Patient Information Sheet – APOSTEL 8 study

The effect of tocolysis on preterm birth outcome, the APOSTEL 8 trial.

Dear Madam,

We invite you to participate in a medical trial. Taking part is voluntary.
If you decide to participate, your signed informed consent is required.
You receive this letter because you are admitted to hospital due to preterm contractions and/or preterm ruptured membranes. This is also called threatening preterm labour.

Before you decide if you wish to participate, we explain the content of the study. Please take the time to read the following information carefully, and ask the investigator to answer any questions you have. You can also ask the independent physician, who is named at the end of this letter, for additional information. You can also discuss with your partner, friends or family. Additional information on participating in a medical trial is present in the Dutch brochure: https://www.rijksoverheid.nl/onderwerpen/medisch-wetenschappelijk-onderzoek

1. General information
This study will involve 1,500 women in about 30 hospitals in the Netherlands. The medical ethical committee approved this study.

2. The aim of the study
The aim of this study is to assess the safety and efficacy of tocolytics drugs (tocolysis) in the treatment of threatening preterm labour. Particularly, we want to assess whether tocolysis has any negative effects on the newborn. The efficacy of the tocolysis will be compared to a placebo. A placebo is a treatment that is deliberately ineffective, a “fake” drug.

3. Background of the study
In 2015, the World Health Organisation (WHO) reported that there is an urgent need to study the safety and efficacy of tocolysis. Is it preferable to administer corticosteroids as well as tocolysis? Or is it better to give corticosteroids without tocolysis? This is what we aim to investigate in the current study.
Annually, in the Netherlands, 12.000 women deliver prematurely. Currently many of these women receive corticosteroids and tocolysis for 2 days. We do this because it has been shown that corticosteroids are beneficial to prematurely born babies as they improve lung maturity. These drugs have maximal effect after two days. This is why we administer tocolysis for 2 days in combination with corticosteroids. After stopping the tocolytics treatment at day 3, we evaluate whether delivery continues.

Gynaecologists in the Netherlands assume that tocolytics are beneficial, in spite of the fact that there is no sound scientific evidence to prove this. There are also countries where, because of the lacking scientific evidence, corticosteroids are administered without tocolytics. One may argue that premature contractions start because of an infection within the uterus. In this case, labour initiating delivery could be a beneficial process.

4. What taking part involves

If you agree to take part, you will receive study medication for 2 days. You are randomised to receive either an intravenous infusion with the tocolytic agent or an intravenous solution with placebo. Participants and treating physicians are 'blind' to the treatment. The corticosteroid treatment is given to both groups.
No additional diagnostic tests are performed on you or your baby.
A few years after the study is finished, we may want to contact you to inquire how you and your child are doing. At that time, you can decide whether you wish to answer our questions.

Furthermore, we ask you to complete two online questionnaires: one at the start of the treatment and one three months after delivery. Completing the questionnaires will take approximately 30 minutes. The questionnaires are completed online on a save and private server. We ask your permission for use of your email address to send you the questionnaires.

5. Possible side effects and complications
The tocolytics drug (atosiban) has been tested extensively and has been used as standard treatment for years. There are hardly any side effects. Reported side effect are nausea, headache, dizziness, hot flushes vomiting, tachycardia, hypotension, inflammation on the infusion and high blood glucose levels. More information on the side effects are present in appendix C. The placebo is a saline solution and has no side effects.

6. Possible benefits and risks
It is important to weigh the pros and cons before you decide to participate. At this moment, it is not clear whether tocolysis contributes to the treatment of threatening preterm labour.
Because the current trial will tell us whether tocolytics are beneficial or not, your participation may help women with threatening preterm labour in the future.

7. If you do not wish to participate or wish to stop your participation
Your participation in this study is completely voluntary. If you do not wish to participate, you will be treated according to local protocol.
If you do participate and later change your mind, you can always stop. We will then treat you with the conventional protocol. You do not have to give any reason. Immediately inform the investigator or your treating physician. The data collected up to that moment will be used for the study.
If any new information important to you becomes available, the investigator will inform you of this. At this point, you will be asked if you are still willing to continue your participation.

8. The end of the study
Your participation will stop;

- Three months after the birth of your child
- If you decide to withdraw
- If you physician decides it's better for you to stop
- If the investigator, the government or the judging medical ethical committee decide to stop the study

The APOSTEL 8 study will finish as soon as we have enough participants and all data has been processed. After analysis, the study team will inform you on the main outcomes.
If you choose so, the study team can reveal the treatment allocation (whether you received atosiban or placebo) to you. If you do not want to know, please tell the investigator. In that case, he/she is not allowed to tell you. As the follow-up of the study can take years, the moment that the investigator can inform you can also take years. The overall results of the study will precede the information on your treatment.

9. Storage and use of your data
For this trial, it is necessary that the medical data of yourself and your child(ren) are collected and used. Every patient will receive a code that is used to label the medical data. Your name and other information that can directly identify you or your child(ren) will not be used.
If you consent to take part in this study, the research team/study investigators will review your medical records for the purposes of analysing the results. Each data file will be marked with a code. In this data file, your name and other personal information identifying you or your baby, will not be shown.

Your data
All your data will remain confidential. Only the local research team will know the code allocated to you. The local research team will only share your data in coded form with the trial initiator of the study. The local investigator is be able to link our name to your study code. Only the local research team knows the key to the code. Reports of the study will only contain the code.

Some people are allowed access to the medical and personal information of you and your children. This is to verify whether the study has been carried out properly and reliably. General information about this can be found in the 'Scientific medical study' brochure (‘Medisch-wetenschappelijk onderzoek’).

Individuals/authorities who have access to your data are the local research team, quality inspectors from the trial initiator, the safety committee, and the Health and Youth care inspectorate. They will keep your personal information strictly confidential. By signing informed consent, you consent to the collection, storage and viewing of your medical and personal information of yourself and your child(ren). For this study, we also collect your ethnicity and level of education. This is needed to correctly interpret the results.

After closure of the study all research-data will be stored for 15 years at hospital where you were treated and 15 years at the sponsor of this study, Amsterdam UMC, location AMC.

This study is registered in the clinical research studies overview ToetsingOnline. This website contains no information retraceable to your person. The website can show a summary of the study results. This trail is labelled ‘APOSTEL 8’.

Further research in the future (follow up)
It is possible that we would like to approach you in the future for follow up research. You can indicate on the consent form whether we can approach you for a follow up research. If you decide that we can not approach you for follow up research, you still can participate in current research.

Additional information on your rights with respect to the processing of data
For general information on your rights regarding the processing of your personal data, you can consult the website of the Dutch Data Protection Authority (Autoriteit Persoonsgegevens).
If you have any questions about the rights of yourself or your baby, we advise you to first contact the local investigators in your hospital, see appendix A for contact details. You can also contact the Data Protection Officer of the relevant organisation or the Dutch Data Protection Authority (see Appendix A for contact details).

10. Patient insurance
Study insurance has been taken out or all participants. The insurance covers damage by the trial. Not

all damage is insured. Appendix B contains additional information on the insurance. It also states to whom you can report any damage.

11. Informing the family doctor
We always send a letter to inform your family doctor of your participation. . This is for your own safety. If you do not approve of this, you cannot participate in this study. If you do not have a family doctor, you cannot participate in the study.

12. Compensation
The study medication is free of charge. You will not be financially compensated for your participation.

13. Questions?
In case of questions, please contact the study group or your treating physician. For independent advice on taking part in this trial you ca contact the independent physician Dr. A. Timmermans. She is a gynaecologist and knows a lot about the study, but is not involved in the study.
In case of a complaint, please contact the complaints officer of your hospital.
Appendix A contains all contact information.

14. Signing informed consent
When you have had enough time to think, we will ask you to decide on participation to this trial. In case you consent, we will ask you to sign the accompanying informed consent form. By signing this form, you declare that you understand the information and consent to participation.

The investigator will keep the signature page. We will give you a copy or a second set.

Thank you for your time.

Attachments:

A. Contact information of your local hospital
B. Information on the trial subject Insurance
C. Side effects Atosiban
D. Consent form

Appendix A: contact information

You can get more information about the research from your doctor or the research staff involved

Local research team LUMC
Dr. M. Sueters
Local principal investigator LUMC
verloskundestudies@lumc.nl
071-526 28 96

Marianne Tendeloo
Research staff LUMC
verloskundestudies@lumc.nl
06-213 68 237

Independent physician:

Dr A. Timmermans can be reached through the Women's Clinic secretary office of the Amsterdam UMC locaion AMC
020-5663754 or by e-mail: a.timmermans@amc.nl

Complaints:

If you are not satisfied with the examination or treatment, you can report this to treating physician. In case you do not want to do this, you can also contact
the patient service office at the LUMC, location H2-11 (route number 473, opposite Leidseplein). Here you can report your dissatisfaction and complete the complaint form. The patient service bureau will inform you as soon as possible about a possible solution and can possibly call in the complaints officer. You can also fill in the complaint form digitally. See website LUMC: https://www.lumc.nl/patientenzorg/praktisch/klacht-indienen/

For additional information on your rights with respect to the use of your personal data:

For general information on your rights with respect to the processing of your data you can consult the website of the Dutch Data Protection Law at: https://autoriteitpersoonsgegevens.nl/

For questions or complaints about the processing of your personal data you can contact the local research team at the top of this page in this hospital. You can also contact the Data Protection Officer: See the contact form on the LUMC website, at the bottom of the privacy statement page, https://forms.lumc.nl/lumc2/feedbacksite.

Appendix B: information about insurance

For everyone who participates in this study, the AMC has taken out insurance. The insurance covers damage caused by participation in the study. This applies to damage during the trial or within four years after its end. The damage will have to be reported to the insurance company within four years.

The insurance does not cover all damage. The text concluding this appendix describes briefly the damage that is not covered.
These provisions are contained in the; 'Besluit verplichte verzekeringen bij medisch wetenschappelijk onderzoek met mensen' (decree on mandatory assurance for medical scientific research in human subjects). This decision is shown on www.ccmo.nl, the Central Committee on Research Involving Human Subjects website (see "Bibliotheek" and then "Wet- en regelgeving").

In case of damage, it is possible to contact the insurance company directly; It is also possible to register and submit your claim online on www.centramed.nl or contact via the company by e-mail.

<u>The insurance company of the study is:</u>
Name: Centramed
Address: PO Box 7374, 2701 AJ Zoetermeer.
Phone: 070 301 70 70
Email: info@centramed.nl
Policy number: 620.872.806

The insurance provides a minimum coverage of € 650 000, - per participant and € 5 million - for the whole study. For all studies of the same contractor, the minimum cover € 7,500,000, - a year.

The insurance does not cover the following damage:
• Damage caused by a hazard about which you are informed of the written information. This does not apply if the risk is more severe than anticipated or if the risk was very unlikely;
• Damage to your health that would also occur if you had not participated in the study;
• Damage due to not (completely) following instructions;
• Damage to your offspring, due to a negative impact of research on you or your offspring;
• Damage from an existing treatment method in research on existing treatments.

We ask you to also contact the principal investigator in case of damage.
Dr. M.A. Oudijk, 020-5663754

Appendix C: Atosiban side effects

Like all drugs, atosiban can have side effects. The reported side effects for the mother are usually mild. Side effects for the fetus or newborn are not known.

For the mother, common side effects include: nausea, headache, dizziness, hot flushes, vomiting, tachycardia, hypotension, inflammation at the injection site and high blood glucose levels.

Less frequently side effect are: fever, insomnia, itch and rash.

Very rare side effect were loss of contractility of the uterus after birth, which can cause haemorrhage.
Allergic reactions have been rarely reported.

Appendix D: consent form

The effect of tocolysis on preterm birth outcome, the APOSTEL 8 trial.

- I have read the information letter. I had the opportunity to ask questions. My questions have been answered to my satisfaction. I have had sufficient time to consider my participation in the study.
- I know that participation is completely voluntary and that I can decide at any time to withdraw from the study without giving any reason.
- I agree that my family doctor is informed on my participation in the study.
- I give consent to retrieve details on my pregnancy, delivery and child(ren).
- I give consent to retrieve details on my unborn child.
- I know that some people have access to my personal data and that of my child. They are listed in the information letter.
- I consent to the collection and use of my own data and that of my child(ren) the according to the way and targeted at the goals described in the information letter. This includes data on my ethnicity and level of education.
- I give permission to store my data for a period of 15 years.
- I give permission to send my contact details to the coordinating investigator in the Amsterdam UMC, location AMC, so they can contact me in the future for follow-up and send me the questionnaires.

- I □ **do**
  □ **do not** give permission to be contacted for follow-up research in the future.

- I □ **do**
  □ **do not** want to be informed on the treatment I received.

- I consent to participation in the trial.

Name:

Personal email address:

Signature: Date: : __ / __ / _____

The undersigned declares that the person mentioned above has been fully informed about the above mentioned study. If during the course of the study information becomes available that could influence the decision of the patient, I will inform her of this.

Name investigator:

Signature: Date: __ / __ / _____

The participant receives a complete information sheet and a copy of the written consent form.