Information for those interested in taking part in the PI4 clinical trial

We wish to ask you whether would like to take part in a clinical trial. In this document, you will find information about the trial and what taking part involves. You will also find information here about what will be expected of you if you choose to take part, and about any risks and benefits of the trial. Please feel free to discuss the trial with your doctor and to ask questions about anything you are unsure about before deciding whether or not to take part.

# What is the aim of the clinical trial, and why do you wish for me to take part?

The aim of this clinical trial is to examine whether the drug metformin extended release (ER) is able to slow down disease progression in early-onset pre-eclampsia and reduce the risk of premature birth. A similar study that was recently conducted in South Africa found that women with pre-eclampsia who were treated with metformin ER were pregnant, on average, for one week longer than women treated with a placebo (a non-active treatment). However, it remains unclear whether the drug will work in women with pre-eclampsia in Sweden, and for this reason this study needs to be conducted. You are being asked to take part as you were diagnosed with pre-eclampsia at between 22 weeks 0 days and 33 weeks 6 days of pregnancy. You have come to our attention as you are under the care of the *Research Hospital* in a unit where the study is taking place.

This clinical trial is being run at the *Research Hospital* in collaboration with Region Västra Götaland. The entity responsible for research (the organisation responsible for the study) and sponsor of the trial is Region Västra Götaland.

This clinical trial has been reviewed and approved by the regulatory medicines authority, which in Sweden is the Swedish Medical Products Agency (Läkemedelsverket), and by the Swedish Ethical Review Authority (Etikprövningsmyndigheten).

# How is the trial conducted?

If you decide to take part in the trial, your normal treatment will not be affected. You will either be given the drug metformin ER, which contains the active ingredient Glucophage, or an inactive substance that looks identical (placebo). Neither you nor the study staff will know whether you are being treated with metformin ER or the placebo. This is what will happen if you choose to take part in the trial:

## Visit 1, in conjunction with the diagnosis of pre-eclampsia

A doctor will ask you whether you wish to take part in this trial. You will be given detailed information about the trial and there will be an opportunity to ask questions. If you wish to take part, you will give your consent by providing a signature.

You will be asked about how you are feeling and about your clinical history, as well as about your current symptoms. This visit lasts for around 40 minutes.

Blood samples (max. 50 ml for the study) and urine will be taken and stored in a biobank for later analyses. Samples will primarily be taken at the same time as the blood tests that need to be performed anyway as part of your

care, which means you will receive as few additional needle sticks as possible. A urine sample will also be taken (max. 10 ml for the study).

You will also be asked to provide swabs from your vagina and rectum. These samples are taken in order to examine the effect of the drug on the bacterial flora of the body. You can take the samples yourself and the process is painless. The samples are taken once before the first dose of the drug and then once again after five days.

All tests are voluntary.

You will be given instructions about the diary, where you must record on a daily basis the number of tablets you have taken and whether or not you have experienced any problems. You can fill in the diary either digitally using the MyCap mobile app or on a piece of paper that you take with you on your visits.

## Twice weekly follow-up until the birth

Please bring along your remaining tablets so that we can see how many tablets you have taken. At each follow-up, you will answer questions about how you have found taking the trial drug and whether or not you have experienced any side effects.

Blood samples (max. 20 ml on each occasion) will be taken and stored in a biobank for later analyses. Samples will primarily be taken at the same time as the blood tests that need to be performed anyway as part of your care, which means you will receive as few additional needle sticks as possible.

These elements will prolong your visit by around 10 minutes.

## Birth

Once it is time to give birth, your treatment will end. At the time of the birth, additional blood samples will be taken (max. 20 ml). If you are given spinal anaesthesia in connection with a caesarean section, in the final stage of delivery or for a procedure immediately after the delivery, a small amount (max. 10 ml) of the spinal fluid that normally drips out when placing the anaesthetic will also be taken along with other tests. This will not involve taking any additional samples.

At the time of the birth, samples will also be taken from the placenta, along with a blood sample from the umbilical cord (max. 10 ml). This does not affect delayed umbilical cord clamping.

## Follow-up visit two to three months after the birth

You will be followed up after two to three months with questions about your health and your experiences of the medicinal treatment.

Blood samples (max. 40 ml) and urine (max. 10 ml) will be taken in order to analyse blood, liver and kidney function and will be stored in a biobank for later analyses.

**Follow-up visit after 2 years**

After two years there will be a follow-up visit where you will answer questions about your health and your experiences of the treatment. You will be asked to donate blood samples, maximum 40 ml, and urine, maximum 10 ml, to analyse blood, liver and kidney function and to be stored in a biobank for later analyses. You will also be asked to provide vaginal and rectal swabs.

**Follow-up in registers**

To evaluate whether treatment with metformin provides health economic benefits for society, the National Prescribed Drug Register, the National Medical Birth register, the Swedish Neonatal Quality Register, the National Cause of Death Register, local hospital registers, the National Patient Register, the Swedish Social Insurance Agency´s register MiDas and LISA will be used.

# Possible consequences, risks and inconveniences of taking part in the trial

Taking metformin ER can lead to side effects. The most common ones are nausea and loose stools. Metformin ER is proven to be safe during pregnancy and is used primarily by pregnant women with diabetes.

There are always risks associated with taking a drug that is being used in a new context, even if it has previously been taken by pregnant women. Side effects of which we are not currently aware may arise during the trial. Every possible measure will be taken to minimise the risks. It is important that you contact us as soon as possible if you are unwell or feel that your health is being affected in some way.

Having blood taken can feel uncomfortable and cause bruising, and in rare cases may lead to local inflammation. To minimise your discomfort, we will try to ensure that blood samples taken as part of the study coincide with the ones you would need to have taken anyway in the course of your normal care. On each occasion, 20 ml of blood (slightly more than a tablespoonful) will be taken. The total amount of blood will depend on how long you are involved in the study for, which will determine on how many occasions blood is taken. On average, a woman is pregnant for one week after diagnosis, but this period can vary from 0 days to 15 weeks, depending on when the diagnosis is made. If you are pregnant for five weeks after your diagnosis (which is a long period), the total volume of blood for the PI4 study will be 400 ml. This compares with the 450 ml taken when giving blood. In rare cases, patients may take part for up to 15 weeks from the time of diagnosis to the birth, which means a total blood volume of 750 ml divided over several months.

# What will happen with my details?

In this clinical trial, information about you will be collected and recorded. This information will be obtained from questionnaires, your diary, interviews and your medical records. Both the General Data Protection Regulation (GDPR, EU 2016/679) and the Swedish Public Access to Information and Secrecy Act (2009:400) will apply to the processing of information. Your answers and results will be processed in such a way as to prevent unauthorised access. The analysis and eventual disclosure in writing of the results of examinations and tests is done at group level only and never for individual participants.

Coded or de-identified information may be forwarded to researchers at other universities and in other research contexts within (and outside) Sweden. (Where the information is transferred for research purposes to a so-called ‘third country’ (a country outside the EU/EEA), such a transfer is always preceded by rigorous

review and is done subject to special provisions under the GDPR and the Swedish Public Access to Information and Secrecy Act.) All information is recorded in a database using a data processing system owned by Region Västra Götaland. Information from the digital diary in MyCap is transferred directly to the same database. Data will be stored using a unique study code. The final database will be stored on a secure data storage platform. Personal details such as the personal ID number and address linked to the study code will be stored separately from the database. The information will be saved for at least 25 years.

# Data collection

During the trial, information will be collected about age, sex, health (e.g. current and previous illnesses), as well as the results of any examinations. Data will also be collected via surveys, which will include information about side effects and health self-assessment. Data collected will be stored on a register and subject to data processing. An analysis of your data will be conducted by the principal investigators who form part of the researcher group for the trial, or by other researchers following an approved ethical review. However, this personal data will be coded at the time of transfer and the other researchers will not have access to the key code.

Information may also be obtained from Swedish registers. The registers in question are: the Patient Register, which holds data on diagnoses in specialised care; the Medical Birth Register, which holds data on pregnancy and childbirth; the Prescribed Drug Register, which holds data on prescribed medication; and Statistics Sweden, which holds data on deaths and emigration. Information will be collected from the time of the pregnancy and up to 25 years after the pregnancy.

This register is held for research purposes. The legal basis for processing personal data is that research is considered to be a matter of public interest. Your details are protected by confidentiality and there is no unauthorised access to the register. Your answers and results will be processed in such a way as to prevent unauthorised access. During data processing, it will not be possible to identify individual participants when the results of the trial are reported or published.

# My rights

Your answers and results will be processed in such a way as to prevent unauthorised access.

The Sahlgrenska University Hospital is responsible for the processing of your personal data. The Data Protection Officer is the person responsible for making sure that your personal data is processed in a legal and correct manner. According to the EU General Data Protection Regulation (GDPR), you have the right to access the data about you that is processed in the study free of charge, and, where appropriate, to have your data corrected. You can also request the erasure of any data held about you, and for restrictions to be placed on the processing of your personal data. If necessary, the Data Protection Officer can assist you with this.

You can contact the Data Protection Officer at the following address: Sahlgrenska University Hospital, Data Protection Officer, SE-413 45 Gothenburg. Telephone: +46 (0)31-343 27 15, [sahlgrenska.universitetssjukhuset.dso@vgregion.se](mailto:sahlgrenska.universitetssjukhuset.dso@vgregion.se). If you are unhappy with how your personal data is being processed, you have the right to file a complaint with the Swedish Authority for Privacy Protection, which is the supervisory authority. Your personal data will only be used for the purposes given above. It may only be used for other purposes if you have given new consent and/or the Swedish Medical Products Agency/other medicines authority in the EU and the Swedish Ethical Review Authority have issued a new approval.

# Quality control and archiving

In order to safeguard quality and to check that the trial is being conducted correctly, it may be appropriate for someone appointed by the sponsor/entity responsible for research or other person in authority to compare the data collected with your medical records. The quality reviewer must sign a confidentiality agreement in order to have access to your medical records. By signing the consent form, you are giving your permission for this access to your medical records. Data will be saved for at least 25 years after completion of the trial.

# What will happen with my samples?

The samples taken in connection with the trial will be stored in a biobank in accordance with the *Swedish Biobank Act (2023:38)*, which regulates the way in which samples may be stored and used. During the study, the samples that you provide will be stored in biobanks at the participating hospitals. A Swedish biobank will be responsible for the samples. The samples are stored in coded (pseudonymised) form, which means that the samples cannot be traced to you as a person. Each sample has a unique code to avoid confusion. The samples and associated identification list (key code) will be stored separately from each other and protected against unauthorised access. The key code will be stored by the local biobank and/or local investigator and may be shared with the principal investigator and responsible biobank. Your blood samples may be sent for analysis to our laboratory or to our partner’s laboratory, both within and outside the EU/EEA. Biomarkers and genes may be analysed. Following any analysis other than by the entity responsible for the trial, the samples will either be returned to the entity responsible for the trial or destroyed.

Results from those clinical tests that are available in the hospital’s organisation will be documented in your patient medical record and will be available to health care staff in *Research Region* , and these will then be covered by the regulations of the Swedish Patient Data Act (2008:355). For this data, *Research Region* is the Personal Data Controller *(Personal Data Controller name, telephone +46 (0)12-3456789,*[*dataskydd@forskarregionen.se*](mailto:dataskydd@forskarregionen.se)*)*. *Research Region* is also the Personal Data Controller for data relating to your biobank samples.

Your samples may only be used in the manner for which you have given your consent. All future, as yet unspecified, research will entail a new ethical review, and the Swedish Ethical Review Authority will then decide whether or not you need to be contacted again with a new request for consent. If you agree to us storing and using your samples for future purposes, you will need to give specific consent for this.

You have the right to say no to having your samples stored, without giving a reason. If you consent to having your samples stored, you have the right to revoke (withdraw) that consent later. In that case, your samples will be disposed of or de-identified. If you wish to revoke your consent, you will need to contact Lina Bergman, the principal investigator (see contact details above). The samples will be saved for a maximum of 25 years.

# How will I receive information about the results of the trial?

The results will be published in a shared EU-wide database of clinical drug trials (CTIS) and scientific journals, and will be presented at national scientific meetings. Only statistics at group level will be presented, and it will not be possible to identify any individual person. Published data will also be shared on the research group’s website, [www.preeclampsiaresearch.com](http://www.preeclampsiaresearch.com/)

You can also ask your doctor to inform you of the results once they are available.

# Insurance and compensation

As elsewhere in the healthcare system, you will be covered by the Swedish Patient Injury Insurance Scheme and the Swedish Pharmaceutical Insurance Scheme.

Taking part in the trial will not entail any additional cost to you. Reasonable travel costs will be paid on production of a receipt.

# Participation is voluntary

It is your choice whether you wish to take part in this trial, and you may cancel your participation at any time without giving a reason. Nor will this affect your future care or treatment. If you do choose to cancel your participation, any data and biological samples already collected will still be used in the trial. No further data or samples will be collected, however*.* If you wish to cancel your participation you must contact the people in charge of the trial (see below).

# People in charge of the trial

**Principal investigator**:

Name: Telephone number: E-mail address: **Research nurse:**

Name:

Telephone number:

E-mail address:

# Consent to take part in a clinical trial

I have been given verbal and written information about the trial and had the opportunity to ask questions. I may keep a copy of the written information.

I confirm that:

* I consent to taking part in the trial and know that my participation is completely voluntary.
* I have studied how my personal data will be processed and how any data collected about me will be stored and processed.
* I hereby permit an appointed quality reviewer to be given access to information in my medical records that is relevant to the current trial.
* I am aware that I may withdraw my consent and end my participation at any time and without giving a reason.
* I consent to my samples being stored in a biobank in the manner described in the information to research participants.
* I consent to my coded details being transferred to a third country, i.e. a country outside the EU/EEA.
* I consent to my details being retrieved from Swedish registers.

## Consent to future research

I have been informed that the samples that I provide may be of relevance to future research that has not been described in the information provided to me as a research participant. I have also been informed that, if my samples are to be used in future research, then the Swedish Ethical Review Authority must perform a review of the new project and, as part of its review, decide whether or not I need to be asked again.

I consent to my samples being saved for future research.

I hereby consent to taking part in the trial:

Signature (Research participant) Print name Date

## Signature of clinic

I have provided information about the trial, verified that the trial participant has understood the information and received answers to her questions regarding the trial.

Signature of doctor responsible Print name Date

for inclusion

***A copy of this signed information should be given to the research participant.***