Project Final Report

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Project acronym: NEMO

Project title: Treatment of NEonatal seizures with Medication Off-patent: evaluation of efficacy and safety of bumetanide

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Final Report

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1.1 Executive summary

NEMO is an EU FP7 funded project that conducted the first multicentre European study of neonatal seizures with a new antiepileptic drug. The project addresses the FP7 health call 'Adapting off-patent medicines to the specific needs of paediatric populations' by investigating the safety and efficacy of bumetanide for the treatment of seizures in babies. Bumetanide was included in the European Medicines Agency (EMEA) revised priority list for studies into off-patent paediatric medicinal products. It is a commonly used loop diuretic and preclinical data suggest that it might be an effective treatment for neonatal seizures.

The programme included non-clinical studies on the mechanism of bumetanide, the development of the investigational product, the set up of the clinical trial including definition of EEG and neurodevelopmental outcome measures, ethical consideration of clinical trials in the newborn period and conduction of the clinical trial.

The aim of the trial was to obtain data on the optimal dose, feasibility and pharmacokinetics of bumetanide when given as an add-on treatment for seizures in full term babies with hypoxic ischemic encephalopathy (HIE) not responding to a loading-dose of phenobarbitone from eight neonatal intensive care units across Europe. Newborn babies were allocated to receive an additional dose of phenobarbitone and one of four bumetanide dose levels at a range of doses from 0.05 to 0.3 mg/kg by use of a bivariate Bayesian sequential dose-escalation design to assess safety and efficacy. The trial was planned to consist of two consecutive stages: Stage 1: a dose-finding and confirmatory stage and Stage 2: a pharmacokinetic (PK) stage at the optimal dose. Overall the plan was that the trial would also evaluate the feasibility of a subsequent larger randomised controlled trial (NEMO2).

Adverse events, pharmacokinetics, and seizure burden were assessed during 48h continuous electroencephalogram (EEG) monitoring. The primary efficacy endpoint was a reduction in electrographic seizure burden of more than 80% without the need for rescue antiepileptic drugs in more than 50% of infants.

Between Sept 2011 and Sept 2012 30 infants who had electrographic seizures due to hypoxic ischaemic encephalopathy were screened. 14 of these infants (10 boys) were included in the trial. All babies received at least one dose of bumetanide with the second dose of phenobarbitone; three were withdrawn for reasons unrelated to bumetanide, and one because of dehydration. All but one infant received aminoglycosides. Five infants met EEG criteria for seizure reduction and all of these 5 received rescue antiepileptic drugs within the observation period. We recorded no short-term dose-limiting toxic effects, but three of the 11 surviving infants had hearing impairment confirmed on auditory testing between 17 and 108 days of age. The most common non-serious adverse reactions were moderate dehydration in one, mild hypotension in seven, and mild to moderate electrolyte disturbances in 12 infants. The trial was stopped early due to the third episode of hearing loss and limited evidence for seizure reduction. Findings of the results were published in Lancet Neurology.

In order not to lose momentum or risk the knowledge, expertise and collaboration developed in NEMO1, the consortium used the remaining time of the NEMO 1 Project to build the ground work for a new trial with lidocaine and midazolam, including a PIP application for Lidocaine which was submitted in Feb 2015.

Over 20 publications were published over the period of 66 months, several in high-ranking journals like Lancet Neurology; of these 15 were in open access journals.

Information about the NEMO project can be found on the following website http://www.nemo-europe.com/.

1.2 Summary description of project context and objectives

Background and Aims

Seizures occur more often during the neonatal period than at any other time in life. Hypoxic Ischaemic Encephalopathy (HIE) is the most common aetiology. It occurs in 2-3/1000 births and is a major cause of both acute mortality and long-term neurodisability. Seizures are the hallmark of HIE and evidence from human and animal studies suggests that seizures amplify hypoxic brain damage. Furthermore, electroencephalogram (EEG) studies have shown that many babies with HIE have a considerable seizure burden which is not reduced by current antiepileptic drugs. Phenobarbitone remains the first line antiepileptic drug (AED) for neonatal seizures world-wide despite the fact that it has limited efficacy. Better treatments for neonatal seizures, particularly in asphyxiated babies, have been identified as a high priority for research by several international expert groups with the ultimate aim to improve long-term outcome.

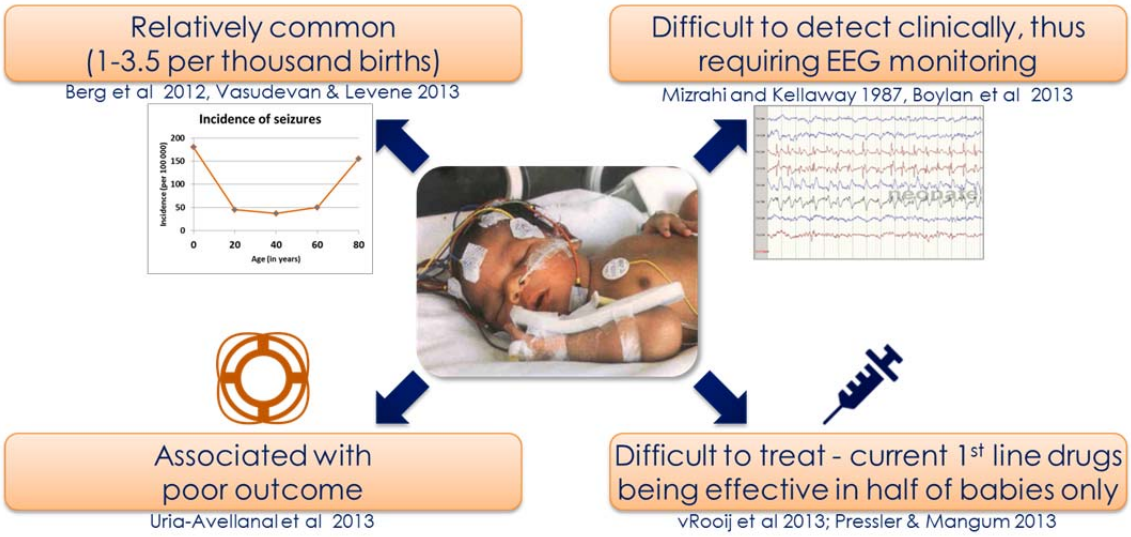

Figure 1: Challenges of seizures in the neonatal period.

The increased susceptibility to seizures and poor response to AEDs may be related to age-dependent differences in intracellular chloride concentrations caused by high expression of the sodium/potassium/chloride co-transporter isoform 1 (NKCC1). This is reflected as a depolarizing (excitatory) response of γ-aminobutyric acid (GABA) receptors in immature neurons, in contrast to hyperpolarization (inhibitory) in adult neurons (Figure 1).

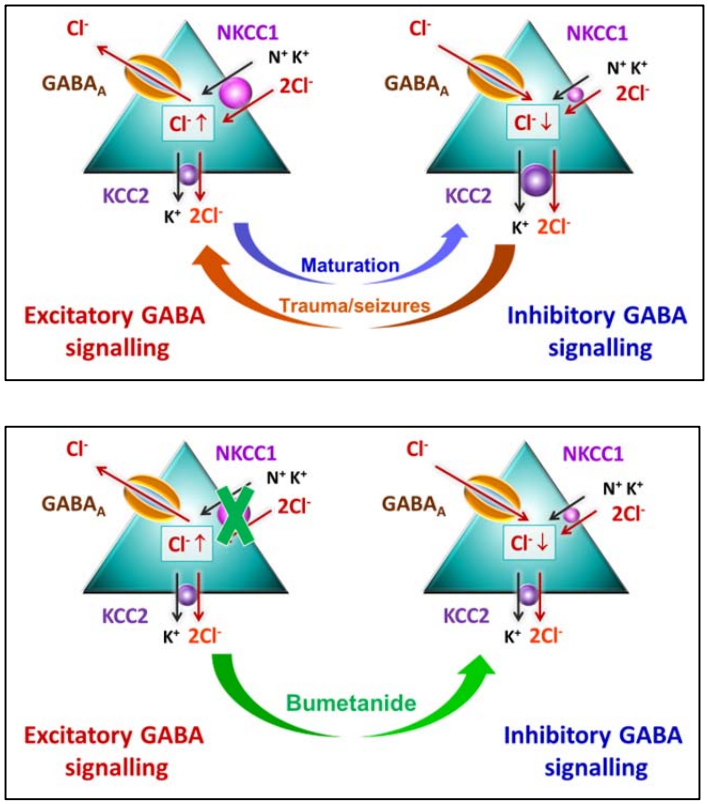

Figure 2 Mode of action: In immature neurons (left) GABAA receptor-mediated Cl currents are depolarizing (excitatory) due to an overexpression of Na+ K+ 2Cl- co-transporter isoform 1 (NKCC1) and under expression of K+ 2Cl- co-transporter isoform 2 (KCC2) resulting in high intracellular chloride. During neuronal maturation a shift from depolarizing to hyperpolarizing GABAa receptor-mediated Cl- currents takes place via down regulation of NLCC1 and up regulation of KCC2; an opposite effect is often seen following epilepsy and trauma. Bumetanide blocks neuronal NKCC co-transporters rendering GABA inhibitory.

Bumetanide, a commonly used loop diuretic, blocks an age dependent high expression of a chloride co-transporter, which is thought to be responsible for the high incidence of seizure in the newborn period and the lack of response to conventional drugs used in older children and adults. It has been shown to significantly reduce seizure burden in immature animals. More recently, animal experiments suggest that bumetanide in combination with phenobarbitone may be even more effective in suppressing seizures in the immature brain. Bumetanide has been used as a diuretic in term and preterm babies for around thirty years and several studies have validated its efficacy and safety including PK and dose finding studies. It is considered a safe drug in the neonatal period, even in critically ill infants. Studies in animals have suggested 0.1-0.2mg/kg as the optimal dose to block the NKCC1 co-transporter, which is at the upper range of the dose used as a diuretic. Bumetanide cannot be tested as an antiepileptic drug on older children or adults as this mechanism ceases to be effective during the first few months of life. However, it is unclear whether bumetanide will be a suitable anticonvulsive in human babies and which dose or dosing regimen would be most effective.

The project addresses the FP7 Health call ‘Adapting off-patent medicines to the specific needs of paediatric populations’ by investigating the safety and efficacy of bumetanide for

the treatment of seizures in babies. Bumetanide is included in the European Medicines Agency (EMEA) revised priority list for studies into off-patent paediatric medicinal products.

Work strategy and general description

The aim of NEMO was to develop an effective antiepileptic drug regimen suitable for treatment of neonates with birth asphyxia using innovative strategies targeted specifically to the needs and peculiarities of babies. The focus on this high-risk group was justified because of the poor neurodevelopmental outcome for babies with seizures, which are resistant to current AEDs. An age dependent high expression of neuronal co-transporter resulting in excitatory rather than inhibitory function of GABA is believed to be responsible for the high incidence of seizures in the neonatal period. By blocking this co-transporter with bumetanide, a loop diuretic, the depolarizing action of GABA will be reversed resulting in reduced neuronal firing. Intensive EEG monitoring enabled us to accurately identify seizures and monitor treatment effect. We aimed to perform a European-wide multicentre dose-finding and feasibility study with bumetanide. If results were supportive we would have performed a randomised controlled trial to evaluate efficacy.

Management structure and procedures

The Project Coordinator ensured the smooth operation of the project and guaranteed that all efforts were focused towards the objectives. She submitted all required progress reports, deliverables, financial statements to the European Commission, and with the assistance of GABO:mi she was responsible for the proper use of funds and their transfers to participants. The NEMO project office was established in London and at GABO:mi in Munich. The Project Office in London was concerned with the scientific management and the co-ordination of all research activities. The Project Office at GABO:mi was responsible for administrative, financial and contractual management and the organisational co-ordination of the project activities.

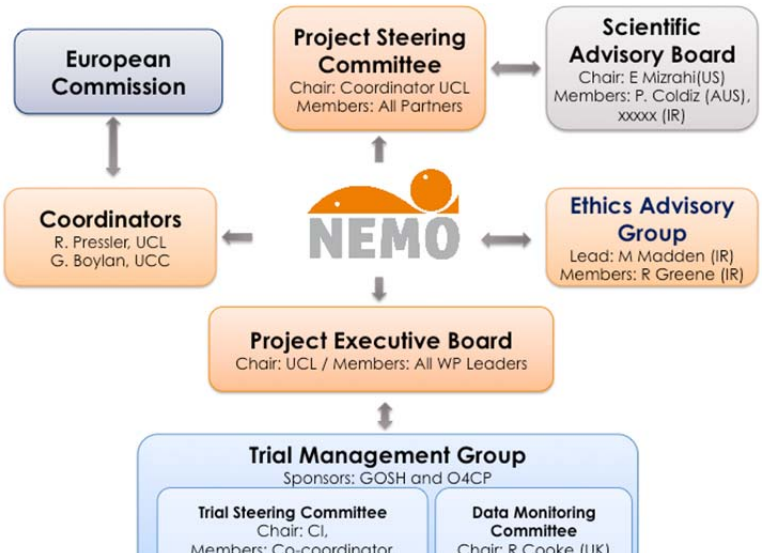

Figure 3: Management structure of NEMO.

The Project Governing Board was in charge of the political and strategic orientation of the project and acted as the arbitration body. It met once a year unless the interest of the project required intermediate meetings. The Project Coordination Committee consisted of all work package leaders, the Co-Principal Investigator and the Coordinator and was responsible for the monitoring of all activities towards the objective of the project in order to

deliver as promised, in due time and within the budget. The Project Coordination Committee met every six months during the funding period. Furthermore, a Scientific Advisory Board was implemented to ensure a high standard of research and to monitor the progress of the project by taking part in the annual Governing Board Meetings.

Objectives of NEMO:

By consolidating efforts from basic science, pharmacology and clinical centres, the objectives of NEMO were:

Primary objectives

- To find the optimal dose of bumetanide when given as an addition to standard therapy (phenobarbitone) for seizures in full term babies with hypoxic ischemic encephalopathy
- To assess the efficacy and safety of bumetanide for the treatment of neonatal seizures in babies with hypoxic ischaemic encephalopathy which are not controlled by phenobarbitone
- To develop and adapt a bumetanide formulation suitable for newborns with seizures and to apply for a Paediatric Use Marketing Authorization (PUMA) if indication for neonatal seizures can be proven.
- If the findings of NEMO-1 do not support a randomised controlled clinical trial of Bumetanide then apply for a Paediatric Investigation Plan (PIP) for lidocaine to assess efficacy as an AED for the control of seizures which are not controlled by phenobarbitone

Secondary objectives

- To assess thepharmacokinetics and pharmacodynamics of bumetanide in neonatal seizure treatment.
- To further evaluate the mechanisms of action for bumetanide in the immature brain.

1.3 Description of the main S&T results/foregrounds of NEMO

NEMO was an EU FP7 funded project representing the largest multicentre European study of neonatal seizures and their treatment. The project addressed the FP7 Health call ‘Adapting off-patent medicines to the specific needs of paediatric populations’ by investigating the safety and efficacy of bumetanide for the treatment of seizures in babies. Bumetanide was included in the European Medicines Agency (EMEA) revised priority list for studies into off-patent paediatric medicinal products.

NEMO investigated the treatment of seizures in neonates with hypoxic ischaemic encephalopathy (HIE). HIE occurs in 2-3/1000 births and is a major cause of both acute mortality and long-term neurodisability. Seizures are the hallmark of HIE and evidence from

human and animal studies suggests that seizures amplify hypoxic brain damage. Furthermore, electroencephalogram (EEG) studies have shown that many babies with HIE have a considerable seizure burden which is not reduced by current antiepileptic drugs. Phenobarbitone remains the first line antiepileptic drug (AED) for neonatal seizures world-wide despite the fact that it has limited efficacy. Better treatments for neonatal seizures, particularly in asphyxiated babies, have been identified as a high priority for research by several international expert groups with the ultimate aim to improve long-term outcome.

Summary of results

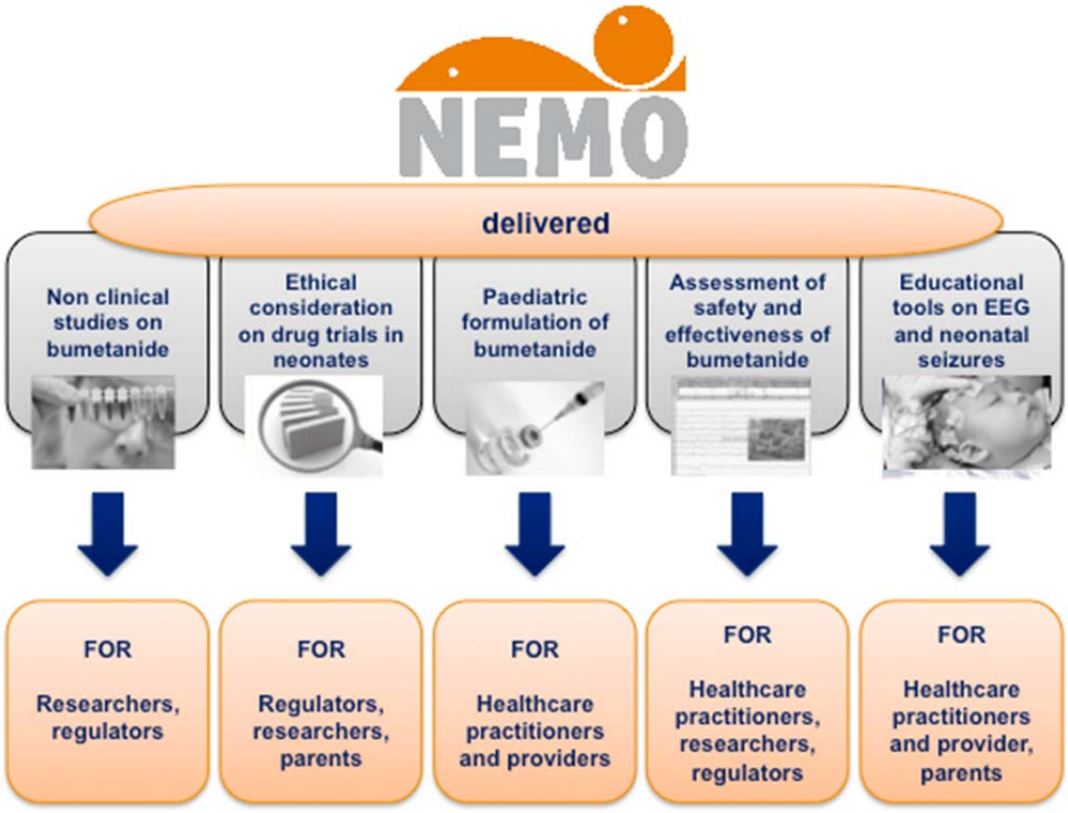

Figure 4 Summary of NEMO output

- The NEMO consortium was established representing a multidisciplinary group of experts from neonatology, paediatrics, neuroscience, neurophysiology, pharmacology, biomedical engineering and industry in 13 European countries and the US. This consortium has by now an international reputation as an expert team for neonatal seizures and drug development.

- Two websites were developed for the project. One was the general NEMO website (**www.nemo-europe.com**) for the general public and the other was for the NEMO clinical Trial (https://www.clininfohosting.com/specif/NEMO/) which contained all of the trial study documents.

- The consortium developed a new neonatal formulation of bumetanide for use in a Phase I/II dose finding and safety study.
- A dose finding and safety study screened 30 patients across * European recruitment sites.
- Bumetanide did not reduce seizures in neonates and there were safety concerns in terms of ototoxicity and therefore the study was halted prematurely.
- An RCT of bumetanide for the treatment of neonatal seizures was not recommended by the consortium.
- The results of the NEMO trial were published in the Lancet Neurology in March 2015
- The consortium diverted their attention to other drugs that might be effective for the treatment of neonatal seizures and submitted a Paediatric Investigation Plan to the European Medicines Agency for Lidocaine for the treatment of neonatal seizures in February 2015.
- The NEMO consortium has remained together at the end of the project and are committed to planning an RCT of lidocaine for the treatment of neonatal seizures. They have submitted a H2020 application for this purpose.
- A new ready-to-use 50 ml formulation of lidocaine 0.1% has been developed by the consortium along with the Investigator Brochure (IB) and Investigational Medicinal Product Dossier (IMPD).
- The consortium are now establishing themselves as a neonatal clinical trial network and aim to work with academia, regulatory agencies and industry to improve outcomes for neonates through effective management of neonatal seizures.
- The coordinators were recently invited to present the work of NEMO to the newly established International Neonatal Consortium at the European Medicines Agency in March 2015.
- The consortium have also developed a very popular educational tool for clinicians and health care professionals which is available on the NEMO website (http://www.nemo-europe.com/en/educational-tools.html)
- An educational tool for parents was also developed and uploaded to the NEMO website (http://www.nemo-europe.com/en/educational-tools.html)
- NEMO is now a well-known international consortium and brand. There have been 27 publications to date, an additional 4 are in press and a further 10 in preparation. The results of NEMO will have a high impact for many years to come.

Scientific results of NEMO:

The results of the clinical trial of bumetanide for the treatment of neonatal seizures were

published in Lancet Neurology: Pressler RM, Boylan GB, Marlow N, et al. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015; May 14:469-76.

Furthermore a comment on the published NEMO article was published: Glass H. Bumetanide for treatment of seizures in neonates. Lancet Neurol. 2015; May 14:456.

The NEMO consortium published an entire edition of the journal ***Seminars in Fetal and Neonatal Medicine*** in 2013 which was edited by the NEMO coordinators Ronit Pressler and Geraldine Boylan (guest editors). Ten different review articles were written by the consortium covering many relevant aspects of neonatal seizures including clinical management, treatment and outcome.

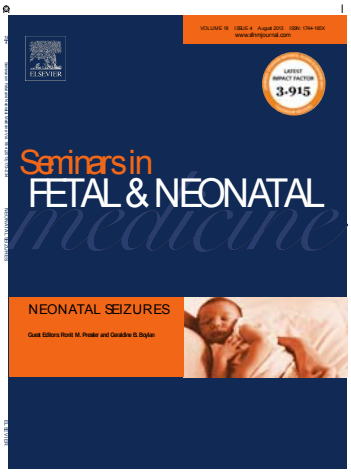

Figure 5 Guest edition on neonatal seizure in Seminars in Fetal and Neonatal Medicine

Using data collected in Sweden, we also investigated the antiepileptic effects of lidocaine for the treatment of seizures when administered without prior phenobarbitone. This showed that lidocaine was less effective when given without phenobarbitone and thus created new knowledge on neonatal seizure management. The study was published in 2013 in a peer-reviewed scientific journal (Lundqvist M, Ågren J, Hellström-Westas L, Flink R, Wickström R. Efficacy and safety of lidocaine for treatment of neonatal seizures. Acta Paediatr. 2013 Sep;102(9):863-7).

We also published a systematic review of surveys published during the 2000's on neonatal seizure management. (Hellström-Westas L, Boylan GB, Ågren J. Systematic review of current strategies for neonatal seizure management, Acta Paediatrica 2014). The main results of this study were as follows:

- ⇒ Phenobarbitone is the first drug of choice by a majority of centres in Western Europe and in the USA
- ⇒ Strategies for second line drugs differ:
  - ➢ Europe: preference for midazolam or lidocaine
  - ➢ USA: phenytoin is the main choice
- ⇒ Despite of any medical evidence regarding safety or efficacy, since no controlled trials have been performed, several non-authorised drugs are used in newborn infants.
- ⇒ Neonatal seizures are still mainly detected by clinical observation despite vast knowledge that a majority of neonatal seizures are subclinical.

We developed an EEG standard operating procedure that is now used across Europe.

The NEMO project resulted in a spin-off project where data from a prior study (UCC) was used to yield a realistic simulation of AED treatment trial. This work aimed to define the

sample size needed for successful future AED treatment trials. First results of the simulation study were presented to the NEMO consortium at the meeting in Paris SEP 2014 and a manuscript will be submitted for publication during 2015.

A manuscript was written on the detailed analysis of NEMO EEG findings, which supplements the findings in the main NEMO paper. This will also be sent for publication in a scientific journal during 2015.

A paper is being prepared evaluating the 26 full-term infants with HIE recruited by the NEMO consortium (SEP 2011-SEP 2012), who had video-EEG monitoring during the first 72hrs after birth, an MRI within the first weeks after birth and neurodevelopmental assessment at two years. EEG background activity, electrographic seizure burden, severity of brain injury on MRI (using a new and an established score), were assessed and correlated with outcome at two years. The results of this study will be presented at the International Brain Monitoring and Neuroprotection Conference taking place in Cork, Ireland in October 2015 (http://newbornbrain2015.comNon-clinical: INSERM Marseille - administration of bumetanide does not alter brain waves in adults as expected in keeping with the fact that intracellular chloride levels are low and hence NKCC1 antagonists will not significantly contribute to their generation.

Non-clinical: Effects of bumetanide on activities in autism. Performed in vivo recordings in head restrained animals in two animal models of seizures –the fragile X model and the in utero Valproate model. We observed significant actions of bumetanide.

Non-clinical: We have discovered that bumetanide does reduce the established mirror foci generated by repeated applications of kainite to one chamber and recordings in the other hippocampus. Bumetanide did not prevent the formation of a mirror epileptogenic mirror focus but this procedure but did reduce the severity of seizures. These observations have led to 2 publications joined to the report (see below).

Non-clinical: Discovery of a novel major observation on the fate of intracellular chloride in autism. Indeed, we discovered earlier that delivery is associated with a major and abrupt reduction of intracellular chloride and a corresponding powerful inhibitory action of GABA. This study published in 2006 by Science has ignited major interest (Tyzio et al Science 2006). This shift that has neuroprotective and analgesic actions of neurons during a highly vulnerable event is in fact mediated by oxytocin signals. We now discovered that his shift is abolished in the two animal models of autism completely leading to permanent depolarising and excitatory actions of GABA in adult neurons. Most importantly a single administration of bumetanide during delivery prevented this failure and restored physiological activities in adults and reduced the typical autistic behavioural features of the animals once adult. Clearly the polarity of GABA during delivery exerts a priming action on the polarity of GABA later and generate aberrant activities in vivo that are sensitive to bumetanide. This clearly reinforces the importance and clinical relevance of the diuretic at least in autism.

Clinical pharmacology: Bumetanide could be quantified in all the plasma samples obtained in NEMO I, which allowed for the PK modelling despite the very limited number of included neonates.

Clinical pharmacology: First PK model for bumetanide in neonates which improved the current knowledge about the pharmacokinetics of bumetanide in neonates.

Clinical pharmacology: No relationship was found between bumetanide exposure and efficacy or the occurrence of hearing loss, which seems to indicate hearing loss is not related to bumetanide exposure within the range of dose used in NEMO1. However, because of the limited number of children included in NEMO1, this lack of correlation may also be the consequence of a lack of statistical power.

1.4 The potential impact

Socio-economic impact and the wider societal implications of the project

Contribution to Community and social objectives

The NEMO project has led the way to developing the first European consortium dedicated to the treatment of neonatal seizures. Many groups have attempted this in the past but were unsuccessful given the challenges that need to be overcome. The consortium set out to address the problem of neonatal seizures in term neonates with HIE because of the poor outcomes associated with this condition. The risk of permanent neurological injury causing lifelong disability after HIE complicated by seizures is high. The disability experienced by survivors includes cerebral palsy, epilepsy and learning difficulties, the cost of care of which remains high (Mwaniki et al 2012). The quality of life however of the child with profound neurological handicap is poor. The amount of care required by disabled children has implications for parents, siblings and the health service. Improvement of neurodevelopmental outcome could have a dramatic impact on these children and their families.

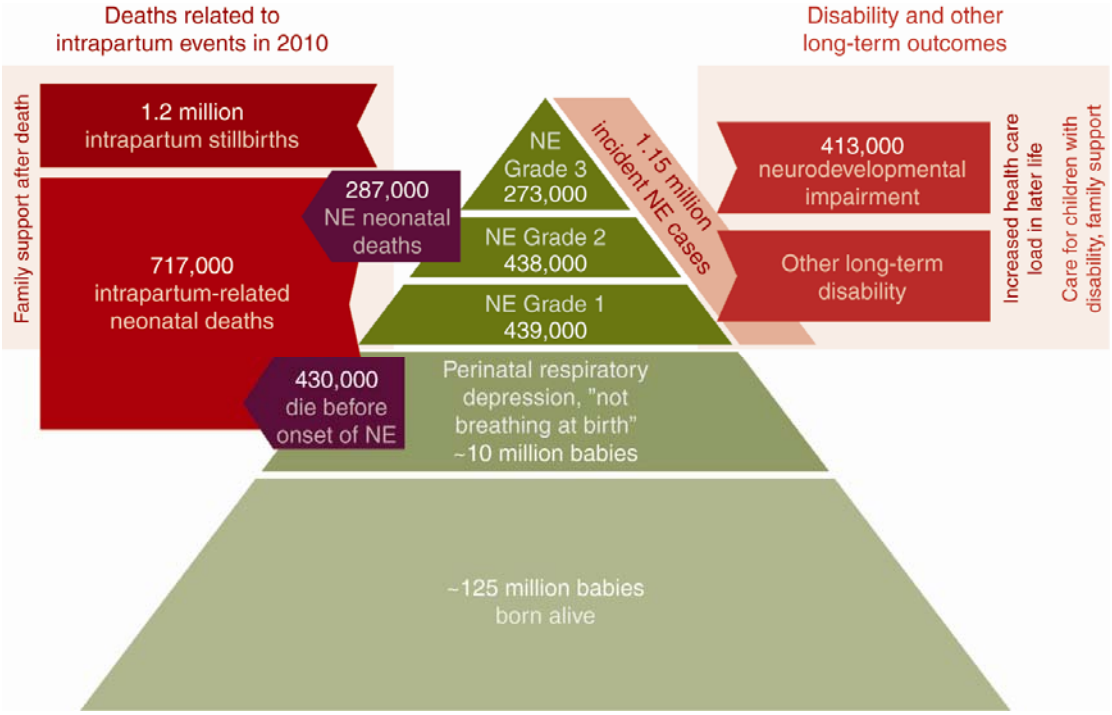

Figure 6 The incidence of neonatal encephalopathy (HIE) and outcomes globally for 2010 (Lee et al, 2013).

The health care costs of children who survive encephalopathy complicated by seizures are enormous. Neonatal Intensive Care Unit (NICU) costs are estimated at €2,000 per day, with an average duration of admission of 10 days. Estimated costs of disabled children range from €30,000-€100,000 yearly for moderately and severely disabled children respectively. A decade ago, the Center for Disease Control (CDC) in the US estimated the average lifetime costs of HIE-induced cerebral palsy to be around $11.47 million (Center for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 2005). The CDC also quoted US Bureau of

Labour statistics, which show total costs of epilepsy in the US at $15.5 billion per annum. Numerous international estimates suggest the average lifetime costs associated with significant motor and cognitive disability are very high, with these costs not including the hidden costs borne by families. Olesen's review (2012) of brain injury costs in Europe showed the 2010 figure at almost €800 billion, including medical and non-medical direct and indirect costs. This study reported that brain disorders are less deadly than cardiovascular diseases or cancer, but cause longer-lasting disability and higher care costs. The estimated direct cost for medical treatment of these disorders was €296 billion – 24% direct healthcare costs in Europe. The cost of care (estimated at €186 billion) and loss of productivity when unable to work (estimated at €315 billion) bring the total cost to €798 billion for that reported year (2010).

We are accruing considerable scientific evidence, which suggests that controlling seizures reduces brain damage (van Rooij et al 2010; Glass et al 2009). On the other hand, over treatment of babies with antiepileptic drugs carries the risk of neurotoxicity from medications prolonging intensive care (with associated costs and parental separation) and increased risk of complications. The current clinical standard of care in most NICUs worldwide is still to treat babies based solely on clinical diagnosis of seizures. EEG studies (performed by ourselves and others) have shown this to be inaccurate, unreliable and to lack any evidence base (Murray et al 2008). Increasingly, clinicians are using cot-side amplitude integrated EEG (aEEG) to guide their therapy but surveys show that interpretation skills are limited and this method does not reliably detect seizures

Neonatal seizures due to HIE are a significant socio-economic problem affecting over a million babies worldwide.

The findings of NEMO1 suggest that at the doses that were studied and in the investigated population, bumetanide did not show signs of clinical efficacy for the treatment of neonatal seizures. In addition, it was associated with a higher risk of ototoxicity. Due to this adverse benefit-risk ratio, further efficacy trials using bumetanide at this dose regimen cannot be recommended thus we propose to move from the planned RCT of bumetanide. We are currently writing up these results as well as a publication on 'How to conduct clinical trials for neonatal seizures - lessons learned from NEMO'.

One of the most important results of NEMO1 is the fact that traditional ways of measuring seizure burden is not reliable for neonatal seizures. The results of NEMO1 will be used to develop a new outcome measure for clinical trials of neonatal seizures (WP6). We anticipate that this will have far reaching implications on how drug trials into neonatal seizures will be performed in the future.

Recent research has shown that MRI can be used as a biomarker for neurodevelopmental outcome (Miller et al 2002; Glass et al 2012; van Rooij et al 2010). A follow–up patient diary was produced which is to be given to the parents once their babies are discharged from hospital and at the 2 year neurodevelopmental follow up, the diary will be collected and analysis of the data entered will be completed (WP7).

In May 2015 the main findings of the NEMO-1 Clinical Trial were published in Lancet Neurology, a peer reviewed high impact journal. This is a major achievement for the NEMO-1 Consortium as the findings of the NEMO-1 trial were negative. Publication of negative findings is often more difficult due to publication bias but never the less important (WP4, WP11).

The Consortium will collaborate to refine novel neonatal dosing regimens that have been developed for lidocaine and pool the expertise and knowledge that currently exists within the group in order the support the PIP approval process for both drugs.

We developed a neonatal formulation for lidocaine (a ready-to-use 50 mL lidocaine 0.1% formulation). An Investigator Brochure (IB) has been completed which contains documentation about the application of the product in the trial and the Investigational Medicinal Product Dossier (IMPD) contains all the manufacturing details (validations, formulation, premises, and equipment) of the lidocaine product.

We appreciate that a full RCT is not feasible given the time remaining in this project; however, we developed a neonatal formulation for lidocaine (a ready-to-use 50 mL lidocaine 0.1% formulation). An Investigator Brochure (IB) has been completed which contains documentation about the application of the product in the trial and the Investigational Medicinal Product Dossier (IMPD) contains all the manufacturing details (validations, formulation, premises, and equipment) of the lidocaine product.

To create awareness of the NEMO project for the broader public Prof. Geraldine Boylan and Dr. Ronit Pressler were interviewed for the Journal International Innovation, Disseminating Science, Research and Technology, Child Health which was published in May 2015. The interview included information about neonatal seizures, their detection and treatment as well as the NEMO project and its results, the NEMO consortium and lessons learned from the project.

Figure 7 The NEMO consortium at their annual meeting in 2014.

Main dissemination activities and exploitation of results

The NEMO Chief Investigator and Principal Investigator have attended and presented at numerous scientific conferences thereby creating awareness of the NEMO project and highlighting the trials challenges and results, including invited lectures, scientific presentations, and poster presentations. A poster about the main results NEMO1 was presented at the European Congress Epileptology 2014 and was awarded best poster prize.

Figure 8 Article about NEMO on the EU website (https://ec.europa.eu/programmes/horizon2020/en/news/treating-seizures-newborn-babies

In addition, several articles about NEMO have been published in journals and the internet such as an interview of Prof. Geraldine Boylan and Dr Ronit Pressler by the Journal of International Innovation, Disseminating Science, Research and Technology, Child Health which was published in May 2015. The interview included information about neonatal seizures, their detection and treatment as well as the NEMO project and its results, the NEMO consortium and lessons learned from the project.

Figure 9 Acritical about NEMO in International innervation (May 2015)

Dr Ronit Pressler was also interviewed for Lancet Neurology which was also published in May 2015. (www.thelancet.com/neurology Vol 14 May 2015)

A total of 27 peer reviewed papers were published and a further nine publications are written and near submission:

1. Weeke LC, Boylan GB, Pressler RM, Hallberg B, Groenendaal F, de Vries LS for the NEonatal seizure treatment with Medication Off-patent (NEMO)consortium: EEG background activity and electrographic seizure burden are associated with brain

injury on MRI and neurodevelopmental outcome in full-term infants with neonatal seizures

2. Nathan Stevensson, Ronit Pressler, Steward Boyd, Linda de Vries, Neil Marlow, Blennow M, Geraldine Boylan, Sampsa Vanhatalo: Analysis of anti-seizure drug effects in the neonate: comparison of conventional and posthoc assessments in a trial using bumetanide.

3. Nathan Stevenson, Geraldine Boylan, Ronit Pressler, Sampsa Vanhatalo: Powering treatment trial for an episodic illness: revisiting trial designs of neonatal antiseizure treatment using empiric data

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5. Thomas Le Saux, Ronit M Pressler, Geraldine Boylan, Boubou Hallberg, Catherine Chiron, Gerard Pons, Vincent Jullien, Determination of phenobarbitone and bumetanide in human plasma using HPLC with coupled UV-Vis and fluorescence detections: application to a pharmacokinetic study in neonates.

6. Murray MM, Murray DM, Pressler R, Hallberg B, Madden D, Greene R, Boylan GB. On behalf of the NEonatal seizure treatment with Medication Off-patent (NEMO) consortium, Obtaining informed consent to clinical trials in neonatal seizures: the NEMO study protocol. Clinical Trials (Finalising Paper)

7. Lena Hellström-Westas, Geraldine Boylan, Johan Ågren, Mairead Murray, Neil Marlow, Ronit M Pressler Survey on Neonatal Seizure Management in Europe

8. Pressler RM, Boylan GB, Marlow N, Blennow M, Chiron C, Cross JH, de Vries LS, Hallberg B, Hellström-Westas L, Jullien V, Livingstone V, Mangum B, Murphy B, Murray D, Pons G, Rennie J, Swarte R, Toet MC, Vanhatalo S, Zohar S. Developing drugs for neonatal seizures – NEMO: lessons learned. (Archives of Disease of Childhood)

9. Pressler RM, Boylan GB, Blennow M, Chiron C, Cross JH, de Vries LS, Hallberg B, Hellström-Westas L, Jullien V, Livingstone V, Marlow N, Murphy B, Murray D, Pons G, Rennie J, Toet MC. Lidocaine for 2nd line treatment of neonatal seizures – a double blind, randomised controlled trial (BMC Pediatrics or Trials)

NEMO produced also web-based dissemination in form of:

1. Educational tool for clinicians and health care professionals on EEG in neonatal seizures.

2. Educational tool for parents on HIE and neonatal seizures.

Both educational tools can be found under the following link: http://www.nemo-europe.com/en/educational-tools.htm

To keep our educational tool for parents as well as for clinicians open as long as possible we decided to prolong its web appearance and transferred it to another server. Thereby it is ensured that parents and clinicians get information via the website for the next few years.

Figure 10: Web based education tool developed by NEMO

Outlook and future research

As stated in our contingency plan in the original application to the EU, if an RCT of bumetanide was not supported by the results of NEMO-1 we would move to an alternative neonatal AED. While we had originally stated that we would consider midazolam, compelling evidence has emerged for the use of lidocaine as a neonatal AED thereby justifying an RCT.

Lidocaine is on the EMA priority list and there are a number of reports of lidocaine's success as an AED (Hellstrom-Westas et al 1988; Kobayashi et al 1999; Boylan et al, 2004; van den Broek et al 2013). Recent publications from UMCU have included PK data for lidocaine in term neonates undergoing therapeutic hypothermia and focused on novel dosing regimens based on simulations using data from a pharmacokinetic model (van den Broek et al 2011; van den Broek et al 2013). In addition, recent as yet unpublished research has indicated that in a human neural stem cell model, cooling attenuates AED apoptosis for phenobarbitone and lidocaine but not for levetiracetam. As cooling is now established as a standard of care for HIE in all tertiary referral centres, our choice of lidocaine as a first choice second line AED is based not only on a novel dosing regimen which has a proven short term safety profile but on emerging data that lidocaine has a reduced apoptotic effect under cooling.

In Europe midazolam is the most commonly used second-line or third-line add-on drug for the treatment of seizures refractory to phenobarbitone. We know that it is effective for the control of status epilepticus in adults and children. Recent evidence from a number of small studies does seem to indicate that midazolam may be a useful treatment for seizures in babies, but the exact dose and dosing regimen has not been established (Boylan et al., 2004; Castro Jr et al., 2005,). Historic studies in small number of infants reported effectiveness as second line treatment with responses of 67 % and 80 % (Shany et al. 2007,

Yamamoto et al., 2007) whereas a recent study reported only 23% in asphyxiated babies under hypothermia (Van den Broek et al., 2015).

The NEMO consortium has gained considerable international reputation during the last 4 years and is considered as the strongest consortium to evaluate neonatal seizures in Europe, maybe even worldwide. We applied for further funding in Horizon 2020 to evaluate if lidocaine is superior in reducing seizure burden compared to midazolam in neonatal seizures refractory to phenobarbitone in a randomised controlled trial (NEMO-Lido). In order not to lose momentum and risk the knowledge, expertise and collaboration developed in NEMO1 we used the remaining time to build the ground work for this new trial with lidocaine and midazolam in the remaining months.

We achieved to developed a neonatal formulation for lidocaine and generated and tested a ready-to-use 50 mL lidocaine 0.1% formulation. Furthermore, an Investigator Brochure (IB) has been completed which contains documentation about the application of the product in the trial and the IMP contains manufacturing details (validations, formulation, premises, and equipment) of the lidocaine product.

For the NEMO-Lido trial we already performed the site selection of participating centres. Moreover, we finalized the NEMO-Lido study protocol and completed a Patient Information Leaflet (PIL) and an Informed Consent Form (ICF) (WP1).

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Section 2 – Use and dissemination of foreground

2.1 Plan for use and dissemination of foreground (including socio-economic impact and target groups for the results of the research)

Section A

List of Scientific Publication

For more information please see the ECAS system.

List of Dissemination Activities

For more information please see the ECAS system.

Section B

No patents, trademarks, registered designs, etc. were applied.

Section 3 – Report on societal implications

Please see ECAS.