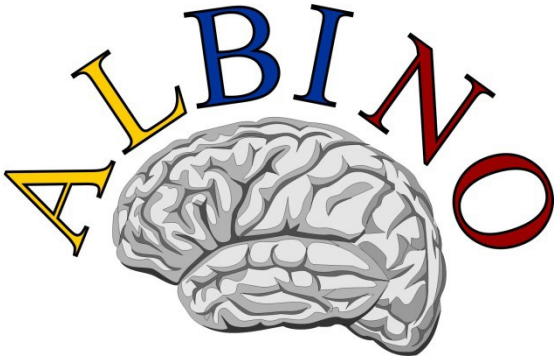
Effect of ALlopurinol in addition to hypothermia for hypoxicischemic Brain Injury on Neurocognitive Outcome
- ALBINO -
– a blinded randomized placebo-controlled multicenter trial
(EUDRACT-No.: 2016-000222-19)



Information for Parents and Guardians

(English version for Belgium, Version 3.1, 11.12.2019,
adapted from English version Tübingen Germany –Version 4.0, 24.02.2019-)

Dear Parents and Guardians,

You receive this information because your child was born under very difficult circumstances with biochemical signs of seriously impaired oxygen supply during birth which might have resulted in brain injury.
The attending paediatrician has already discussed with you your baby's individual situation and treatment. The following pages are to inform you in detail about the ALBINO study and help you to reach a decision on your child's participation.

The hospital where you gave birth to your baby is participating in the ALBINO study because the attending paediatricians, after careful consideration of benefits and risks, expect a neuroprotective effect (that means protecting the brain) by administering the drug "Allopurinol" very early after birth. Based on an expected favorable benefit/risk-ratio and with the approval of all relevant institutions and ethics committees, your child has received a dose of the study medication (Allopurinol or placebo) without your prior explicit consent. This procedure different to the standard (information, period of reflection, consent, participation in the study) was necessary because it was impossible to ask you for your consent in the emergency situation immediately after birth before administration of the study medication.

We kindly ask you to carefully read the following pages and discuss possible questions with your local study investigator. We hope that you will give your consent for further participation in the study. (This procedure is called "deferred consent" and is an established procedure for clinical research in emergency care settings.)

Background information on the problem of brain injury due to impaired oxygen supply during birth ("hypoxic-ischemic brain injury")
Despite all efforts of obstetricians and midwifes for the well-being of the mother and the newborn, in 1-4 of 1000 births, unforeseen complications may occur which result in impaired oxygen supply to the yet unborn child. The body can cope with a certain degree of impaired oxygen supply: all cells can also gain energy without oxygen, producing lactic acid which can be recognized in the acid value in the blood. However, in the above described rare cases of severely impaired oxygen supply, the brain can be damaged. Additionally, impaired oxygen supply may provoke complex

cascades (sequence of processes) of “secondary events” that may ultimately result in long-term mental or neurological impairments in some of these infants (e.g., reduced intelligence, paralyses, seizures). The only established therapy so far is therapeutic hypothermia, a procedure which aims at reducing the above mentioned secondary events and hence brain injury and permanent impairments by cooling the body (and hence the brain) of the infant to 33.5°C for 72 hours. Unfortunately, despite this therapy, up to 40% of infants will still have life-long impairments.

Aim of this study

It is the aim of this ALBINO study to evaluate the study medication (allopurinol) which has the potential to reduce “oxygen radical formation” and thus reduce the frequency and degree of severity of permanent impairments after impaired oxygen supply. (Oxygen radicals are harmful oxygen molecules which damage cells and contribute to the ‘secondary’ brain injury following perinatal oxygen deprivation).

Allopurinol

Allopurinol is an “old” drug, well-known for many decades from the treatment of gout in adults. Allopurinol inhibits an enzyme (‘Xanthine Oxidase’), which, in the context of hypoxic-ischemic brain injury, generates oxygen radicals. Furthermore, allopurinol may scavenge oxygen radicals directly and bind and detoxify iron atoms, which are set free during hypoxia and may themselves generate oxygen radicals. Studies in animals show that allopurinol reduces the formation of oxygen radicals and brain damage with perinatal hypoxic-ischemic brain injury.

What is being done in this ALBINO study?

To examine, whether allopurinol indeed has the expected neuroprotective effect, half of the study participants receive 1-2 doses of allopurinol whereas the other half receive an ineffective substitute (placebo). Allocation to the treatment groups is carried out automatically in a random sequence. Neither parents nor physicians are able to influence this treatment allocation. (This procedure is called “randomization” and aims to allocate known and unknown risk factors equally to both treatment groups).

Newborn infants with biochemical signs (increased lactate in the blood) of impaired oxygen supply during birth and clinical signs of *potential* consecutive brain injury receive 20mg/kg body weight study medication (allopurinol or placebo) within 30 min after birth.

To prevent that our expectations of benefit will inadvertently change the study results, neither your child’s doctor nor yourself will know which type of medication was given until the study is completed (‘blinded study’).

A second dose (10mg/kg) of the same study medication is given 12 hours after the first dose, provided the infant meets criteria for therapeutic hypothermia and you gave consent to study participation by then.

Almost 900 infants will be recruited into the ALBINO study in more than 60 hospitals in at least 13 European countries.

All infants will receive all supportive therapies considered standard of care including therapeutic hypothermia whenever such therapies are clinically indicated.

Why is the ineffective substitute (placebo) “Mannitol” being administered in the ALBINO study?

Doctors and patients (and their parents) tend to expect a positive effect from new medications. By using the placebo, it shall be excluded that the expectation of a benefit shall pretend an effect of the medication “Allopurinol”. Mannitol is used as an excipient in many other medications (e.g. Paracetamol, a frequently used medication to reduce fever and treat pain in newborns) and is also administered to newborn infants frequently in much higher doses than in the ALBINO study.

In addition, Mannitol has been used for decades in much higher doses as a diuretic. For the ALBINO study, a minimal dosage of Mannitol shall be administered. Thus, no effect (nor side effects) are being expected at all.

Discharge home, duration of the study, follow-up examination at the age of 24 months Your baby does not have to stay longer in hospital due to the study, but will be discharged home whenever your doctor thinks your child is „fit enough to go home“. The study will end with a standardized neurodevelopment assessment at 24 months of age.

Assessment of outcome

The following examinations aim to assess the effect of allopurinol on brain injury. These examinations are considered standard of care for infants following perinatal oxygen deprivation and hence ‘clinically indicated’ in the majority of study centers. If, at the institution where your child is cared for, any of these examinations should not be part of routine care, the investigator will inform you which of these examinations will be study-driven, will provide additional information and ask for additional consent separately.

1. Neurodevelopment assessment at 24 months of age

This examination does not cause any pain or stress. It is very similar to routine check-ups by pediatricians. Your baby’s mental and physical progress will be assessed as well as his/her ability to walk, to perceive pictures and to concentrate while coping with a task. Most kids have fun doing these tests.

This examination is the most important part of the ALBINO study because it enables to assess brain functions such as cognition, language, gross and fine motor skills.

2. Cerebral ultrasound (CUS) examinations at 1, 3 and 5 days of age, and Magnetic Resonance Imaging (MRI) at 2-10 days after birth

CUS is a painless, quick examination without relevant side-effects which is routinely performed in ill newborn infants.

MRI is also a painless, but more elaborate examination for which your infant is placed into a scanner while being supervised by a trained technician, nurse or doctor.

Both examinations provide (restricted) information on the existence, the severity and the localization of brain injury due to impaired oxygen supply.

3. Electroencephalogramm (EEG)

EEG is a painless way of recording the electrical activity of the brain. It helps to assess whether the brain has been affected by the oxygen deprivation and whether hypothermia treatment should be done. It also helps to assess whether your child suffers from seizures following perinatal oxygen deprivation. Your child will be assessed by aEEG (amplitudeintegrated EEG) or by multichannel EEG, before, during and after start of cooling therapy. EEG will also be performed before discharge home.

If at the institution where your child is cared for, any of the above mentioned examinations (13) should not be part of routine care for your child (e.g. because he/she has recovered so quickly); the investigator will inform you which of these examinations will be *study-driven*: He will provide additional information and ask for *additional consent* for the *study-driven* examinations.

Additional study-driven examinations (limited to specific study centers for costs and logistic reasons).

1. Blood and urine examinations

In the participating Belgium hospitals no additional study-driven blood- or urine samples will be taken.

2. Near-infrared Spectroscopy

To measure the brain’s oxygen supply during intensive care For this painless examination light is sent into the tissue and by measuring the light which returns to the surface, the oxygen supply can be determined. Devices are approved for use on babies.

Benefits for your baby and the society in case you decide to participate to the trial
When you decide that your child can participate to the study, allopurinol may or may not prove beneficial for the treatment of your child. Your child has a 50% chance to have received the active study medication (allopurinol), (and in case of hypothermia treatment will receive a second dose). 'Preliminary' studies in human infants with brain injury due to impaired oxygen supply suggest that there may be a reduction of death or long-term neurodevelopmental impairment (reduced intelligence, paralyses, seizures) by up to ~60%. If your child receives the placebo (also 50% chance), no benefit is being expected.
However, an additional potential benefit for all participants is that supervision and very detailed neurodevelopment follow-up in the context of this study may help to diagnose minor developmental deficits earlier and hence enable earlier interventions.

Disadvantages or potential risks for study participants
Your child will not have any predictable disadvantages from study participation, In any case your child will receive the full established therapy available for infants with impaired oxygen supply during birth.
The risk of serious adverse effects of allopurinol is considered very, very small but the following adverse effects might occur:
1. Local irritations of para-vascular tissue at the injection site
The main adverse effect shown in former studies with allopurinol with newborns and infants was the irritation of para-vascular tissue at the injection site, particularly if the intravenous access was not well placed. In the former studies with intravenous administration of allopurinol to 58 newborns and 178 infants these irritations have always disappeared. In some patients it might lead to skin irritations with appearance of scars which may lead to permanent cosmetic consequences.
2. Hypersensitivity reactions to allopurinol
Severe hypersensitivity reactions to allopurinol are reported for adults (mainly from Asia) which mainly affect the skin but may also affect other organs and which in rare cases may even be fatal. Normally, these reactions occur after several weeks of treatment. The exact risk for such a severe hypersensitivity reaction in the setting of the ALBINO study is unknown, but probably less than 1 : 10,000). During treatment of more than 700 newborns and premature babies with allopurinol so far, there have not been any of such reactions, but it is possible that unexpected effects appear

Potential benefits for future patients
The ALBINO investigators hope that the study will show efficacy and safety of the study drug and thereby provide a new, well-studied treatment option for newborn infants. It might be that more babies can be discharged healthy in the future. Furthermore, we hope to improve our ability to predict outcome of infants with perinatal oxygen deprivation and thereby support decision making of parents and medical teams in the future.

The study has been critically reviewed and approved
The study protocol, and particularly the deferred consent procedure have been critically reviewed and approved by well-known medical experts not involved in the study, by parents and ethicists, and by the relevant ethics committees and regulatory authorities. The central ethical committee is the ethical committee of UZ Leuven. You should under no circumstances regard the positive advice of the ethics committee as an incentive to participate in this study.

The study is continuously supervised
To ensure maximum safety of all study participants and to ensure that the study will be modified or stopped early in case there will be new evidence of harm, the study is supervised by an independent Data Monitoring Committee (Committee of experts who don't participate in the study) at specified intervals. All serious adverse events which might be related to the study medication must be reported (without name and address) to the coordinating study center and the industry

partner within 24 hours. In case of imminent danger for the patients, they will immediately stop the study and report these events to the public authorities and the ethics committees.
In case a problem occurs or in case something goes wrong , you can always contact the study doctor or the ombuds service of the hospital where your baby is being treated.

The study is being realized by public funds
The study is funded by the European Commission after having been selected out of several hundred applications. The study is being „sponsored“ (guided and supported) by the Universitätsklinikum Tübingen, Germany, i.e. the Universitätsklinikum Tübingen is responsible for the sound conduct of the study. No extra compensation is provided for the participants. There are also no extra costs for the participating patients.

Participation in the study is voluntary
Of course, the participation in this study is voluntary. Your child's doctor will ask you to sign a consent form and thereby confirm that you have been completely informed about the study and understood the aim. If you refuse the participation, this will not have any negative impact for you and your baby nor will your decision influence the relation to your child's doctor or nursing staff. Your baby will still receive the best possible treatment.

Data protection
At all times, the identity of your child will only be identifiable at the institution where your child is being cared for. After removal of the name/address of your child, only appropriately 'pseudonymized' data (without name and address) will be transferred to the protected study database at the 'Sponsor' of the study, where it will be stored for at least 25 years. Thereafter, all data which could enable re-identification will be re-moved (study code, exact dates, etc.). Publications of study data will exclusively rely on 'anonymized' data (which will no longer enable identification).

Your baby can leave the study without prior notice
Even if you have given your consent to participation in the study, you can revoke it without prior notice and without mentioning the reason. Your decision to do so will not have any negative impact on your baby's medical treatment or your relation to the medical team. In this case, the data collected about your baby up to that point of time will still be evaluated because also incomplete data might contain important information that may help other babies.
If the study doctor thinks that there might be any negative impacts for your baby (which, however, are not expected), he/she can terminate the participation of your child even without your authorization. In this case the doctor would continue to treat your child according to the best medical knowledge without being part of the study.
The study can be stopped by the sponsors, the ethical committee or the authorities. The further follow-up will then happen as described as above.

Of course, you will be informed about changes
You will be informed about the results of the study. If there are any changes concerning the study, we will again ask you for your consent.

Insurance coverage
Any participation in a clinical study involves a risk, however small it is. Even if there is no fault, the sponsor accepts responsibility for damage caused to the participant (or in the event of death, his/her dependants) and directly or indirectly linked to his/her participation in the study. The sponsor has taken out insurance for this responsibility[1].

You are therefore asked to report any new health problem to the investigator. He/she will be able to provide you with additional information concerning possible treatments.

[1] In accordance with Article 29 of the Belgian Law related to experimentson humans (7 May 2004)

If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of your disease or the known side effects of your normal treatment), he/she will inform the study sponsor, which will initiate the declaration procedure to the insurance company. The latter will appoint an expert - if it considers it necessary - to assess whether there is a link between your new health problems and the study.

In the event of disagreement either with the investigator or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or - in case of death - your dependants may bring proceedings against the insurer directly in Belgium (Vanbreda Risk& Benefits NV, polisnumber 299.053.700, Plantin en Moretuslei 297, 2140 Antwerpen, België).

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer's registered offices.

Further questions

If you have any further questions relating to this study or to your rights and duties as parents of a child that participates in the study, please do not hesitate to contact your local study doctor. You can also contact the relevant regulatory authority (FAMHP: Federal Agency for Medicines and Health Products) who has approved the study.

Your study doctor: .....

Department: .....

Address: .....

Tel: .....

E-mail: .....