it has
331 been suggested that this combination will increase the risk of intestinal perforation.
332 If, subsequently, the patient can't be extubated following medical treatment or
333 requires surgical PDA closure, he/she should be included in the study - provided that
334 all inclusion criteria are met.
335 3. If the physician considers extubation not an option because of the general condition
336 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
337 distension) inclusion in the study can be postponed until the maximum of 14 days
338 PNA.
339

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.

724 Data Monitoring Committee

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

728

729 Clinical Project Manager / Central Study Coordinator

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

739

740 Study Monitoring

741 The study will be monitored by an experienced monitor from MCRN throughout its duration
742 by means of personal visits to the Investigator's facilities and through other communications
743 (e.g., telephone calls, written correspondence).
744 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the
745 study and at frequency deemed appropriate for the study.
746 These visits will be conducted to evaluate the progress of the study, ensure the rights and
747 wellbeing of the subjects are protected, check that the reported clinical study data are
748 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
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APPENDIX 39

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.

12. REFERENCES

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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
3-jan-11	5 mg/kg/dg	4 x	0 mg.
4-jan-11	5 mg/kg/dg	4 x	0 mg.
5-jan-11	5 mg/kg/dg	4 x	0 mg.
6-jan-11	5 mg/kg/dg	4 x	0 mg.
7-jan-11	5 mg/kg/dg	4 x	0 mg.
8-jan-11	5 mg/kg/dg	4 x	0 mg.
9-jan-11	5 mg/kg/dg	4 x	0 mg.
10-jan-11	3.75 mg/kg/dg	3 x	0 mg.
11-jan-11	3.75 mg/kg/dg	3 x	0 mg.
12-jan-11	3.75 mg/kg/dg	3 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.

	Dagdosis per lichaamsgewicht	Frequentie	mg/dosis
15-jan-11	2.5 mg/kg/dg	2 x	0 mg.
16-jan-11	2.5 mg/kg/dg	2 x	0 mg.
17-jan-11	2.5 mg/kg/dg	2 x	0 mg.
18-jan-11	2.5 mg/kg/dg	2 x	0 mg.
19-jan-11	2.5 mg/kg/dg	2 x	0 mg.
20-jan-11	1.25 mg/kg/dg	1 x	0 mg.
21-jan-11	1.25 mg/kg/dg	1 x	0 mg.
22-jan-11	1.25 mg/kg/dg	1 x	0 mg.
23-jan-11	1.25 mg/kg/dg	1 x	0 mg.
24-jan-11	1.25 mg/kg/dg	1 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.

2068 PROTOCOL

2069 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**

2070 **infants: the SToP-BPD study**

2071 **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
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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 ($MAwP \times FiO_2$) 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.

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:*

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.

2940 **12.2 Data Monitoring Committee**

2941 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.
2942 The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a
2943 description of the membership, tasks and responsibilities of the DMC.

2944

2945 **12.3 Clinical Project Manager / Central Study Coordinator**

2946 An experienced clinical project manager (CPM) from MCRN will manage the quality of the
2947 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring
2948 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical
2949 research associate (CRA) will arrange that the study personnel is adequately trained in GCP
2950 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,
2951 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and
2952 all other relevant parties to assure study progress, quality and financials are according to
2953 planning. The CPM will coordinate regulatory authority and ethics committee submissions.
2954 The CPM provides regularly an overall study status report to the Steering Committee

2955

2956 **12.4 Study Monitoring**

2957 The study will be monitored by an experienced monitor from MCRN throughout its duration
2958 by means of personal visits to the Investigator's facilities and through other communications
2959 (e.g., telephone calls, written correspondence).
2960 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the
2961 study and at frequency deemed appropriate for the study.
2962 These visits will be conducted to evaluate the progress of the study, ensure the rights and
2963 wellbeing of the subjects are protected, check that the reported clinical study data are
2964 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		First administration	
Name		Date/time	
Date of birth		Lowering dosage regimen	
Weight	gram	Date/time	

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

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

3241 PROTOCOL

3242 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**

3243 **infants: the SToP-BPD study**

3244 **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

4003 outcome data are available. Data summaries for the DMC will be prepared by a statistician
4004 who is not a member of the investigating team. The safety data will include, but not be
4005 restricted to, serious adverse events and the safety outcomes listed as secondary outcomes.
4006 The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the
4007 data manager will be stand-by to reveal the allocation labels if the DMC thinks this is
4008 necessary. If the DMC recommends modification or cessation of the study protocol, this will
4009 be discussed with the Steering Committee, who will make the decision. The DMC will be
4010 composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician
4011 who has experience with trials, and some experience on previous DMCs and a
4012 pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in
4013 neonates. The Steering Committee will propose a detailed mandate and review this with the
4014 DMC, from the outset. Identification and circulation of external evidence (e.g., from other
4015 trials/systematic reviews) is not the responsibility of the DMC members. It is the
4016 responsibility of the PI to provide any such information to the DMC.
4017
4018 To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been
4019 added to the CRF and the website (SUSAR), “The Alert Procedure”. This tool is used to
4020 monitor special conditions and acute situations that need the direct attention of the
4021 principle investigator and the study coordinator. If necessary the Steering Committee can
4022 decide to alert the DMC. Furthermore, the Steering Committee will provide a summary
4023 report after every 10 alerts to the DMC.
4024
4025 There are 5 situations when the **Alert Procedure** must be used:
4026 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.

4052 **10.3 Benefits and risks assessment, group relatedness**

4053 Burden: All infants participating in (either treatment arm of) the study are subjected to
4054 routine neonatal intensive care. The administration of the study intervention itself
4055 (hydrocortisone or placebo administration) does not pose an extra burden on the patients
4056 since intravenous access will be necessary for other clinical reasons. If this is no longer the
4057 case, study medication may be administered via the oral route. This study does not require
4058 extra investigations or interventions.
4059 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
4060 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
4061 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
4062 hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia,
4063 hypertension and systemic infection. Although the increased risk of gastrointestinal
4064 perforation has up to now only been reported during the early (within the first 96 hours of
4065 life) administration of corticosteroids, the risk may also be increased when administering
4066 hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use
4067 of dexamethasone has been associated with an increase risk for neurodevelopmental
4068 sequelae. Historical cohort studies investigating the use of hydrocortisone after the first
4069 week of life have found no evidence to support this. Infants assigned to the placebo group
4070 will not benefit from the aforementioned possible beneficial effects nor be subjected to the
4071 possible adverse effect of hydrocortisone.
4072 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
4073 intervention aiming to reduce the risk of this complication therefore needs to be studied in
4074 this specific population at risk.
4075

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		First administration	
Name		Date/time	
Date of birth		Lowering dosage regimen	
Weight	gram	Date/time	

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

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

4449
4450 PROTOCOL

4451 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**
4452 **infants: the SToP-BPD study**
4453 **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.

4596 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
4597 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
4598 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
4599 hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension,
4600 systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However,
4601 gastrointestinal perforation and delayed neurodevelopment have only been reported in
4602 studies administering corticosteroids in the first week of life and/or during combinations
4603 with other medication. In this study the risk of gastrointestinal perforation and delayed
4604 neurodevelopment may be reduced because hydrocortisone will be administered after the
4605 first week of life and combinations with other drugs will be avoided as much as possible.
4606 Infants assigned to the placebo group will not benefit from the aforementioned possible
4607 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.
4608 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
4609 intervention aiming to reduce the risk of this complication therefore needs to be studied in
4610 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

4635 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
4636 have stated that clinical trials should be performed to investigate the use of alternative anti-
4637 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.[30,31]
4638
4639 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
4640 approximately 10% of the preterm infants at risk for BPD.[32-34] Dexamethasone is still the
4641 most widely used glucocorticoid drug, but its dose has been significantly reduced and
4642 administration is often postponed until the 3rd or 4th week of life.[27]
4643
4644 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
4645 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.[35]
4646 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
4647 first week in life in ventilator dependent preterm infants.[36] Six RCTs investigating a low
4648 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
4649 clear reduction in the incidence of BPD.[37-42] Only one of these trials reported long-term
4650 follow-up, showing no differences in adverse neurodevelopmental sequelae.[43] These
4651 findings are supported by several historical cohort studies, showing no increased risk of
4652 adverse neurodevelopmental outcome in hydrocortisone treated infants.[44-46]
4653
4654 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
4655 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
4656 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
4657 supported by other interventions, such as diuretics and inhalation therapy. With this
4658 approach, some infants can be successfully weaned and extubated. Only those infants that

4659 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
4660 primary objective to wean and extubate.
4661 Although this approach will undoubtedly result in successful extubation of most infants with
4662 the lowest possible use of glucocorticoids, the question remains if this is also the best
4663 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.
4664 This question seems justified and relevant because BPD, and not failure to extubate, is
4665 associated with adverse medium- and long-term outcome. This is the main reason why the
4666 primary outcome of this study is death or BPD and not failure to extubate.
4667
4668 The NICU at the University Medical Center Utrecht has historically used hydrocortisone for
4669 chronically ventilated preterm infants. Retrospective studies seem to indicate that
4670 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.
4671 However, these findings need to be confirmed or refuted by a large randomized placebo
4672 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
4673 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
4674 NICUs is undesirable and has also been debated in the public press.[47] As a first step to
4675 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
4676 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
4677 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
4678 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
4679 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.
4680
4681 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
4682 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.

4900 5.1.7 Inhalation corticosteroids: There is currently insufficient evidence that inhaled
4901 corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled
4902 corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is
4903 not an exclusion criterion. Data on timing, dose and duration will be collected.
4904
4905 **5.2. Use of co-intervention**
4906 All randomized patients will be treated according to the guidelines of the individual NICUs.
4907 All participating NICUs explore treatable causes of ventilator dependency during the first
4908 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and
4909 treat these according to the department protocol. Although all of these conditions can be an
4910 alternative cause of respiratory failure, they are known risk factors for developing BPD and
4911 therefore are not considered exclusion criteria.
4912
4913 This trial will monitor the prognostic important co-interventions and conditions, as described
4914 in section 8.2.
4915

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:

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		First administration	
Name		Date/time	
Date of birth		Lowering dosage regimen	
Weight	gram	Date/time	

Day in regimen	Time	Times per day	mg/dose		Daily dose/kg
Day 1	0-01-00 0:00 0-01-00 6:00 0-01-00 12:00 0-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 2	1-01-00 0:00 1-01-00 6:00 1-01-00 12:00 1-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 3	2-01-00 0:00 2-01-00 6:00 2-01-00 12:00 2-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 4	3-01-00 0:00 3-01-00 6:00 3-01-00 12:00 3-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 5	4-01-00 0:00 4-01-00 6:00 4-01-00 12:00 4-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 6	5-01-00 0:00 5-01-00 6:00 5-01-00 12:00 5-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 7	6-01-00 0:00 6-01-00 6:00 6-01-00 12:00 6-01-00 18:00	4 x	0.00	mg.	5 mg/kg/d
Day 8	7-01-00 0:00 7-01-00 8:00 7-01-00 16:00	3 x	0.00	mg.	3.75 mg/kg/d
Day 9	8-01-00 0:00 8-01-00 8:00 8-01-00 16:00	3 x	0.00	mg.	3.75 mg/kg/d
Day 10	9-01-00 0:00 9-01-00 8:00 9-01-00 16:00	3 x	0.00	mg.	3.75 mg/kg/d
Day 11	10-01-00 0:00 10-01-00 8:00 10-01-00 16:00	3 x	0.00	mg.	3.75 mg/kg/d
Day 12	11-01-00 0:00 11-01-00 8:00 11-01-00 16:00	3 x	0.00	mg.	3.75 mg/kg/d
Day 13	12-01-00 0:00 12-01-00 12:00	2 x	0.00	mg.	2.5 mg/kg/d
Day 14	13-01-00 0:00 13-01-00 12:00	2 x	0.00	mg.	2.5 mg/kg/d
Day 15	14-01-00 0:00 14-01-00 12:00	2 x	0.00	mg.	2.5 mg/kg/d
Day 16	15-01-00 0:00 15-01-00 12:00	2 x	0.00	mg.	2.5 mg/kg/d
Day 17	16-01-00 0:00 16-01-00 12:00	2 x	0.00	mg.	2.5 mg/kg/d
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.

Statistical analysis plan (SAP)

For the long-term outcomes of 2 years corrected age of the SToP-BPD study

Trial registration: Netherlands Trial Register, NTR2768. Registered on 17 February 2011.

EudraCT, 2010-023777-19. Registered on 2 November 2010.

Version 1, 16 March 2020.

Authors:

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On behalf of the SToP-BPD study group, this SAP is signed and dated by:

Name	Signature	Date
Principal Investigator A. van Kaam, principal investigator		16-3-2020

Supplement:

Statistical analysis of the long-term outcomes at 2 years corrected age of the SToP-BPD study*.*

This supplement is an update of and should be read in conjunction with the previously published statistical analysis plan (SAP) of the SToP-BPD study (1). Its purpose is to elaborate the statistical analyses of the long-term outcomes at 2 years corrected age (CA). We based this supplement on previously published recommendations (2). This supplement was prepared, signed and dated before the database of the long-term follow-up data at 2 years CA was locked and before unblinding of the researchers, outcome assessors, healthcare providers and parents of the patients.

Analysis

1. Outcome definitions

Key long-term secondary outcome

The key long-term secondary outcome at 2 years CA is a composite of death or neurodevelopmental impairment (NDI) at 2 years CA. To comply with the currently, generally used definition of NDI, the classification criteria cerebral palsy, hearing and vision loss were added to our previous NDI definition based on Bayley scores solely (1). This results in NDI being defined as the presence of anyone of the following:

- a Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version (BSID-III-NL) (3) or corrected (see section 2) BSID-II (4-6) cognitive or motor composite score below 85, or an estimated cognitive delay of more than 3 months (see section 6 below); *OR*
- cerebral palsy with a Gross Motor Function Classification System (GMFCS) of more than 2; *OR*
- hearing loss requiring hearing aids or deafness; *OR*
- severe visual loss (blind or abnormal (limited vision, but the ability to see anything)).

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Other long-term secondary outcomes

Other long-term secondary outcomes include both individual components of the composite key long-term secondary outcome (death, NDI at 2 years CA), survival to 2 years CA (time-to-event), BSID-III composite cognitive and composite motor scores, cerebral palsy and its severity using the GMFCS (7), hearing problems severity (i.e. normal (no hearing problems), mild abnormal (light hearing loss for which control or treatment), abnormal (neurosensory hearing loss (partially) corrected with hearing aid) and severely abnormal (neurosensory hearing loss, deafness)), visual loss severity (i.e. normal (no problems with sight), mild abnormal (treated by ophthalmologist/orthoptist for abbreviation (goggles) or strabismus/amblyopia), abnormal (limited vision, but the ability to see anything) and severely abnormal (blind)), behaviour problems assessed by the Child Behaviour Checklist (8), number of hospital readmissions since first discharge to home (especially for respiratory reasons, vaccinations, surgical operations and intensive care admission with mechanical ventilation), growth at 2 years CA (weight, length and head circumference), use of inhalation medication, number of antibiotics courses and number of steroid courses for asthmatic exacerbations during the last year, and use of (para)medical support during the 2 years follow up period.

2. Calculations or transformations used to derive any outcome from the original data.

Bayley Scales of Infant and Toddler Development

During the recruitment period of the study the BSID-III-NL was the instrument used for neurodevelopmental outcome assessment in most centers, whereas in some centers the BSID-II-NL or the American norms were still used. To compensate for discrepancies between the BSID-II-NL and the BSID-III-NL, 5 points to the cognitive composite score and 10 points to the motor composite score will be added to the BSID-II-NL, as described previously (4-6). If the BSID-III was used with the American norms, for comparison with the Dutch norms, 4 points will be subtracted from the

cognitive composite score based on the American norms. For the motor composite score no correction of the American score is necessary (9).

Anthropometric measurements

The anthropometric measurements (weight, length and head circumference) at 2 years CA will be expressed as a *z* score. The *z* score will be calculated by using the deviation from the mean value for the sex- and age-specific reference population, divided by the SD for the reference population. The *z* scores are generated using the Dutch reference growth charts specified for age and gender (10).

3. Statistical analysis

The analyses will be performed according to the intention-to-treat principle, including all randomised patients, regardless of protocol deviations or use of open-label corticosteroids. Descriptive statistics will be used to summarize baseline characteristics and outcome parameters using the mean and standard deviation or the median and interquartile range for continuous, normally and non-normally distributed outcomes respectively. Categorical outcomes will be summarized using counts and percentages. Treatment effect estimates will be expressed in absolute and relative effect sizes, as appropriate. Statistical uncertainty will be expressed in 95% confidence intervals (CI); all analyses will be performed using 2-sided tests and $P < .05$ are regarded as statistically significant. No adjustments for multiple comparisons will be made.

Key long-term secondary composite outcome

Statistical analysis of the key long-term secondary composite outcome, death or NDI at 2 years CA, will be performed similarly to the analysis of the short-term primary outcome (composite of death or BPD at 36 weeks' postmenstrual age) (1, 11). Crude estimates of the absolute risk difference and odds ratio for the key long-term secondary composite outcome of the hydrocortisone group compared with the placebo group will be calculated.

A logistic regression model correcting for the stratification factors gestational age and study center will be used to estimate the adjusted odds ratio for the key long-term secondary composite outcome. A generalized linear model with a binomial distribution and identity link will be used to estimate the absolute risk difference adjusted for the stratification factors for the key long-term secondary composite outcome.

Other long-term secondary outcomes

The effect of hydrocortisone compared with placebo on the other long-term secondary outcomes will be analysed using regression models, as appropriate. If required, non-normally distributed continuous variables will be appropriately transformed or a non-parametric alternative analysis approach, as appropriate, will be used instead. In case of less than 20 (non)events, Fisher's Exact test will be performed. Survival analysis up to 2 years CA will be performed using Kaplan-Meier curves and the log-rank test; time-to-event will be calculated as the time between randomisation and death, 2 years CA (censoring event), or in case of lost to follow up, date of last contact (censoring event), whichever occurs first; the effect size will be expressed in a crude hazard ratio if the proportionality assumption is met, which will be checked using graphical examination and use of a time-dependent covariate in a Cox model. These outcomes, although all pre-specified, should be considered exploratory, yielding hypothesis-generating findings, and so no formal adjustments for stratification or multiple comparisons will be made.

4. Sensitivity analyses

To check the robustness of the analysis of the key long-term secondary composite outcome, we will perform a per-protocol analysis, including only infants treated according to the study protocol. If possible, we will perform sensitivity analyses on the key long-term secondary composite outcome to investigate the impact of correlation between infant outcomes within twin or higher-order multiple births using generalized estimating equations with a logit link function. A mixed-effects logistic

regression model with site as random effect will be performed as an additional sensitivity analysis to check the robustness of the main analysis of the key long-term secondary composite outcome, if possible.

5. Subgroup analyses

We will perform exploratory subgroup analyses of the effect of hydrocortisone on the key long-term secondary composite outcome and its individual components by examining treatment × sub-group interaction effects in logistic regression models. Statistical tests for interaction directly examine the strength of evidence for the treatment effect varying between subgroups (12-14). Treatment effect estimates within each specific subgroup category with their corresponding 95% confidence interval will be reported (15), independently of whether the test of the specific interaction term is statistically significant. We will perform four subgroup analyses for both the key long-term secondary composite outcome and its individual NDI component at 2 years CA, each examining one sub-group: gestational age groups (less than versus greater or equal to 27 weeks), small for gestational age (defined as birth weight below the 10th percentile for the gestational age on the Fenton growth charts, yes versus no) (16), parental education (low versus middle and high educational level) (17, 18) and multilingual environment (mono- versus multilingual environment) (19). For the individual component death at 2 years CA , subgroup analyses will be performed conform the first phase of the trial: gestational age (less than versus greater or equal to 27 weeks), small for gestational age (yes versus no), the respiratory index (RI) at randomisation (less than or equal to versus greater than the median), sex (male versus female), and multiple birth (single versus multiple) (11). Each of these analyses will require four parameters to be estimated in the logistic regression model. If there are fewer than 40 patients with and/or fewer than 40 patients without the event of interest at 2 years CA, these analyses will not be performed.

6. Missing data

In case of missing data, every attempt will be undertaken to retrieve the data. Missing data will not be imputed, with the exception of the key long-term secondary composite outcome. Parents of participants who do not attend the 2-year assessment at the outpatient clinic will be invited by telephone once more. If they refuse to attend, the reason for refusal will be documented and they will be considered as lost to follow up. If no BSID III test can be done because of impairment or the cognitive composite score is missing, the attending pediatrician is asked to fill in an estimate of cognitive delay in three categories: no delay, 3-6 months delay or >6 months delay. A delay of ≥ 3 months is considered as neurodevelopmental impairment and equivalent to a BSID-III cognitive and motor composite score <85. If the motor part of the assessment is missing, the motor composite score is considered to be in the normal range (above 85), if the neurological examination of the participant is assessed as normal. In case of missing data for one of the other components of NDI, i.e. neurological examination, vision or hearing, a committee of three independent experts will assess whether the participant has neurodevelopmental impairment or not on the basis of the available clinical information of their neurological and developmental (ab)normality, if reasonably possible. These experts will be kept blinded to the allocation arm during this assessment. If there is insufficient information to classify the key long-term secondary composite outcome in > 5% of the participants, missing outcomes will be imputed using multiple imputation using baseline characteristics. As previously recommended (20), we will obtain a number of imputed datasets equal to the percentage of missing data. These datasets will be combined using Rubin's rules (20, 21). Inspection and imputation of missing data will be performed during the blinded review of the data. This strategy will be updated if, during the blinded data review, unexpected patterns are detected, requiring an appropriately adapted handling procedure. In that case, relevant deviations will be clearly documented and justified. If multiple imputation is performed, additional sensitivity analyses will be performed to check the robustness of the results using complete cases only and by applying best case and worst case imputation scenarios.

7. Additional analyses

For the key long-term secondary composite outcome a multivariable logistic regression model will be performed including gestational age (<27/≥ 27 weeks), small for gestational age (defined as birth weight below the 10th percentile for the gestational age, yes/no) (16), parental education (low/ middle and high education) and multilingualism (mono-/multilingual) (19). Parental educational level is defined as low if one or both parents have attended lower professional school or less or one parent low and the other middle; middle if both parents have attended medium professional school or one low and the other high; and high if one or both parents have attended higher professional school or university or one parent high and the other middle, as described previously (18). Because particularly lower parental education is predictive of cognitive impairment (17), the parental educational level of education is dichotomized (low/middle and high educational level).

Furthermore an additional multivariable logistic regression model will be performed to assess the treatment effect on death at 2 years CA, including gestational age, small for gestational age, severity of lung disease as measured by respiratory index, sex and multiple birth, conform the first phase of the trial (11).

8. How will harms be reported?

All clinically relevant serious adverse events occurring in the period between discharge home and follow up at 2 years CA are included in the outcomes of this study and will be presented and analysed as described above. Eventual other serious adverse events (SAEs) not listed in the outcomes, that may occur in the period between discharge home and the follow up at 2 years CA are out of view of the NICU clinicians and can mostly be considered as a consequence of childhood rather than related to the study intervention under evaluation. As approved by the accredited medical ethics committee these SAEs were not reported.

9. Statistical software

All statistical analysis will be performed in IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, NY). If necessary, for statistical computing the R environment is used (R Foundation for Statistical Computing, Vienna, Austria).

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