Information for participants about taking part in medical-scientific research

What is the role of immune cells in the kidney in lupus nephritis (LN)?

The role of macrophages and monocytes in (proliferative) lupus nephritis; the MAPLE study

Introduction

Dear Sir/Madam,

With this information letter, we would like to ask if you want to take part in medical-scientific research. Taking part is voluntary. You are receiving this letter because you have been diagnosed with (a flare of) systemic lupus erythematosus (SLE), and there is a suspicion that your kidneys are involved (lupus nephritis, LN). Your doctor has asked if you are interested in taking part in this study.

This letter explains what the study is about, what it means for you, and what the advantages and disadvantages are. It is a lot of information. Please read it carefully and decide whether you want to take part. If you want to take part, you can fill in the form in appendix C.

Please ask your questions

You can make your decision based on the information in this letter. We also advise you to do the following:

- Ask the researcher who gives you this information any questions you have.
- Talk with your partner, family, or friends about this study.
- Read the information at www.rijksoverheid.nl/mensenonderzoek.

1. General information

Amsterdam UMC set up this study. Below, we always call Amsterdam UMC the ‘sponsor’. Researchers – these can be doctors, researchers, and research nurses – carry out the study. The study takes place at the AMC location of Amsterdam UMC.

People who take part in medical-scientific research are often called ‘subjects’. Both patients and healthy people can be subjects. This study needs a total of 30 LN subjects, 15 SLE subjects, and 10 healthy subjects. The Medical Ethics Review Committee of Amsterdam UMC has approved this study.

2. What is the purpose of the study?

The purpose of the study is to find out what role specific immune cells play in the start and continuation of LN. We want to look at how many of these cells are present in the kidney before and after treatment. We also want to look at whether changes in the immune cells affect the patient’s health. In addition, we want to check whether certain immune cells can be found in the blood or urine. This may help us detect or monitor LN better in the future.

3. What is the background of the study?

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect all organs in the body. An autoimmune disease is a disease in which the immune cells attack the body itself, causing inflammation and damage. Normally, immune cells protect the body against germs from outside.

When SLE causes inflammation in the kidneys, we call this LN. Possible effects of LN are loss of protein and blood cells in the urine, high blood pressure, loss of kidney function, and eventually even kidney failure. It is still not fully known what exactly goes wrong in the kidney in LN.

Recent research shows that macrophages, a type of immune cell, play a role in the development of LN. What we do not yet know is exactly which macrophages are present in the kidney and how this changes during treatment. We also do not know exactly how they affect the outcome of treatment.

LN is diagnosed by taking a small piece of the kidney (a kidney biopsy). This must be done before treatment starts. To treat LN better, it is important to understand more about what happens to the immune cells in the kidney. Kidney biopsies and blood and urine values that have already been taken could help with this. For this reason, a second kidney biopsy will be taken 3 months after the start of treatment for this study.

At the moment, there are several treatments for LN. For a long time, treatment with 2 medicines (prednisolone and mycophenolate mofetil, from here on shortened to MMF) was standard. Recently, a third medicine, voclosporin, is sometimes added. We suspect that voclosporin specifically blocks the macrophages in the kidney and may give a better result for some patients. However, using more medicines also increases the risk of side effects.
In daily practice, your doctor decides which treatment is best for you. At the moment, there is no clear preference for one treatment plan over the other. For this study, the choice between treatment with prednisolone and MMF, or treatment with prednisolone, MMF, and voclosporin, will be decided by a random draw (like drawing lots). This is needed so we can look as clearly as possible at the effects of treatment on the immune cells.

4. How does the study work?

How long does the study last?
If you take part in the study, it will last 2 years in total.

Step 1: are you eligible to take part?
After your treating doctor has given you information about the study and you are interested in taking part, one of our researchers will give you detailed information by phone. During your visit to Amsterdam UMC, you will sign to take part.

First, we check whether you can take part in the study. Your own doctor will ask you a number of questions and take blood during your regular outpatient appointments. Based on these results, the researcher decides whether you are eligible to take part.
If your kidney function is too poor, if you have an infection (such as tuberculosis, hepatitis B or C, or HIV), or if you are being treated for another autoimmune disease with specific immune-suppressing medicines, unfortunately you cannot take part. If the kidney biopsy (taken as part of regular care) shows that you have LN class I, II, or only class V, you cannot take part further in the study.

The study runs alongside your normal treatment for LN. You do not need to come to the hospital at extra times. All material collected for the study (described below) is taken during your regular outpatient appointments. Before your appointment, you will be given the materials you need (questionnaires, containers for urine and stool).

Step 2: kidney biopsy and treatment

The treatment
If you are eligible to take part, treatment will start.

For this study, there are 2 groups:
- Group 1. Patients in this group get a combination of prednisolone and MMF.
- Group 2. Patients in this group get a combination of prednisolone, MMF, and voclosporin.

The only difference between the two groups is that patients in group 2 also get voclosporin prescribed.

A computer decides by random draw which treatment you will get. If you do not take part in the study, your doctor will decide together with you which treatment you get.

What if the treatment does not work well enough?
If you decide to take part in the study, a random draw will decide which of the two recommended treatments you get. Your safety always comes first when taking part in scientific studies. If the treatment does not work well enough, your doctor can always change your treatment. If your treatment is changed before the second kidney biopsy, unfortunately you cannot continue in the study. If your treatment is changed after the second kidney biopsy, you can continue to take part in the study.

The kidney biopsy after starting treatment
3 months after starting treatment, another small piece of kidney tissue will be taken (a kidney biopsy). This is the same test you already had before starting treatment, done in the same way as the biopsy that was earlier taken as part of regular care.

A kidney biopsy is a test in which tissue is taken from the kidney using a needle. This biopsy will be done by a radiologist or a nephrologist (kidney specialist) in the hospital. For this, you will come to the hospital and be admitted for one day. If you use blood thinners, you will make arrangements in advance with your doctor about when to (temporarily) stop taking them. After the biopsy, you must lie flat on your back for 6 hours. If everything goes well and you have no complaints, you may get out of bed after 6 hours and go home at the end of the day.

Step 3: tests and measurements
During your treatment for LN, you will come to the hospital for your normal outpatient appointments. Information about your disease and blood test results will be collected from your file. The researcher will also ask about your ethnic background. We do this because we know that SLE and LN can behave differently, and occur more often, in people with a non-Western background. By collecting this information, we hope to better understand why this is the case.

At 7 points in time during these appointments, extra material for the study (such as kidney tissue, blood, urine, and stool) will be collected, and/or you will be asked to fill in a questionnaire. The table below shows an overview of the times and samples taken for the study:

Start of treatment (day 0)	Week 4	Month 3	Month 6	Month 12	Month 18	Month 24
• Questionnaire • Blood sample • Urine sample • Stool sample	•Questionnaire	• Kidney biopsy • Questionnaire • Blood sample • Urine sample	• Questionnaire • Urine sample	• Questionnaire • Blood sample • Urine sample	• Questionnaire	• Questionnaire • Blood sample • Urine sample • Stool sample

<u>Kidney biopsy</u>
For information about the extra kidney biopsy, see the paragraph above.

<u>Questionnaire</u>
We ask you to fill in a questionnaire about your experience with the disease and its impact. The questionnaire is on paper. It takes about 7-8 minutes to fill in. You may fill in the questionnaire at home or during your outpatient visit to the hospital.

<u>Blood sample</u>
For the study, 9 extra tubes of blood will be taken at the first appointment, and 7 extra tubes at three further appointments. In total, this is about 70 ml the first time and about 60 ml each time after that. Over the full 2 years, a total of about 250 ml of extra blood will be taken for the

study. All extra blood samples are taken during the regular blood draw before your outpatient appointment, so you will not need an extra needle prick.
This amount of blood does not cause problems in adults. For comparison: someone who donates blood at the blood bank gives 500 ml of blood each time.
With the blood samples, we study the presence of specific immune cells.

Urine sample
For the study, you will be asked to bring a urine sample to your outpatient appointment on 5 occasions.

Stool sample
For the study, you will be asked to bring a small container of stool to your outpatient appointment on 2 occasions.

Other information about physical examination, and blood and urine values, will be collected from your patient file. No extra samples or visits are needed for this.

What is different from regular care?
Most of this study is no different from regular care. There are a few extra parts, such as a second kidney biopsy, extra tubes during blood draws, handing in urine and stool, and questionnaires.
Several treatments are approved and recommended for LN. Normally, your doctor decides which treatment you get. If you take part in the study, this choice is made by a random draw.
Below is an overview of which tests are part of routine care, and which tests are extra because you are taking part in this study.

Routine	Extra for the study
Check-up appointments with your doctor at the outpatient clinic	–
Treatment for LN	A random draw decides which treatment you get
Blood pressure, weight, height	Questionnaire (LupusPRO)
Urine	2x stool and 5x extra urine samples
Routine blood sample (~20 ml)	Extra tubes (1x ~70 ml and 3x ~60 ml at 4 different times over 2 years), taken together with the routine sample
Kidney biopsy for diagnosis	Extra kidney biopsy 3 months after starting treatment

5. What arrangements do we make with you?

We want the study to go well. That is why we make the following arrangements with you:

- You take the medicines in the way the researcher has explained to you.
- You do not take part in another medical-scientific study while taking part in this one.
- You come to every appointment.
- You hand in the stool and urine in the containers you were given.
- You may keep taking your prescribed medication as usual. If in doubt, discuss this with your treating doctor or the researcher.

You contact the researcher in these situations:

- You want to start using new medicines. This also applies to homeopathic products, herbal remedies, vitamins, or medicines from the drugstore.
- You are admitted to hospital or treated there.
- You suddenly get health problems.
- You no longer want to take part in the study.
- Your phone number, address, or e-mail address changes.

Can you or your partner become pregnant during the study?

Treatment for LN can have effects on an unborn child. In particular, MMF can cause a miscarriage and birth defects in the baby. Your doctor has already discussed this with you at the outpatient clinic, and has told you how to best prevent a pregnancy. Talk about this with your partner. The arrangements about pregnancy below apply to everyone being treated for LN, but are repeated here for extra emphasis because of this study:

- Women who are pregnant or breastfeeding cannot take part in this study. Women also may not become pregnant during the study.
- Are you a man with a female partner? Then you must make sure she cannot become pregnant by you while you are taking part in the study.

Pregnant anyway?

If you do become pregnant during the study, tell the researcher right away. Together with the researcher, you must then stop the study as soon as possible. If your partner becomes pregnant by you during the study, ask her permission to tell the researcher. This way, the pregnancy can be monitored extra closely, and information about the course and outcome of the pregnancy can be requested from other healthcare providers – but only if you or your pregnant partner give permission for this. Finally, we will report the pregnancy to the sponsor of this study.

Becoming pregnant after the study?

The researcher will discuss with you whether taking part in the study could have any effect if you want to become pregnant later.

6. What side effects, harmfull effects, or discomfort can you experience?

What are the risks of a(n) (extra) kidney biopsy?

After a kidney biopsy, there can be blood in the urine. This usually goes away on its own. Sometimes a small tube needs to be placed in the bladder to rinse out the blood. Rarely, bleeding in the kidney can occur. In that case, a blood transfusion and/or angiography (imaging of the blood vessels using contrast fluid) may be needed. During an angiography, the blood vessel that is bleeding can then be closed off from the inside. This can cause a lasting decline in kidney function.

What are the side effects of the treatment given?

All medicines given can cause side effects. Important: warn your doctor right away if you get:

- Fever
- Skin problems
- Severe muscle weakness, tingling, or paralysis

The following side effects are common:

- Upper airway infection
- Anaemia (low red blood cell count)
- Headache
- High blood pressure
- Cough
- Diarrhoea, stomach pain
- Reduced kidney function

The following side effects are rare, but can be serious:

- Too much potassium in the blood
- Higher risk of severe infections

More information about MMF, prednisolone, and voclosporin is in the medicine's package leaflet. You will always get this leaflet when you pick up your medicines from the pharmacy.

7. What are the advantages and disadvantages of taking part in the study?

Taking part in the study can have advantages and disadvantages. We list them below. Think about this carefully, and talk about it with others.

Because both treatments are also given to LN patients outside the study, taking part in the study has no extra advantage for you. By taking part, you can help gain more insight into the treatment of LN.

Taking part in the study can have these disadvantages or consequences:

- Because of the second kidney biopsy, you must be admitted for one extra day at the hospital's day-care unit. You also have a small chance of a complication from the second kidney biopsy.
- You may get side effects that can occur with the use of voclosporin.
- Taking part in the study costs you extra time.
- You must keep to the arrangements that belong to the study.

Do you not want to take part?

You decide for yourself whether you take part in the study. If you do not want to take part, your doctor will choose, together with you, which treatment you get. Your doctor can tell you more about the treatment options available, and their advantages and disadvantages.

8. When does the study stop?

The researcher will let you know if new information about the study becomes known that is important for you. The researcher will then ask if you want to continue taking part.

In these situations, the study stops for you:

- All tests according to the schedule are finished.
- You have become pregnant.
- You want to stop the study yourself. You may do this at any time. Tell the researcher right away. You do not need to say why you are stopping. Treatment for your LN will simply continue, based on the judgement of your treating doctor.
- The researcher thinks it is better for you to stop.
- One of the following bodies decides that the study must stop:
    - the sponsor (Amsterdam UMC)
    - the government, or
    - the medical ethics committee reviewing the study.

What happens if you stop the study?

The researchers use the data and body material (blood, urine, stool, and pieces of tissue) collected up to the moment you stop. If you want, collected body material can be destroyed. Let the researcher know if you want this.

The whole study is finished once all participants are done.

9. What happens after the study?

Can you keep using the medicines?
Depending on availability, you can keep using the medicines you used during the study after the study ends. The researcher will discuss with you what other medical care you will get.

Will you get the results of the study?

About 2 years after the study ends, the researcher will let you know the main results of the study. If you do not want to know this, tell the researcher. He/she will then not tell you.

10. What do we do with your data and tissue?

If you take part in the study, you also give permission to collect, use, and store your data and body material.

Which data do we store?

We store this data:

- your name
- your sex
- your address
- your date of birth
- data about your health
- (medical) data we collect during the study
- data about your ethnic background. We store this because we know that SLE and LN can behave differently, and occur more often, in people with a non-Western background. By collecting this information, we hope to better understand why this is the case.

Which body material do we store?

We collect, use, and store tubes of blood, urine, stool, and tissue (biopsies).

Why do we collect, use, and store your data and body material?

We collect, use, and store your data and body material to answer the questions of this study, and to publish the results. Data and/or body material can be used by the sponsor and by companies that help the sponsor carry out the study.

How do we protect your privacy?

To protect your privacy, we give your data and body material a code. Only this code is put on all your data and body material. The key to the code is kept in a secure place in the hospital. When we process your data and body material, we always use only this code. In reports and publications about the study, no one will be able to trace this back to you.

Who can see your data?

Some people can see your name and other personal data without the code. This may be data collected specially for this study, but also data from your medical file.

These are people who check whether the researchers carry out the study properly and reliably. These people may have access to your data:

- An auditor who works for the sponsor.

- National and international regulatory authorities.

These people keep your data confidential. We ask your permission for these people to view your data. The Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd) can view your data without your permission.

How long do we store your data and body material?

We store your data for at least 25 years after the study ends, at the hospital. We also store your body material at the hospital. It is stored for up to 5 years after the study ends, so that new tests related to this study can still be done during that time. As soon as this is no longer needed, we destroy your body material.

May we use your data and body material for other research?

Your collected data and (remaining) body material may also be important for other scientific research into kidney disease. For this, your data will be stored for at least 25 years. On the consent form, you indicate whether you agree to this. If you do not give permission, you can still take part in this study. You will receive the same care.

Your body material will be stored in a biobank for up to 50 years after the study ends. On the consent form of the biobank's information leaflet, you can indicate whether or not you agree to this. If you do not agree, you can still take part in the current study – in that case, your material will be destroyed once the main study is finished.

What happens with unexpected findings?

During the study, we may accidentally find something that is not directly relevant to the study, but is relevant to your health. The researcher will then contact your specialist. You will then discuss with your specialist what needs to happen. The costs of this are covered by your own health insurance. With the form, you give permission to inform your specialist.

Can you withdraw your permission to use your data?

You can withdraw your permission to use your data at any time. Tell the researcher if you want this. This applies to use in this study and to use in other research. Please note: if you withdraw your permission, and the researchers have already collected data for a study, they may still use this data. For your body material, the researchers will destroy it after you withdraw your permission. But if measurements have already been done with your body material, the researcher may still use those results.

Do you want to know more about your privacy?

- Do you want to know more about your rights regarding the processing of personal data? Go to www.autoriteitpersoonsgegevens.nl.
- Do you have questions about your rights, or a complaint about the processing of your personal data? Contact the person responsible for processing your personal data. For your study, this is:

- Amsterdam UMC. See appendix A for contact details and website.

- If you have complaints about the processing of your personal data, we advise you to discuss this first with the research team. You can also go to the Data Protection Officer of Amsterdam UMC, or file a complaint with the Dutch Data Protection Authority (Autoriteit Persoonsgegevens).

Where can you find more information about the study?

You can find more information about the study on the following website(s): www.onderzoekmetmensen.nl and/or https://euclinicaltrials.eu. After the study, the website may show a summary of the results. You can find the study by searching for 'MAPLE study'.

11. Will you get paid for participating?

The study medicines, extra tests, and treatment for the study cost you nothing. For taking part in this study, you will get a payment of €150.

You may need to declare the payment for taking part in this study to the Dutch Tax Administration (Belastingdienst) as 'income from other work'. If needed, ask the Tax Administration about this.

12. Are you insured while taking part in the study?

An insurance policy has been taken out for everyone taking part in this study. The insurance pays for damage caused by the study, but not for all damage. Appendix B has more information about the insurance and its exceptions. It also states who to contact if you have any damage to report.

13. We will inform you GP, treating specialist and pharmacist

The researcher will send your GP, treating specialist, and pharmacist a letter or e-mail to let them know you are taking part in the study. This is for your own safety. In case of unclear situations or questions, we may contact your doctor – for example, about your medical history or the medicines you use.

14. Do you have questions?

You can ask questions about the study to drs. S.D. Crum or dr. M. Hilhorst.
Do you have a complaint? Discuss this with the researcher or the doctor treating you. Would you rather not do this? Then go to the hospital's complaints officer. Appendix A tells you where to find them.

15. How do you give consent for the study?

You can first take time to think calmly about this study. Please take at least 2 days for this. Afterwards, tell the researcher whether you understand the information, and whether or not

you want to take part. If you want to take part, fill in the consent form that comes with this information letter. You and the researcher will both get a signed copy of this consent statement.

Thank you for your time.

16. Appendices

A. Contact details for Amsterdam UMC

B. Information about the insurance

C. Consent form(s)

Appendix A: contact details for Amsterdam UMC

Drs. S.D. Crum, physician-researcher, Department of Internal Medicine – Nephrology. Meibergdreef 9 | 1105 AZ Amsterdam | The Netherlands. Tel: 020-5663195 | E-mail: s.d.crum@amsterdamumc.nl

Principal investigator (2nd point of contact):
Dr. M. Hilhorst. Internist-nephrologist and researcher, Department of Internal Medicine – Nephrology. Meibergdreef 9 | 1105 AZ Amsterdam | The Netherlands. Tel: 020-5661300 | E-mail: m.l.hilhorst@amsterdamumc.nl

Data Protection Officer:
E-mail: privacy@amsterdamumc.nl
Complaints: tel: 020 566 3355, e-mail: patientenvoorlichting@amc.nl
For more information about your rights:
https://www.amc.nl/web/sitewide/algemeneprivacyverklaring.htm

Any complaints can be addressed to:
Patient Service Zorgsupport, AMC location
E-mail: PAZO-AMC@amsterdamumc.nl

Patient Service Zorgsupport, VUmc location
E-mail: PAZO-VUmc@amsterdamumc.nl

Appendix B: information about insurance

Amsterdam UMC has taken out insurance for everyone who takes part in the study. This insurance pays for damage that you suffer because you took part in the study. This means damage that occurs during the study, or within 4 years after the end of your participation. You must report any damage to the insurer within 4 years.

Do you have damage caused by the study? Report this to the insurer:

The insurer of the study is:

Insurer name: Centramed B.A.

Address: Postbus 7374, 2701 AJ Zoetermeer

Telephone: 070 301 70 70

E-mail: info@centramed.nl

Policy number: 624.100.044

The insurance provides coverage of €650,000 per subject, with a maximum of €5,000,000 for the whole study, and €7,500,000 for damage resulting from medical-scientific research reported per insurance year.

Please note: the insurance does not cover the following damage:

- Damage caused by a risk we informed you about in this letter. This does not apply if the risk turned out to be bigger than we expected, or if the risk was very unlikely.
- Damage to your health that would also have occurred if you had not taken part in the study.
- Damage caused because you did not follow instructions or guidance, or did not follow them correctly.
- Damage to the health of your children or grandchildren (unless the study specifically concerns an existing pregnancy, birth, or embryos with the aim of achieving a pregnancy – in that case, damage to the child/children concerned is covered).
- Damage caused by a treatment method that already exists, or by research into a treatment method that already exists.

These rules are set out in the ‘Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015’ (Compulsory Insurance for Medical-Scientific Research with Humans Decree 2015). This decree can be found in the Dutch government’s legal database (https://wetten.overheid.nl).

Appendix C – Subject Consent Form

For the study:

What is the role of immune cells in the kidney in lupus nephritis (LN)?

- I have read the information letter. I was also able to ask questions. My questions were answered well enough. I had enough time to decide whether to take part.
- I know that taking part is voluntary. I also know that I can decide at any time not to take part after all, or to stop. I do not have to say why I want to stop.
- I give the researcher permission to let my doctors (specialist, GP, and pharmacist) know that I am taking part in this study.
- I give the researcher permission to request information from my GP, specialist, or pharmacist about my medical history or medication.
- I give the researcher permission to inform my GP or specialist about unexpected findings from the study that are relevant to my health.
- I give the researchers permission to collect and use my data and body material. The researchers will only do this to answer the research question of this study.
- I know that some people may already view my data to check the study. These people are named in this information letter. I give these people permission to view my data for this check.
- I know that I may not become pregnant, and that I may not get my partner pregnant, during the study.
- The researcher has discussed with me how to best prevent me or my partner from becoming pregnant.

Please tick yes or no in the table below.

I give permission to store my data for use in other research, as described in the information letter.	Yes ☐	No☐
I give permission to possibly be asked, after this study, whether I want to take part in a follow-up study.	Yes ☐	No☐

I want to participate in this study.

My name is (subject): ……..

Signature: …… **Date** : ____ / ____ / _____

I declare that I have fully informed this subject about the study named above.
If, during the study, information becomes known that could affect the subject's consent, I will inform the subject in time.

Naam of researcher (or representative):……
Signature:…… Date: __ / __ / __

Additional information was given by:

Name:……..
Function:……
Signature:…… Date: __ / __ / __

The subject receives a full information letter, together with a signed copy of the consent form.