Information for Parents and Consent for Participation to the Clinical Trial

Study: Erythropoietin for the Repair of Cerebral Injury in Preterm Infants

Full version of the trial title: Erythropoietin for the repair of cerebral injury in very preterm infants - a randomized, double blind, placebo-controlled, prospective, and multicenter clinical study

Sponsor: Department of Neonatology, University Hospital Zurich

Dear Parents

We kindly ask you hereby to agree to the participation of your newborn infant to the clinical study investigating the effect of erythropoietin on the repair of cerebral injury. The relevant information in order to take a well-informed decision will be given to you by a physician. The most important aspects are described here to allow you to read them at any time.

Objective of the trial

The objective of this study is to investigate the effect of Recormon with the active ingredient erythropoietin on the outcome of very preterm infants. We aim at evaluating whether Recormon has the potential to ameliorate the neurodevelopmental sequelae of intraventricular hemorrhage in preterm infants.

General information about this clinical trial

In spite of optimal care, preterm infants have an increased risk for damage to their immature brain, and thereby for a developmental delay later on. Recormon (erythropoietin, EPO), a hormone naturally produced by our own body stimulating red blood cell production, has been proposed to reduce brain damage when given in higher doses.

This is an international study with study sites in Switzerland and Germany. As opposed to Germany and the United States of America, Recormon is not approved for the use in preterm infants in Switzerland. Nevertheless, it has been used in Switzerland for many years to stimulate the production of red blood cells in the bone marrow. It is a safe and well-tolerated treatment, as demonstrated by a recently finished study in our clinic.

This is a blinded study. Neither the parents of the included infants nor the physicians and nurses will know which treatment will be applied. Medication and placebo (medication without active ingredient) cannot be differentiated. Allocation to one or the other group will be done at random, which means that there is a probability of 50% for your infant being treated with Recormon. The key of allocation to one or the other group can be opened in case of urgent need.

The dosage used in the study will be higher than the one to treat anemia. The medication will be given intravenously to be carried directly to where it is needed within the brain. Study treatment comprises the administration of 5 doses erythropoietin or physiologic saline, starting on the 5th day of life, continuing on days 6, 7, 14, and 21.

Apart from the administration of the study medication there is no procedure within this study, which is not part of routine management of very preterm infants. No single additional prick or blood sample for study reasons will be performed in your baby. Besides routinely performed ultrasound examinations of the head, a magnetic resonance imaging (MRI) of the brain at term is another component of our study. This examination is clinically indicated in all infants suffering from brain damage. All very preterm infants will additionally be included in a follow-up programme to test the psychomotor development at 2 and 5 years. These are important examinations, first to detect developmental delays in order to establish adequate therapies, and second, to interpret the efficacy of our study medication.
The study will be carried out in accordance with Swiss legislation and internationally approved guidelines. It has been endorsed by the independent Cantonal Ethics Committee in charge.

Voluntary participation
Your participation in this study is voluntary. If you do not wish to take part in it, it will not be at a disadvantage with regard to the medical treatment of your baby. This also applies if, once you have agreed to take part, you then change your mind at a later point. You are entitled to withdraw your agreement at any time. You are not required to justify your decision. If you withdraw, the data collected so far will be used for research purposes.

Trial structure
For each patient, the study will include a 3-week-treatment with the study medication (EPO or physiologic saline), a brain MRI at term and neurodevelopmental follow-up examinations at 2 and 5 years of age. The results of routinely performed cranial ultrasound examinations during hospitalization will additionally be included in the final analysis. A specialized team will perform the MRI examination here in Zurich at the department of neonatology, when your baby is in natural sleep. This examination will not take more than an hour. The follow-up examinations, for which you will be invited separately, will also take place in Zurich at the University's Children Hospital.

Obligations on the part of the parents
As parents of participating infants, it is your duty to obey the medical instructions of your investigator and respect the study protocol (taking part in the MRI examination at term and in the psychomotor follow-up examinations with 2 and 5 years of age).

Other treatment methods
Beyond the study, there aren't any other procedures to reduce brain damage after an intracerebral hemorrhage has happened.

Advantages for the participants
Taking part in this study won't give your baby a confirmed advantage. Nevertheless, your baby has a 50% chance to receive EPO and to benefit from the supposed advantages, which might for example be a reduced need for blood transfusion, as mentioned above. Taking part can generally contribute towards improving the treatment for babies who develop the same brain injury.

Risks and disagreeable aspects
EPO is an established and approved treatment in preterm infants for preventing/treatment of anemia. In this study, EPO is given in higher dose and earlier than in the treatment of anemia. It is a safe and well-tolerated treatment, as demonstrated by a recently finished study in our clinic. Nevertheless there may be other risks that have not been identified at present.
As you already know, an MRI examination around term will be part of the study. Some babies will have an uncomplicated course and will already be dismissed, when the MRI will take place. These babies will be invited separately, whenever possible simultaneously with the first active immunization, which in preterm infants is normally conducted under cardiorespiratory monitoring in a stationary setting.

New findings
During the study, the investigator will inform you of all new findings that could influence the utility of the study or its safety and thus your agreement to take part in the study. You will receive this information orally and in writing. In the case of incidental findings (e.g. from MRI), that could contribute towards preventing, confirming and treating an existing illness or one that could be expected in the future you may choose either a) to be informed directly of these findings, b) you do not wish to be informed, or c) you leave the decision to your attending physician (see statement of consent).

Confidentiality of data
During this study, personal and medical data about your baby will be collected. This data will be encrypted, i.e.

given a code. Only encrypted data is made accessible to experts for scientific evaluation. Special experts from the sponsor may investigate whether the study is carried out within the framework of quality controls. These experts, as well as – in the framework of inspections – members of the competent authorities and ethics commitees may be granted access to your baby's non-coded medical history, via your investigator. In the case of any harm, representatives of the insurance company are also granted access to your medical data, via your investigator, but only to the extent that this is necessary to handle the claim. Throughout the entire study and during the examinations mentioned, strict confidentiality is ensured. Your name will under no circumstances be published in reports or publications arising from the study.

The attending pediatrician will be informed about participation of your baby in the study by a summarizing report. The sponsor in Switzerland is responsible for complying with national and international data protection directives.

Costs
The study-specific examinations mentioned in this information sheet for participants are free of charge. Neither you nor your health insurance scheme needs to pay additional costs in connection with your participation. Expenses (e.g. travel) will be reimbursed as follows on presentation of the corresponding proof of payment, and in agreement with the investigator. The cost of medicinal products and treatments that you use for your baby independently of the study are not covered by the sponsor of this trial.

Payment for trial participants
You will receive no payment for taking part in this clinical study.

Involuntary discontinuation of the trial
The investigator or the sponsor can interrupt your participation (e.g. impossibility to take part in the neurodevelopment test at 5 years or detection of a genetic disorder not known prior to the beginning of the study).

Coverage of damages
The University Hospital of Zurich (USZ) will compensate you for damage that occurs within the framework of the clinical study. For this purpose, the USZ has taken out insurance in your favor with "Zürich Versicherungsgesellschaft AG, Postfach, 8085 Zürich". If the health of your baby is impaired or if it suffers any damage during or after the clinical study, please contact the investigator responsible for this study. He will initiate the necessary steps for you.

Contact persons
If anything is not clear, or in the case of unexpected or undesirable side effects that occur during or after the study, you may contact without hesitation the staff given below at any time by using the common phone number: 044 255 53 40 or by using the given address.

Staff:
PD. Dr. S. Wellmann, Prof. Dr. H.U. Bucher, Prof. Dr. JC. Fauchère, Dr. C. Hagmann, Dr. C. Rüegger

Address: Klinik für Neonatologie, Universitätsspital Zürich, Frauenklinikstrasse 10, 8091 Zürich

Phone number with 24 hour access: 044 255 53 51

Date: 10.04.2014