



PUBLISABLE SUMMARY (M19-M36)

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. 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 will setup 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 will be done 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: 1. 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 second period M19-M36. As already stated in the P1 report, 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 randomised clinical trials to compare SVC-flow targeted treatment with dobutamine or placebo in both preterm and term neonates. The new plan involves 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 randomised 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. They range from complete elimination of some tasks, replacement of others with new tasks, addition of some and complete change of the timing of most (start ahead or behind of original time, be prolonged or shortened). Formal changes to the project plan are introduced through an amendment.

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.

In this sense work of the period was focused on:

1. the completion of the PIP amendments and approval of the final documents
2. preparation and approval of all the regulatory documents regarding NEOCIRC001
3. preparation for and opening of the 1st trial NEOCIRC001A
4. finalization of WP4 experimental work

Expected final results and potential impacts

The current status of the project will be significantly affected by the outcome of the Grant amendment request that is under preparation and which involve the following changes:

- Extension of the project period for two years, i.e. the expected end date of the project is 30/09/2018 (M84).
- New end dates for most WPs apart from WP4
- New delivery and achievement dates for most of the deliverables and milestones apart from D7.1, D8.1 and MS18.
- Insertion of three new and renaming of the original deliverables at WP5
- Changes in the distribution of the project budget and indicative effort among the partners

Once these changes are accepted, the consortium will be able to continue towards achievement of the final project goals without major deviations.