PUBLISHABLE SUMMARY (M37-M54)

Summary description of project context and objectives

Many medicines used in children, especially neonates, have never been tested to the level seen in adult healthcare. Dose, dosing schedules and even routes of administration have often been established by simple extrapolation from clinical trials in adults. Children and neonates are often treated with drugs that are unlicensed or off-label. Age-related differences in drug absorption or metabolism result in drugs being started at doses which turn out to be suboptimal. Pragmatic adjustments are then made to improve the target outcome, but the evidence-base for these decisions is weak. The lack of formal studies in babies and children means that adverse events are poorly understood. There is an urgent need to resolve this unsatisfactory state of affairs. The new EU and US Paediatric Drug Regulations require the industry to provide age appropriate formulations of medicines in neonates through to adolescents. In Europe, new drugs must have a Paediatric Investigation Plan (PIP) as part of their development. As an incentive the company obtaining a Marketing Authorisation after a PIP will receive an extension of the patent period. The problem with currently used off label / off licence old drugs is that the pharmaceutical industry has little incentive to invest in such studies. As a consequence the European Commission has specifically allocated funding for studying frequently used off label drugs in newborns and children in order to achieve a Paediatric Use Marketing Authorisation (PUMA) for age- appropriate formulations that have minimal toxicity. This funding is targeted at drugs on a priority list issued by EMA/FDA. The priority list includes dobutamine. We have selected this drug for two reasons. First, because there is a pressing need for effective therapies for disturbances to the neonatal circulation. Second, dobutamine is unique among proposed treatments for the neonatal circulation in that there is evidence that the use of dobutamine is likely to reduce the incidence of disability. This evidence relates to the use of dobutamine to treat low superior vena cava (SVC) flow. Thus, the primary aim of the proposed research is to conduct work that leads to a PUMA for dobutamine as a treatment for low SVC flow.
The project has two aims:
(1) to develop and study an age appropriate formulation of the drug Dobutamine for newborns and
(2) to develop a new definition of neonatal shock.
It is well established that the individual response of preterm and newborn babies to dobutamine treatment varies from an extremely good response to total resistance even if high doses are given.

Genetic factors alter the individual response to many medications including dobutamine. However, no data are available so far for the pharmacogenetics of dobutamine in preterm and newborn infants.

NEO- CIRC has been working towards the setup of a biobank of maternal and infant DNA (including infant umbilical cord tissue, which will be available for further metabolomic and

proteomic studies). Genome wide array studies in more than 2000 preterm infants have started in 2011 by the German Neonatal Network (GNN), a consortium which is led by WG at ULU. Since blood pressure on day one of life is an outcome parameter of the GNN, this reference group will add substantial information to the analysis of the well characterized NEO-CIRC cohort, which will contribute important pharmacokinetic and pharmacodynamic data. Clinical practice and research currently are hampered by the lack of a shared definition of neonatal shock. The platform for research that we have developed to work on the PIP for dobutamine will allow us to develop a definition of neonatal shock and embed it in clinical guidelines. Thus, NEO-CIRC aims to deliver pharmaceutical, pre-clinical and clinical work that will contribute to a PUMA for dobutamine as treatment for low SVC flow

A. Develop a PIP for dobutamine.
B. Develop an age-appropriate formulation for dobutamine.
C. Optimise a dosage-regimen for dobutamine in neonates.
D. Conduct preclinical studies to investigate the safety and mechanism of action of dobutamine.
E. Develop consistent approaches to measuring SVC flow and other markers of neonatal shock, with a training package to ensure that SVC flow is measured.

Description of work performed and main results

In general the Project has continued to make good progress towards achieving the fulfilment of its aims in the third period M37-M54. As already stated in the P1 and P2 reports, there were EU Paediatric Regulation requirements from the EMA after Scientific Advice and PDCO opinion that had to be outlined in the Paediatric Investigation Plan (PIP). The PIP for the studies relating to the age appropriate formulation of dobutamine was approved after amending the original plan of performing two randomized clinical trials to compare SVC-flow targeted treatment with dobutamine or placebo in both preterm and term neonates. The new plan involved a series of three clinical trials on the use of a new neonatal formulation of dobutamine in the treatment of haemodynamic insufficiency in the immediate postnatal period in preterm neonates: NEOCIRC001 (a therapeutic exploratory study and pharmacokinetics and pharmacodynamics sub-studies), NEOCIRC002 (a dose-finding study) and NEOCIRC003 (a randomized controlled safety and efficacy confirmatory study); plus one systematic review of the use of dobutamine in patients from 33 weeks GA to less than a postnatal age of 28 days (NEOCIRC004).

These new requirements resulted to extensive changes to the project work plan which were implemented in period 3.

The restructuring of most work packages' activities, and specially WP5, resulted in more intense engagement of the partners involved in the clinical trials' preparations, and less intense engagement of the ones contributing as clinical trial sites mainly.

The work of the period 3 was focused on:

1. preparation and approval of all the regulatory documents regarding NEO-CIRC001
2. Preparation for opening and completion of the 1st trial NEO-CIRC001A
3. Preparatory work on the next planned trials NEO-CIRC002 and 003
4. Completion of WP4 experimental animal work
5. Completion and publication of NEO-CIRC004

After completion of NEO-CIRC001A the available data from this and other new studies were reviewed and a PIP amendment was submitted to EMA. The result of this submission is currently awaited. The consortium suggested in the PIP amendment to pursue the large randomized trial NEO-CIRC003 based on the new evidence available.

Expected final results and potential impacts

The current status of the project will be significantly affected by the outcome of the PIP amendment request that is under review by the EMA and which involve the following changes:
- Preparatory work and opening of NEO-CIRC003
- Changes in the distribution of the project budget and indicative effort among the partners

Once the proposed changes are accepted, the consortium will be able to continue towards achievement of the final project goals.