PRELIMINARY FINAL REPORT

Introductory Note

This preliminary version of the final report will be submitted upon the termination of the EU funding period as of 31 August 2015. The final version of this report will be submitted after the completion of the follow-up study scheduled for 31 March, 2016."

4.1 Final publishable summary report

Executive Summary

Background and rationale

Bronchopulmonary dysplasia (BPD) contributes to the mortality of preterm infants and is associated with impaired neurosensory development and an increased risk of pulmonary morbidity in adolescence and young adulthood. Early systemic corticosteroids reduce the risk of BPD in extremely preterm infants, but they may negatively affect the developing brain. The effects of inhaled corticosteroids on outcomes in these infants are unclear.

Plan at outset

The Neonatal European Study of Inhaled Steroids (NEUROSIS) is a randomized placebo-controlled, international clinical trial. We planned to randomize 850 infants of 23–27 weeks' postmenstrual age during the first 12 h of life to budesonide or placebo. We intended to determine the primary outcome of survival without BPD at 36 weeks' postmenstrual age and to follow our study patients and assess neurodevelopmental outcomes at a corrected age of 18–22 months.

Objectives achieved

Between 2010 and 2013, we randomized 863 infants (gestational age of 23 0/7 to 27 6/7 weeks) to early inhaled budesonide or placebo in 40 study centres in 8 European countries and in Israel. The primary outcome was death at 36 weeks or bronchopulmonary dysplasia. Of 437 infants assigned to budesonide, 175 died or had bronchopulmonary dysplasia (40.0%), compared with 194 of 419 assigned to placebo (46.3%) (relative risk, stratified for gestational age, 0.86; 95% CI 0.75-1.00; P=0.05). The rate of bronchopulmonary dysplasia was 27.8% in the budesonide group vs. 38.0% in the placebo group (relative risk, stratified for gestational age, 0.74; 95% CI, 0.60-0.91; P=0.004) and mortality was 16.9% vs. 13.6% respectively (relative risk, stratified for gestational age, 1.24; 95% CI 0.91-1.69; p=0.17). An

assessment of neurodevelopmental disability is currently being conducted at 18-22 months corrected age and the results will be available in 2016.

Conclusion

The primary objectives of NEUROSIS were achieved completely. The assessment of the long-term follow-up is ongoing until 2016 and the results will be very important for future guidance.

Summary Description of project context and objectives

Project context:

Survival of Extremely Low Birth Weight (ELBW) infants has improved in recent decades but BPD remains a major health care problem. BPD is a chronic lung disease that occurs in premature infants requiring mechanical ventilation and oxygen therapy, but also develops in preterm neonates who require little or no ventilatory or oxygen support (Kinsella 2006). BPD not only contributes to the mortality of preterm infants but is also associated with impaired neurosensory development in ELBW survivors (Schmidt 2003, Doyle 2005). Furthermore, a diagnosis of BPD has been associated with greater hospital readmission rates for respiratory morbidity during the first 5 years of life and an increased risk of asthma (Palta 1998, Greenough 2001). BPD is also associated with respiratory symptoms in childhood and reduced pulmonary function in infancy, childhood, adolescence and young adulthood (Palta 2001, Hofhuis 2002, Greenough 2000, Kennedy 2000, Korhonen 2004, Doyle 2001, Northway 1990). All of this does not only put an enormous burden on individual patients and their families, but also on collective health resources.

A number of approaches to prevent or treat BPD have been evaluated in the context of controlled studies (Soll 2000, Woodgate 2001, Greenough 2004, Courtney 2002, Johnson 2004, Ballard 2006, Kinsella 2006, Van Meurs 2005, Schreiber 2005, Darlow 2002, Schmidt 2006). Among the interventions studied are antenatal and postnatal corticosteroids (Roberts 2006, Lister 2000, Shah 2000, Shah 2003, Halliday 2003). *Systemic* postnatal corticosteroid treatment is perhaps the most controversial area of BPD care.

Despite these efforts, the incidence of ELBW survivors with BPD is increasing and new modalities for prevention and treatment need to be explored.

Pathogenesis of BPD: Inflammation

A variety of mechanisms has been identified to play a role in the pathogenesis of BPD. Along with genetic factors, pre- and postnatal exposure of the developing lung to inflammation is central to the development of BPD (Kallapur 2006) and can lead to airway injury and paren-

chymal fibrosis of the lung alternating with emphysema, a clinical picture that has first been described by Northway and colleagues and is referred to as „classical BPD“ (Nortway 1967). Alternatively or in addition, inflammation can interfere with lung development and lead to a cessation of alveolar septum formation, a picture that is more common in infants weighing <1 kg who did not have much lung disease soon after birth (Rojas 1995, Charrafeddine 1999) and that is referred to as „new BPD“ (Jobe 1999).

Biological rationale for the treatment of BPD with Corticosteroids

Corticosteroids are widely used to treat various inflammatory diseases. The most common use of corticosteroids today is the treatment of asthma. Inhaled corticosteroids have become established as first-line treatment in adults and children with persistent asthma, the most common chronic inflammatory disease (Barnes 2003). As in asthma, the biological rationale of corticosteroid therapy in infants with evolving or established BPD is based on its anti-inflammatory properties.

Systemic postnatal steroids

In 1983, the first randomised controlled trial (RCT) of dexamethasone to treat BPD was published in a peer-reviewed journal (Mammel 1983). In the following years, numerous studies followed (Kari 1993, Ohlsson 1992, Kazzi 1990, Harkavy 1989, Cummings 1989, Avery 1985), some of them showing improved clinical outcomes, including oxygen dependency at 28 days of life and at 36 weeks post-menstrual age, the traditional definition of BPD. These findings led to a widespread use of systemic steroids that peaked in the late 1990s with more than 25% of all very low birth weight infants being exposed to postnatal systemic steroid therapy (Walsh 2006). Around the same time, the first convincing reports of adverse effects of dexamethasone on growth and neurodevelopmental outcomes appeared (Yeh 1998, O’Shea 1999), which turned the enthusiastic use of systemic postnatal steroids into almost complete avoidance. Paediatric societies around the world published statements that called for limitation in the systemic use of postnatal corticosteroids (AAP 2002). However, cortico-

steroid use has not been eliminated from the nursery: the Vermont Oxford Network reported that 23% of 14321 ELBW infants received postnatal corticosteroid treatment in 2002 (Jobe 2004). In another retrospective analysis of cohort data within 3 large network registries including 472 centres, 8% of infants weighing less than 1500g were still treated with postnatal corticosteroids. These data underscore the pressing need for finding alternatives to systemic steroids for the prevention of BPD.

Inhaled postnatal steroids

Theoretically, administration of inhaled corticosteroids may allow for beneficial effects on the pulmonary system with a lower risk of undesirable systemic side effects. In clinical practice, lung inflammation is detected by inflammatory cells in tracheal aspirates from intubated infants and studies have shown that inhaled steroids reduce inflammatory cells and their products in tracheal samples of patients with BPD (Halliday 2001). We therefore conducted the **N**eonatal **Euro**pean **S**tudy of **I**nhaled **S**teroids (**NEUROSIS**), a multinational, randomized trial to test the hypothesis that, in preterm infants born before 28 weeks' gestation, inhaled budesonide administered within 24 hours after birth would decrease the incidence of bronchopulmonary dysplasia and death at 36 weeks' postmenstrual age.

Main objectives

The primary objectives as described in Annex-1 of the NEUROSIS proposal were as follows:
"To determine if the early prophylactic use of inhaled corticosteroids (Budesonide) in very preterm infants (gestational age 23 0/7-27 6/7 weeks) requiring any form of positive pressure support (mechanical or nasal ventilation or continuous positive airway pressure (CPAP)) increases survival without bronchopulmonary dysplasia (BPD) at 36 weeks gestational age."

We are happy to report that the primary objectives of NEUROSIS have been reached completely and the primary outcome results were published on October 15th 2015 in the New Engalnd Journal of Medicine:

Description of main S & T results/foregrounds

Main S & T results (=Primary outcome results)

A total of 863 infants were enrolled between April 1st, 2010, and August 3rd, 2013, from 40 study centres in 9 countries (8 European countries + Israel) and the primary outcome was ascertained in all 856 infants for whom adequate data were available. The observed rate of death or bronchopulmonary dysplasia was 40.0% (175 of 437 infants) in the budesonide group compared with 46.3% (194 of 419) in the placebo group (relative risk, stratified for gestational age, 0.86; 95% CI 0.75-1.00; P=0.053). As a secondary analysis the adjustment for covariates in a logistics regression resulted in an odds ratio of 0.71 (95% CI, 0.53-0.97; P=0.03). The net treatment effect on the composite outcome was achieved through a substantial decrease in bronchopulmonary dysplasia: of the 363 infants assigned to budesonide and alive at a postmenstrual age of 36 weeks, 101 (27.8%) had a diagnosis of bronchopulmonary dysplasia compared with 138 of the 363 infants (38.0%) assigned to placebo (relative risk, stratified for gestational age, 0.74; 95%CI 0.60-0.91; P=0.004). This was offset by a non-significant observed excess in mortality with budesonide (16.9% vs. 13.6%; relative risk, stratified for gestational age, 1.24; 95% CI 0.91-1.69; p=0.17).

In summary, NEUROSIS found a difference in the primary composite outcome – bronchopulmonary dysplasia or death- of borderline statistical significance between infants randomly assigned to inhaled budesonide and those assigned to placebo. The net effect of budesonide was a combination of a significant reduction in the risk of bronchopulmonary dysplasia which was offset by a non-significant observed excess in mortality. In this context, the results of the long-term follow-up become even more important and may facilitate future guidance.

Main results per work Package (WP)

NEUROSIS includes 12 different work packages with specific objectives. On the following pages we will review the results that have been achieved in each individual work package and will summarize the overall scientific/technological results at the end of this section.

Main results achieved under work package 01: Development of study infrastructure at local centers

Study infrastructure was set up at 40 centers in 9 countries. Objectives of work package were achieved completely.

Main results achieved under work package 02: Development of central study infrastructure

The central study infrastructure (including the study data base) was developed at the NEUROSIS coordinating center at University of Tuebingen, Germany. From there, the study was successfully coordinated. Objectives of work package were achieved completely.

Main results achieved under work package 03: Patient recruitment and outcome assessment

Although patient recruitment started later than originally anticipated 863 newborn infants were finally enrolled in the clinical study. The assessment of all a priori defined outcomes will go on until the follow-up of infants at 18-22 months corrected age has been completed. The assessment of the primary outcome results and all in-hospital outcomes has been completed and these outcomes are published (Bassler et al NEJM 2015). Objectives of work package were achieved completely.

Main results achieved under work package 04: Study monitoring (assessment of progress and results)

This is still ongoing simply due to the fact that all patients enrolled are followed up until a corrected age of 18-22 months. The study is centrally monitored in the NEUROSIS coordinating center in Tuebingen, Germany and nationally monitored in the respective countries under the responsibility of the national principal investigator. Once follow-up is completed, the objectives of this work package will have been achieved completely.

Main results achieved under work package 05: Data entry and patient safety management

This is still ongoing simply due to the fact that all patients enrolled are followed up until a corrected age of 18-22 months. All data from the initial hospital stay of the study participants have been entered successfully into the NEUROSIS database. Once follow-up is completed in 2016, the objectives of this work package will have been achieved completely.

Main results achieved under work package 06: Neurodevelop-mental follow-up

The objectives of this work package have almost been achieved but the follow-up is not yet completed. By 2016, it will be completed, data will be cleaned, analyses conducted and results reported in a manuscript that will be submitted to a peer-reviewed journal for publication. As can be seen in the table below, the rate of follow-up for the NEUROSIS patients will likely be > 90%.

FU Documentation (Status until 14.10.2015)

Center	Number of FU assessments (all eligible patients for FU)	FU conducted		FU not conducted (no data entry in database)			
		Complete data entry in database	Incomplete data entry in database	FU still within tolerable time period	FU: Tolerable time period exceeded	Lost to Follow-Up (also including partly Lost to Follow-Up data)	Percentage Lost to Follow Up per Center
B-0001	9	7	1			1	1 of 9 (=11%)
B-0002	9	8	1				
B-0003	3					3	3 of 3 (=100%)
B-0004	8	8					
CZ-0001	59	59					
CZ-0003	35	34				1	1 of 35 (=3%)
CZ-0004	16	16					
CZ-0005	15	15					
CZ-0006	10	10					
CZ-0007	15	15					
D-0001	38	38					
D-0002	62	58	1			3	3 of 62 (=5%)
D-0003	4	2	1			1	1 of 4 (=25%)
D-0004	16	8	5			3	3 of 16 (=19%)
D-0005	10	5	1		1	3	3 of 10 (=30%)
D-0006	14	12	1			1	1 of 14 (=7%)
D-0007	11	7			2	2	2 of 11 (=18%)
D-0008	30		18			12	12 of 30 (=40%)
D-0009	16	10	1		2	3	3 of 16 (=19%)
D-0011	9		1			8	8 of 9 (=89%)
D-0013	7	7					
F-0001	49	44				5	5 of 49 (=10%)
F-0002	33	22				11	11 of 33 (=33%)
F-0003	5	4				1	1 of 5 (=20%)
FIN-0001	35	24	1			10	10 of 35 (=29%)
FIN-0002	4					4	4 of 4 (=100%)
FIN-0003	30	26				4	4 of 30 (=13%)
FIN-0004	24	24					
FIN-0099	8	8					
I-0001	25	25					
I-0002	6	5			1		
I-0003	3	3					
I-0004	2	2					
I-0005	3					3	3 of 3 (=100%)
IL-0001	18	15	1			2	2 of 18 (=11%)
IL-0002	14	14					
IL-0003	11	5	1			5	5 of 11 (=45%)
IL-0004	7	7					
IL-0005	33	23				10	10 of 33 (=30%)
NL-0001	10	4	2		1	3	3 of 10 (=30%)
SUM	716	574	36	0	7	99	
Percentage	100% of: 716 patients	80% of: 716 pat.	5% of: 716 pat.	0% of: 716 pat.	1% of: 716 pat.	14% of: 716 pat.	

Countries:

B = Belgium
CZ = Czech Republic
D = Germany
F = France
FIN = Finland+Estland
I = Italy
IL = Israel
NL= Netherlands

Colouring:

Missing data
0-10% Lost to FU
11-20% Lost to FU
> 20% Lost to FU

Center has finished FU
No more patients for FU, but not finished yet

Main results achieved under work package 07:Data analyses (interim / final)

Apart from the analysis of the follow-up data, all objectives of this work package have been achieved completely throughout the study. This includes the statistical analysis plan, one interim analysis for efficacy and the four interim analyses for safety.

Main results achieved under work package 08: Data presentation and preparation of study report for peer-reviewed publication (dissemination)

NEUROSIS-results have been presented at 5 national and international meetings between 2014 and 2015 (see separate table on dissemination activities).

During the last reporting period, the main study report for the peer-reviewed publication was prepared. The manuscript was submitted on February 12th 2015 and published on October 15th 2015.

Main results achieved under work package 09: Industry involvement and PUMA development

Together with a partner from industry that came on board while the study was already ongoing, a paediatric investigation plan (PIP) was submitted to the EMA and finally approved. Whether this will ultimately end with a PUMA, mainly depends on the long-term follow-up data of the study patients. Once these data are collected, cleaned and analysed (which will be achieved in 2016), a revised PIP will be submitted including the new data. Based on this submission, the PDCO will make a decision regarding the PUMA.

Main results achieved under work package 10: Clinical pharmacology of budesonide (PK-PD analysis)

A microanalytical assay for detection of budesonide and metabolites in small volumes of plasma has been developed and validated during all study periods. The analysis of blood samples from study patients continued and efforts were undertaken to link the results with clinical outcomes (PK / PD analyses). The analyses are not yet completely finalized but will be ready for publication in a scietific journal in 2016. However, the total number of blood

samples that were obtained in the NEUROSIS study is lower than anticipated because of a separate consent procedure for the clinical and the pharmacological study (Parents were much more reluctant to give their consent for the additional blood sampling which was required for the pharmacokinetic study).

Main results achieved under work package 11: Genetic substudy

Bronchopulmonary dysplasia (BPD) is traditionally considered to be the consequence of lung injury taking place during preterm perinatal transition, followed by pulmonary inflammatory response and impaired structural development. The pathogenesis of BPD involving disturbed homeostasis of multiple genes and their interactions is not well understood. On the basis of the difference in concordance rates of BPD between homozygotic and heterozygotic twins, the genetic predisposition accounts for 65% (95% CI 53-80%) of the variance in the risk. The individual genes influencing the genetic susceptibility to BPD remain to be defined. In addition, gene-environment interactions are likely. According to main hypothesis of the project, inhaled budesonide decreases the risk of BPD without causing adverse effects. The aim of the genetic sub-study (WP11) has been to investigate whether the chosen candidate genes explain the inter-individual differences in the effects of budesonide.

The objectives of the present Neurosis-Gen study (WP 11) are as follows:

1. long term
    a. to associate single nucleotide polymorphisms (SNP) with the risk of BPD
    b. to define the function of BPD-predisposing genes and to define new strategies for prevention of BPD
2. short term
    a. to obtain the consent from the parents, collect, record, isolate, perform the quality control of DNA from infants participating the NEuroSIS randomized trial and their parents;
    b. to collect DNA from consented parents and their preterm infants that are at risk of developing BPD and their parents;

c. to perform the whole genome association analysis (GWAS) to preliminarily identify genes influencing the susceptibility to BPD;
d. to perform three consecutive replicate analyses to confirm the identity of the BPD-predisposing genes.

Based on the primary objectives, we chose to enhance the research towards the long term objectives that were originally described. The centres that were able to obtain permission from the ethics committees for the genetic study and got consents from the families, were involved in NEuroSIS-Gen study. The activities requiring deflated high-tech approaches (whole genome analysis, design chip technology) were performed towards the end of the grant period. This strategy allowed a prolonged time to collect the DNA specimens required for the GWAS study.

DNA extraction and quality control has been performed for all specimens currently available for the study. The high success rate in obtaining high quality of DNA during the later years was at least in part due to adoption of saliva-DNA collection kit, replacing buccal smear-DNA collection.

Instead of candidate gene study involving several SNPs, as described in the original plan, we elected to perform the preferred primary whole genome association analysis (GWAS). Although the number of specimens was at least as high as initially planned, the population was still small in size. As a result of the lack of statistical power, we designed three consecutive replication studies testing the validity of the genetic discoveries. The first replication study evaluating 100 best SNPs will be followed by the second replication study that evaluates the five best SNPs from GWAS and 1st replication study combined. In 2nd replication, DNA from the Finnish centers during the period from 2/2015 to early 2016 will be studied. The third replication study deals with the transmission-disequilibrium test (TDT). It involves NEuroSIS-Gen and NEuroSIS DNA families, and it aims to confirm the genetic association with specific SNPs that have passed the GWAS-test and the two replication tests. The GWAS-study and the 1st replication-study have been performed; 2nd and 3rd replication studies are actively proceeding.

The plan briefly outlined above mimics the plan initially described for the NEuroSIS study, with the difference that in the new plan a higher infant population and decisively higher number of SNPs will be studied. In order to complete the NEuroSIS GWAS replication study, additional funding from further sources will be acquired. The project continues throughout year 2015 and we hope to be able to get more funding for 2016.

Main results achieved under work package 12: Management

The NEUROSIS-study and the consortium have been supported by comprehensive management and coordination activities throughout the entire project implementation period. Financial and administrative project management was primarily located at the Coordinator's head office at the Medical Faculty of the Eberhard-Karls-Universität Tübingen and took place in close and excellent cooperation with the project team at the department of neonatology at the University Children's Hospital. In the course of the project, three persons have acted as financial and administrative project manager for NEUROSIS. The following results and achievements of the management team shall be highlighted:

- Support to the grant preparation, grant Agreement and consortium agreement
- Preparation and execution of 5 amendments to the grant agreement
- Preparation and submission of 5 scientific and financial periodic reports
- Preparation of 12 presence meetings
- Financial management of 8 clinical sub-centers in Germany

Summary of the main scientific/technological results

(Abstract from the NEJM publication as available from PubMed)

METHODS:

We randomly assigned 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) to early (within 24 hours after birth) inhaled budesonide or placebo until they no longer required oxygen and positive-pressure support or until they reached a postmenstrual age of 32 weeks 0 days. The primary outcome was death or bronchopulmonary dysplasia, confirmed by

means of standardized oxygen-saturation monitoring, at a postmenstrual age of 36 weeks (see figure 1 below).

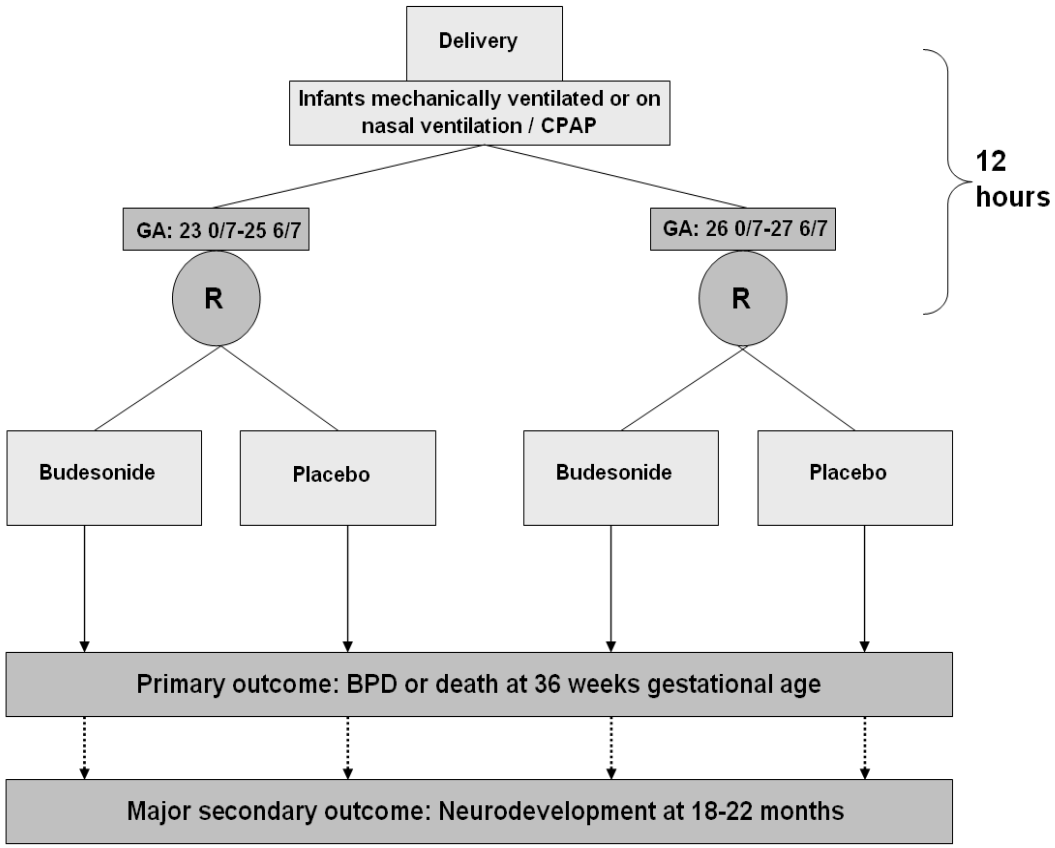
RESULTS:

A total of 175 of 437 infants assigned to budesonide for whom adequate data were available (40.0%), as compared with 194 of 419 infants assigned to placebo for whom adequate data were available (46.3%), died or had bronchopulmonary dysplasia (relative risk, stratified according to gestational age, 0.86; 95% confidence interval [CI], 0.75 to 1.00; P=0.05). The incidence of bronchopulmonary dysplasia was 27.8% in the budesonide group versus 38.0% in the placebo group (relative risk, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; P=0.004); death occurred in 16.9% and 13.6% of the patients, respectively (relative risk, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; P=0.17). The proportion of infants who required surgical closure of a patent ductus arteriosus was lower in the budesonide group than in the placebo group (relative risk, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; P=0.004), as was the proportion of infants who required reintubation (relative risk, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96; P=0.03). Rates of other neonatal illnesses and adverse events were similar in the two groups.

CONCLUSIONS:

Among extremely preterm infants, the incidence of bronchopulmonary dysplasia was lower among those who received early inhaled budesonide than among those who received placebo, but the advantage may have been gained at the expense of increased mortality. (Funded by the European Union and Chiesi Farmaceutici; ClinicalTrials.gov number, NCT01035190.).

Figure 1: Study flow



Potential impact and main dissemination activities and exploitation of results

Societal implications

Bronchopulmonary dysplasia affects at least 10.000 preterm infants in the United States of America each year (Schmidt B 2015). It is the single most common complication that occurs in extremely preterm infants that are born < 28 weeks of gestation (Schmidt B 2015). BPD constitutes a significant burden far beyond the neonatal period and has a negative impact on the quality of life of affected infants and their parents (Korhonen 1999). Furthermore, BPD children at school age display more internalising behaviour than preterm controls, with marked differences on comparison with classroom controls (Gray 2007). An effective and safe treatment for BPD would therefore favourably impact on the quality of life and behaviour of preterm infants and the everyday life of the child's family.

The expected impact listed in the EU work programme focused on evidence for a better use of off-patent medicinal products in paediatric populations. While NEUROSIS provided conclusive evidence for a better use of Budesonide, that is currently used off-patent in preterm infants, the impact of NEUROSIS exceeds the expected impacts listed in the work programme due to the significance of BPD for pulmonary morbidity later in life. BPD has not only been associated with an increased morbidity in infancy and childhood (Schmidt 2003, Doyle 2005, Greenough 2001, Palta 2001, Hofhuis 2002, Greenough 2000), but also in adolescence and young adulthood (Palta 1998, Doyle 2001, Northway 1990). Simply due to the fact that the first generations of ELBW survivors have not yet reached retirement age, no data are available to date addressing the association between BPD and pulmonary diseases of the elderly, such as Chronic Obstructive Pulmonary Diseases (COPD).

Developing drugs to prevent or treat BPD, a major goal of neonatal care over the past 20 years, would substantially decrease long-term morbidity and reduce health-care costs of premature infants. The associated economic impact and quality-of-life implications of poor lifelong lung health resulting from BPD warrant a renewed research emphasis on the prevention of this important cause of pulmonary morbidity throughout the life course (NHLBI workshop 2014).

In 1983, the first randomised controlled trial (RCT) of dexamethasone to treat BPD was published in a peer-reviewed journal (Mammel 1983). In the following years, numerous studies followed (Kari 1993, Ohlsson 1992, Kazzi 1990, Harkavy 1989, Cummings 1989, Avery 1985), some of them showing improved clinical outcomes, including oxygen dependency at 28 days of life and at 36 weeks post-menstrual age, the traditional definition of BPD. These findings led to a widespread use of systemic steroids that peaked in the late 1990s with more than 25% of all very low birth weight infants being exposed to postnatal systemic steroid therapy (Walsh 2006). Around the same time, the first convincing reports of adverse effects of dexamethasone on growth and neurodevelopmental outcomes appeared (Yeh 1998, O'Shea 1999), which turned the enthusiastic use of systemic postnatal steroids into almost complete avoidance. Paediatric societies around the world published statements that called for limitation in the systemic use of postnatal corticosteroids (AAP 2002). However, corticosteroid use has not been eliminated from the nursery: the Vermont Oxford Network reported that 23% of 14321 ELBW infants received postnatal corticosteroid treatment in 2002 (Jobe 2004). In another retrospective analysis of cohort data within 3 large network registries including 472 centres, 8% of infants weighing less than 1500g were still treated with postnatal corticosteroids. These data underscore the pressing need for finding alternatives to systemic steroids for the prevention of BPD. Theoretically, administration of inhaled corticosteroids may allow for beneficial effects on the pulmonary system with a lower risk of undesirable systemic side effects. To date, trials of inhaled glucocorticoids involving preterm infants who are at risk for BPD have been small and inconclusive, individually, and if pooled in systematic reviews and meta-analyses.

The Neonatal European Study of Inhaled Steroids (NEUROSIS) was powered to provide conclusive evidence on a patient relevant efficacy outcome (survival without BPD at 36 weeks gestational age). The NEUROSIS protocol includes follow-up of the large cohort of infants up to a corrected age of 18-22 months to assess neurodevelopmental outcomes. The list of off-patent medicinal products of the Paediatric Working Party of the European Medicines Agency (EMEA) listed inhaled steroids in infants < 1 year as a priority for future studies

with an emphasis on efficacy and safety, including long-term safety. NEUROSIS provided convincing information to guide the use of inhaled corticosteroids in preterm infants, a pharmaceutical product that is currently used off-patent and off-label in this age group. More guidance can be expected from the results of the long-term follow-up.

Economic impact

We are not aware of a reliable estimate of the cost of treating preterm infants with chronic lung disease in Europe. In the United States, the overall yearly costs of treating infants with BPD are estimated to be $2.4 billion. This amount is second only to the costs for treating asthma (Source: National Institutes of Health). A safe therapy that would lead to a difference in BPD incidence, even if the difference is relatively small, would be extremely valuable, not only from an individual patient perspective but also from an economic health care perspective. To be able to demonstrate such a relatively small, statistically significant difference, a large number of preterm infants were required and the study needed to be multicentre across different nations. NEUROSIS showed a statistically significant reduction in the incidence of BPD and has the potential to make an economic impact. However, the unexpected mortality results of the NEUROSIS study make the interpretation of the statistically significant findings of NEUROSIS, which are all in favour of budesonide, more complicated and the results of the long-term follow-up need to be considered before definite recommendations can be made.

NEUROSIS made an impact on another important level; it enhanced collaboration among European neonatologists, methodologists and basic scientists. The paucity of adequate European trials in the neonatal population is on the one hand due to the unique physiology and developmental diversity of newborns, which may impact both the efficacy and toxicity of the drugs used (McIntyre 2004), and on the other hand due to the enormous collaborative efforts required when studying such a unique population of patients. This is even truer, when long term follow-up is included in the study protocol. NEUROSIS brought together European researchers with expertise in neonatology, neonatal pulmonology, pulmonary physiology and pathophysiology, clinical trial methodology and conduct, as well as basic science. This multi-

layer approach, together with the scale of the study increased European competitiveness and boosted innovative health-related research, while at the same time it addressed a very relevant health issue.

Exploitation of results

In Annex 1 we referred to the planned exploitation of results as follows:

"From a purely scientific point of view, exploitation of results is best achieved by publication of the results in widely recognised peer-reviewed journals. The three top general medicine journals with the highest impact for clinical studies are the New England Journal of Medicine, the Lancet, and the Journal of the American Medical Association. Several of the NEUROSIS investigators and members of the external advisory board have in the past successfully published as first and/or co-authors in these journals. The SC will aim at publishing the results of NEUROSIS in one of these three journals to achieve the widest recognition possible."

We are happy to report that our initial plan has worked out with a publication of the primary outcome results of NEUROSIS in the New England Journal of Medicine (NEJM). The NEJM is the most widely read, cited, and influential general medical periodical in the world.

In Annex 1, we further referred to the planned exploitation as follows:

"From a commercial point of view, exploitation of trials results is best achieved by collaboration with partners from industry….NEUROSIS also aims at establishing a collaboration with one of the manufacturers of the, in the meanwhile, off-patent, interventional drug. Several companies (TEVA, Ratiopharm, Astra Zeneca) have been contacted with negotiations still ongoing. The ultimate goal is to eventually get a PUMA for Budesonide…"

A major breakthrough has already been achieved in period 2 of the project: Together with Chiesi Farmaceutici the Neurosis consortium submitted a Pediatric Investigation Plan to the European Medicines Agency (EMEA-001120-PIP01-10). On November 30th 2011, the European Medicines Agency agreed on our paediatric investigation plan which focuses not only on the results of the primary outcome but also on the results of the 18-22 months follow-up.

Thus we will have to wait until 2016 and the completion of the follow-up phase before further steps can be undertaken. Whether there will ever be a PUMA for Budesonide is uncertain at the moment but NEUROSIS has established a sound basis for a thorough risk-benefit assessment of early budesonide for the prevention of BPD in extremely preterm infants. If in the end it will turn out that there will be no PUMA, this will be based on a comprehensive decision by the EMA grounded on the NEUROSIS study results.

Dissemination of results

In Annex 1 we referred to the planned dissemination of the results in a table which is copied below.

Measures for the dissemination and/or exploitation of project results

Several steps will be taken to ensure adequate dissemination of NEUROSIS results and the proposed measures are summarised in the table below.

Table: Summary of measures for the dissemination/exploitation of NEUROSIS results

Dates	Type	Type of audience	Countries addressed	Size of audience	Partner respon-sible / involved
2009	Trial registration	Scientific community,	n.a.	n.a.	PIs

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NEUROSIS; Proposal No.: 223060; Technical Annex I – Amendment 5 – Date: 13 January 2014:

Dates	Type	Type of audience	Countries addressed	Size of audience	Partner respon-sible / involved
		medical journals			
2009	Web page	General public	all	large	SC, PIs
2014	Conferences / Abstracts	Scientific community	all	relatively small	SC, PIs
2014	Peer-reviewed publications	Scientific community	all	large	PIs
*	Press release	General public	all	large	SC, PIs
*	Direct contact	Industry	n.a.	n.a.	PIs

*Dates depend on negotiations with the pharmaceutical industry

Web page

A free accessible web page for NEUROSIS has been set up that provides an overview of aims, partners, study plans, progress and milestones, meetings, findings, and news. Publication on the internet facilitated the public dissemination of research results.

Conferences / Abstracts

In Annex 1, we report the following plans:

"Once analysis for the primary outcome is completed, results will be presented at the two major international neonatal conferences, the European Society of Paediatric Research (ESPR) and the North American PAS (Paediatric Academic Societies). Additionally, results will be presented at national European paediatric/neonatal conferences…. For these purposes, NEUROSIS results will be published as abstracts. NEUROSIS investigators realise that the contribution of such abstracts to scientific knowledge is limited, especially with respect to their inclusion in systematic reviews of completed randomised controlled trials. Thus, abstracts are not an acceptable form of final public dissemination and only regarded as a preliminary step followed by the full publication of trial results in a peer-reviewed journal".

NEUROSIS has been presented twice at ESPR / jENS meetings: The first presentation was in Barcelona in 2015 and the second presentation was in Budapest in 2015. The following abstract based on the presentation in Barcelona has been published in Archives of Diseases in Childhood:

NEUROSIS: Primary outcome

Primary Outcome	Placebo	Budesonide	Relative Risk (95% CI)	Relative Risk Adjusted for GA (95% CI)	P Value
Primary Outcome	194/419 (46.3)	175/437 (40.0)	0.86 (0.74-1.01)	0.86 (0.75-1.00)	0.053
Components of primary outcome					
Death at <36 wk of gestational age	57/419 (13.6)	74/437 (16.9)	1.24 (0.91-1.71)	1.24 (0.91-1.69)	0.165
Survival with BPD	138/363 (38.0)	101/363 (27.8)	0.73 (0.59-0.90)	0.74 (0.60-0.91)	0.004

Bassler D, Arch Dis Child 2014;99:A1-A2

The PAS meeting in the USA is always in spring and the NEUROSIS results were for the first time ready for presentation in summer. Thus, a decision was made not to wait 9-10 months for a presentation of the results in the USA and rather present NEUROSIS at an earlier meeting. NEUROSIS results were presented at the "Hot Topics in Neonatology" conference in Washington D.C. in December 2014. For over 30 years, Hot Topics has been THE premiere neonatal conference, with more than 1000 neonatologists and perinatologists attending each year.

Additionally, as initially described in Annex 1, NEUROSIS results were also presented at the meeting of the Germany Society for Neonatology and Pediatric Intensive Care (GNPI) in Stuttgart, Germany in 2015 and at the international meeting "Recent advanes in neonatology" in Wuerzburg, Germany in 2014. According to their webpage "neonatologists from 65 nations enjoyed the exceptionally high quality of the scientific and clinical presentations and the unique opportunity to discuss relevant topics with the members of the faculty."

Peer-reviewed publication

Please see paragraph "exploitation of results" above.

Press release

A joint press release "Protecting the lungs of the very youngest" between the University Hospital Zurich and the University Hospital Tuebingen was released on October 15th, accompanying the publication in the New England Journal of Medicine:

Direct contact with industry

In the past years, contact between the NEUROSIS PIs and Chiesi Farmaceutici has been intensified. For example, during a meeting in Tuebingen on May 5th 2015, the options for an industry funded 5-year follow-up of the NEUROSIS cohort were explored.

Further measures

Trial registration

The first step to ensure appropriate dissemination of NEUROSIS results was trial registration which has become a prerequisite for publication in many medical journals, among them the most prestigious journals with the highest impact. NEUROSIS investigators chose Clinical-Trials.gov for registration (NCT01035190.

Systematic reviews

In order to summarize and pool all the appropriate available study data on the early administration of inhaled corticosteroids published today, some members of the NEUROSIS Steering Committee wrote a protocol for a systematic review “Use of inhaled corticosteroids for the prevention and/or treatment of bronchopulmonary dysplasia in preterm infants: a systematic review protocol”. This protocol is published in Systematic reviews and will be followed by a completed systematic review and meta-analysis. This is another measure that will ensure widest dissemination and exploitation of NEUROSIS results.

Shinwell ES, Portnov I, Meerpohl J, Karen T, Bassler D. Use of inhaled corticosteroids for the prevention and/or treatment of bronchopulmonary dysplasia in preterm infants: a systematic review protocol. Syst Rev. 2015 Sep 25;4(1):127.

Further attachments

Official project logo:

Full list of beneficiaries:

Beneficiary Number	Beneficiary name	Beneficiary short name	Country
1 (Coordinator)	Eberhard-Karls-Universitaet Tuebingen	EKU-Tue	Germany
2	Belfast Health and Social Care Trust	QU-Bel	United Kingdom
3	Univerzita Karlova v Praze	CU-Pra	Czech Republic
4	Oulun Yliopisto	Uoulu	Finland
5	Clalit Health Service	KMC	Israel
6	Assistance Publique - Hôpitaux de Paris	APHPCCH	France
7	Azienda Ospedaliero Univesitaria Ospedali Riuniti Umbertoprimo	DP-Pad	Italy
8	Erasmus Universitair Medisch Centrum Rotterdam	EU-Rot	Netherlands
9	Dr. Margarete Fischer-Bosch-Institut fuer Klinische Pharmakologie	IKP	Germany
10	Pohjois-Pohjanmaan Sairaanhoitopiirin Kuntayhtyma	PPH-Oulu	Finland
11	Aristotelio Panepistimion Thessalonikis	AUTH	Greece
12	Universitaetsmedizin Goettingen, Georg-August-Universitaet	UMG-GOE	Germany
13	Technische Universität Dresden	TUD	Germany
14	Centre Hospitalier Universitaire Saint – Pierre	CHU-SP	Belgium
15	Universitaet Zuerich	UZH	Switzerland