



Many medicines used in children and neonates have never been tested to the level seen in adults. Dose, dosing schedules and 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. As a result, there is an urgent need to resolve this unsatisfactory state of affairs.

The new EU and US Paediatric Drug Regulations require industry to provide age appropriate formulations of medicines for 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 off label / off licence old drugs currently used 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 new-borns 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 which includes dobutamine.

The importance of research on dobutamine is twofold:

1. There is a pressing need for effective therapies for disturbances to the neonatal circulation.
2. Dobutamine is unique among proposed treatments for neonatal circulation in that there is evidence that its use is likely to reduce the incidence of disability. This evidence relates to the use of dobutamine to treat low superior vena cava (SVC) flow.

The first aim of the research proposed by NEO-CIRC (Dobutamine for NEOnatal CIRCulatory failure defined by novel biomarkers), a project funded under the EU's 7th Framework Programme (FP7), is to develop and study an age appropriate formulation of dobutamine for new-borns and deliver pharmaceutical, pre-clinical and clinical work that will contribute to a PUMA for dobutamine as treatment for circulatory failure. This will be accomplished by:

- A. Developing a PIP for dobutamine to produce evidence on its safety and efficacy.
- B. Optimising a dosage-regimen for dobutamine in neonates.
- C. Conducting preclinical studies to investigate the safety and mechanism of action of dobutamine.
- D. Studying specific markers of neonatal shock and developing consistent approaches to measuring these markers in the clinical trials.
- E. Conducting genetics studies: 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 new-born infants. NEO-CIRC is working together with the German Neonatal Network (GNN), a consortium led by NEO-CIRC partner ULU, to close this research evidence gap.

The second aim of the proposed research is to develop a definition of neonatal shock and embed it in clinical guidelines using the platform for research developed to work on the PIP for dobutamine. Clinical practice and research are likely to benefit by a shared definition of neonatal shock which is non-existent at the moment.

The NEO-CIRC Consortium includes international experts in neonatal medicine, pharmacology, pharmacogenomics, drug formulation and pre-clinical neonatal models and an experienced group of multicentre clinical trials NICU's.

During this period three Requests for Modification (RfM) of the PIP were negotiated with the EMA Paediatric Committee to agree on a way forward for the project. This has delayed the start of the NEOCIRC-003 Clinical Trial and all project activity dependent on trial data. In spite of this the various work packages have shown good progress as described next; mainly because consortium partners have tried to minimise the impact of the delay by working on activities in parallel to RfM negotiations where possible, and because of the intense collaboration and communication between consortium partners during this period.

The work performed by each of the NEO-CIRC work packages during the period 1st April 2016 to 30th September 2017 is summarized next:

WP1 - Pharmacokinetic (PK) and Pharmacodynamic (PD) models

Results of the NEOCIRC-001A study were used in the design of the PK/PD sections of the protocol for NEOCIRC-003; mainly to establish timing of PD evaluations, to determine the PK blood sampling schedule, and to update the corresponding Standard Operative Procedures.

WP2 - Pharmacogenetics

A tool for genetic blood pressure estimation in preterm infants was developed, by using existing genome wide association data from the German Neonatal Network. This allowed for the definition of a genetic model for susceptibility for shock in preterm infants, which will be applied to the analysis of the individual response to dobutamine treatment in infants recruited into NEOCIRC-003.

WP3 - Non-invasive biomarkers to measure/define shock in neonates

The objectives and endpoints of advanced biomarkers to be included in the study protocol of NEOCIRC-003 were established and the biomarkers SOPs were updated. Relevant study staff from the clinical centres continued local training and research activities to assess the applicability of biomarkers in preparation for the next trial.

WP4 - Neonatal / Juvenile animal models

The animal studies were completed in the previous period of the project.

WP5 - Clinical trials

Significant work was carried out during this period on the design of the new clinical trial to incorporate the outcomes of the PIP RfM process; producing a robust study protocol and preparing all the regulatory documents necessary for the trial. A study plan is now in place, with a formal distribution of responsibilities between the partners to allow an effective execution of the clinical trial.

WP6 - PIP and PUMA

Substantial work was carried out in managing the PIP RfM submissions to the EMA, developing a strategy for the supply of blinded study medication, manufacturing the actual study medication and providing support for the preparation of the regulatory submission package for NEOCIRC-003.

WP7 - Knowledge Translation and Training

Dissemination of the research findings through peer reviewed publications and conference presentations continued during this period. In preparation for the NEOCIRC-003 Trial, the clinical sites continued their local training in trial related assessment and parents were involved in the design of the informed consent documentation. In preparation for the implementation of the forthcoming new definition of neonatal shock, local clinical guidelines on the management of circulatory failure were produced and the consortium interacted with external consortiums including the FP7-funded HIP trial and the International Neonatal Consortium.

WP8 - Management

A major achievement was a successful Mid Term Review meeting with the NEO-CIRC EU Project Officer and an external expert, held as part of the NEO-CIRC Consortium meeting in Hannover, Germany.

The expected final results of the NEO-CIRC project are as follows:

- Pharmaceutical, pre-clinical and clinical work necessary to progress a PUMA for dobutamine as treatment for circulatory failure:
 - Pharmacokinetic, Pharmacogenetic and Advanced Biomarkers studies on the efficacy of dobutamine.
 - Evidence on the safety and efficacy of dobutamine in neonates.
- An updated definition of neonatal shock as the basis for international guidelines for the assessment and treatment of circulatory failure.
- Answers to key clinical practice uncertainties, including variability of response to dobutamine in circulatory failure seen in new-born infants and the impact on longer term developmental outcomes which are so important to the patients, families and wider society.

The actual and potential impacts of these results are as follows:

- The project has already led to the development and testing of an age appropriate formulation of dobutamine for the use in the new-born period. This will impact on the variety of drugs available for use in new-borns and was one of the major aims of this project.
- The new dobutamine will achieve a PUMA thereby supporting the implementation of the Paediatric Drug regulation approved by the European Parliament.
- The project results will contribute to a new definition of circulatory failure and or shock in the new-born period which can be used by all clinicians treating this highly vulnerable population. The new definition will support a better outcome for affected new-born infants through targeted and individualized treatments based on the results of the genetics and clinical studies.
- Better neurodevelopmental outcome will reduce the economic on-cost of prematurity beyond the stay in hospital thereby reducing health care costs across EU member states and beyond. This will be a benefit to all EU citizens.
- The consortium has brought together academic partners from European and American institutes and industry working together on a common goal. These collaborations can be used in the future to develop other new products and scientific knowledge for the treatment of conditions affecting the new-born infants. The industry partners should also benefit from these collaborations by growing their expertise and business portfolio.
- Further international collaborations through the participation in the International Neonatal Consortium should strengthen the links between different continents and improve the care of the new-born infants around the world.

Project Title

NEO-CIRC

Dobutamine for NEOnatal CIRCulatory failure defined by novel biomarkers

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For more information www.neocirculation.eu/contact.shtml