



**Medicine
Endocrinology and Metabolism**

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PARTICIPANT INFORMATION AND CONSENT FORM

Oral micronized progesterone for perimenopausal vasomotor symptoms

(Peri-P-236267-01 Study)

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Sponsor: Canadian Institutes of Health Research (CIHR)

Emergency Telephone Number: In case of emergency, call (604) 875-4111 and ask for the Endocrinologist on call and advise her/him that you are participating in this study. This emergency number is available 24 hours per day, 7 days a week.

1. INVITATION

You are being invited to take part in this research study because you have hot flushes and/or night sweats and have menstruated within the past 12 months.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. You also need to know that there are important differences between being in a research study and being cared for by your doctor. When you participate in a

research study, the main goal is to learn things to help other patients in the future. Outside a research study, your doctor's sole goal is to care for your health. Nevertheless, the researchers have a duty of care to all participants and will inform you of any information that may affect your willingness to remain in the study.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THE STUDY?

The Principal Investigator has received a research grant from the Canadian Institutes of Health Research (CIHR). Besins Healthcare, manufacturers of the drug and placebo (pill with no effect) are donating study medication and placebo. You may request details of this funding if you wish to do so.

4. BACKGROUND

Most women in perimenopause experience hot flushes and night sweats (vasomotor symptoms, or VMS), during the transition to menopause. Menopause is defined as beginning one year after the last menstruation. About 80% of perimenopausal women experience night sweats and hot flushes and 9% experience moderate to severe symptoms. These are the most common reasons that women seek hormone therapy.

There are no proven therapies for perimenopausal hot flushes and night sweats. Doctors frequently prescribe either oral contraceptives or menopausal hormone therapy. However, neither of these therapies has been tested and shown to be effective for perimenopausal women. In the one good study of oral contraceptive pills in perimenopausal women, the difference between oral contraceptive pills and placebo (dummy pill) was both small (one fewer flush in 5 days) and not statistically significant.

Oral micronized progesterone has been approved and available in Canada since 1995. It is identical to the progesterone hormone made by women's ovaries. It has not been tested as a therapy for hot flushes and night sweats in perimenopausal women.

We recently completed a study showing that this same medicine, oral micronized progesterone (without estrogen) is an effective therapy for hot flushes and night sweats in healthy menopausal women.

The reasons for testing progesterone therapy for hot flushes in perimenopausal women are:

- 1) This is a time when estrogen levels average higher than normal and progesterone levels tend to decrease. Therefore perimenopause involves an estrogen-progesterone imbalance that taking progesterone will improve.
- 2) Estrogen and progesterone both have receptors in every tissue of our bodies. Progesterone's job is to complement or counterbalance estrogen's actions in every tissue. Some of the results of higher perimenopausal estrogen levels

(such as heavy flow and sore breasts) may also be helped by progesterone treatment.

- 3) Progestins (synthetic cousins of progesterone) and now oral micronized progesterone (in the trial we just completed) have been shown to improve hot flushes in menopausal women. Therefore it is logical to test progesterone for hot flushes in perimenopausal women.

This study uses a placebo control because hot flushes and night sweats commonly respond well to placebo treatment and a placebo-controlled trial is needed before it is appropriate to do a study comparing progesterone directly with other possible hot flush therapies (such as oral contraceptives or estrogen). Although estrogen therapy is the gold standard of treatment in menopausal women, it is unproven for perimenopausal women. So, there is also no standard, proven effective treatment with which to compare.

This is a Phase III study. A Phase III study is a study of an experimental drug or treatment which is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information to determine whether the experimental drug or treatment can be used safely.

5. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this Phase III study is to test whether a 12-week treatment with oral micronized progesterone is an effective therapy for hot flushes and night sweats in perimenopausal women, in comparison with an identical placebo. We also plan to use some of the questionnaire data you provide to understand how reliable our tools are and to compare women with hot flushes and night sweats in this study to similarly aged women in the general population. Oral micronized progesterone is currently available (as Prometrium®) in Canada, and is approved to prevent endometrial cancer in menopausal women who have not had a hysterectomy and are taking estrogen therapy. It is not approved for commercial use for the purpose of treating hot flushes and night sweats, but it has been approved by Health Canada for use in this study.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You can participate in this study if:

- You have at least four hot flushes and/or night sweats per day, on average, and they are moderate to severe in intensity. If you have fewer than this, but your night sweats wake you up at least twice a week, then you are also eligible.
- You are at least 35 and not older than 58 years old.
- You have had a menstrual period within the past 12 months and have not had a hysterectomy.
- If you have recently given birth or had an abortion, are breast-feeding or have recently stopped using a long-acting hormonal contraceptive (such as depo-

Provera), you should have had three spontaneous episodes of menstrual flow before you start the study.

- You are willing and able to follow the study procedures, including keeping a daily diary record each day.
- You have not used hormonal birth control or hormonal therapy (such as estrogen, progesterone or progestin) within the past 6 months, and do not plan to start any of these before you have completed the study.
- Your use of other therapies (herbal or natural therapies, thyroid medication, antidepressants, etc.) is established and kept stable during the study.
- You are not pregnant and not planning pregnancy during the study.
- You can understand, speak, read and write in English.

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You should not participate in this study if:

- You have had a hysterectomy.
- You no longer menstruate (have not had a period in the past 12 months).
- You have recently given birth, had a miscarriage or an abortion, are breastfeeding or have recently stopped using a long-acting hormonal contraceptive (such as depo-Provera), and have had fewer than three spontaneous episodes of menstrual flow.
- You are planning a pregnancy or are sexually active without using birth control.
- You are taking hormonal medications (estrogen, progesterone, progestins, hormonal contraception such as birth control pills, patch or vaginal ring).
- You have taken these hormonal medications within the past 6 months or plan to start taking them during the next 4 months.
- You have another medical reason for having hot flushes or night sweats.
- You have a peanut allergy (the study medication contains peanut oil)
- You are over 40 and have not had a normal screening mammogram within the last 12 months. You will become eligible once you get this.
- You have not had a normal clinical breast examination (usually by your family doctor) within the last 12 months
- You cannot understand, speak, read or write English.

If you are sexually active with a man, you are at risk of pregnancy, even if your menstrual cycles have become infrequent and irregular. In perimenopause, ovulation may also occur at unusual times relative to menstrual flow, so it is important that you always use an effective birth control method (e.g., a physical barrier such as a condom, diaphragm or cervical cap and each with a vaginal spermicide).

8. WHAT DOES THE STUDY INVOLVE?

Overview of the Study

We plan to enroll 175 volunteer participants for this single-site study being conducted in Vancouver, BC. The study includes initial and final questionnaires as well as daily record keeping during the study. The study starts with four weeks of baseline record keeping, followed by twelve weeks of either oral micronized progesterone (300 mg at bedtime) or identical placebo, chosen randomly (like the flip of a coin). This dose of progesterone has been used in our previous menopause hot flush study and in clinical practice with perimenopausal women. Progesterone in this dose keeps the blood level within the range that is normal for the second half of the menstrual cycle. A placebo does not have active ingredients, but looks identical to the study medication. In total, participation in the study will take about four months.

This study is double blind, meaning that neither you nor the research coordinator and study team will know which study medication you take. However this information is available in case of an emergency. Once you have completed your part of the study, the research pharmacy will tell you which group you were in. You should not share this with anyone in the research team, so that we can remain unaware of the study assignments and results until we are ready for analysis of the data.

If you agree to take part in this study, the procedures and visits you can expect will include the following:

Initial Visit/Before You Begin the Study/Screening Visit

Your first visit will take approximately 60 minutes, and will start with reviewing and signing this consent form. The research coordinator will ask you some questions, you will complete two questionnaires yourself and you will watch an instructional video that explains how to keep the Daily Perimenopause Diary. You do not have to answer any questions that you do not feel comfortable answering.

For the next four weeks, you will complete the Daily Perimenopause Diary each day. This is the main way that we will know how many hot flushes and night sweats you are having, and this baseline Diary will tell us how you are before you take any therapy. Completing the Diary should take less than two minutes each evening. During this time, if you haven't had a screening mammogram (and are 40 years or older) you should arrange this through the BC Screening Mammography Program. You will need to show your letter indicating that your test was normal before you can be enrolled. Also, during this month, if your doctor hasn't done a clinical breast examination with you in the last year, please also organize that.

Randomization Visit

After a month, you will come to the office with your baseline Daily Perimenopause Diary sheet(s). The research coordinator will make a copy of your mammogram letter (giving it back to you), confirm that you have had a clinical breast examination and review your Diaries with you (making copies and giving originals back to you). The research coordinator will take your body measurements (weight, height and waist circumference) and measure your blood pressure. You will complete four questionnaires yourself, and the research coordinator will ask you some questions to

complete another questionnaire. This second visit should take about 90 minutes. If you have had enough hot flushes and night sweats during the first month, and if there are no problems with your completion of the Diary, then you will be given a prescription for the study drugs to take to the research pharmacy (Shoppers Drug Mart in the Gordon and Leslie Diamond Centre, 2775 Laurel Street, Vancouver, British Columbia). This prescription will include information on whether you are in early or late perimenopause, according to your menstrual cycle lengths over the previous year. The pharmacist will also need to record your name, address, telephone number, date of birth and personal health number to add the study treatment to your personal medication list in the Pharmanet system. The system can only be accessed by pharmacists and physicians and is important so that you are not prescribed medications which interfere with those you are already taking. The pharmacist will check with a computer and give you either oral micronized progesterone or an identical placebo for you to take.

You will be given a wallet-size card explaining that you are participating in this study and you are taking either oral micronized progesterone or placebo. It will also have contact information for the study doctor and research coordinator. Please keep this card with you at all times and show it to any health professional involved in your care during study participation.

You should take three capsules (progesterone or placebo) each evening just before you go to sleep. The medication can cause drowsiness or dizziness for some women, so it is important that you *only take it as you get into bed for your usual sleep* and do not take it in the morning. If you have not been sleeping well, when you first start taking progesterone you may find that you need to catch up by sleeping longer than usual, so it is ideal to begin when you can sleep in the next morning. This is normal, and improves in a few days. Improved sleep on progesterone, however, is variable and some women may notice no changes. During the time that you are taking the study medicine, the research coordinator will get in touch with you by telephone or email to see how you are doing, and to make sure you have no questions or concerns.

Final Visit

The final visit will take about 90 minutes, and will be scheduled for three months after you start taking the medication. You should bring all of your Diaries and the medication bottle along with any remaining pills. At this meeting the research coordinator will take some measurements (weight, height, waist circumference, blood pressure), ask you some questions, and you will complete six questionnaires yourself.

Once you have finished the study, you can go to the research pharmacy to learn whether you were taking progesterone or placebo. This will let you learn from the study.

9. WHAT ARE MY RESPONSIBILITIES?

Your responsibilities are to make sure you have had a mammogram and clinical breast exam before starting medications, to keep the Daily Perimenopause Diary, and to record your therapy use in the diary. Although we will contact you monthly while you are on medication, you also need to let us know any time during the study if your medical situation changes, if you become pregnant, or if you want to start or stop any medications. You should also call the research coordinator if you experience any changes that concern you and you believe may be due to the medication.

10. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Progesterone is a natural hormone identical with the progesterone our bodies make when we are menstruating and ovulating normally. Oral micronized progesterone is approved for use in Canada (since 1995) and has been used in France since 1980. The dose of 300 mg at bedtime daily achieves a level of progesterone in the blood that stays for 24 hours within or above the range following normal ovulation.

Progesterone has no serious side effects compared with placebo. The most common 'side effect,' which is drowsiness, can be a benefit for those with disturbed sleep. If taken just before sleep, daytime drowsiness and dizziness are very unusual (less than 5%). **Progesterone can cause drowsiness and should not be taken when you need to be up and alert.** Also, women who are sleep-deprived should plan for some extra "catch-up" sleep for a few days. If you are sleep-deprived, it may help to start the medication on a weekend, or when you can sleep late.

If you were to become pregnant, you should stop taking the medication. Progesterone will not harm a fetus (it is made in high amounts by the body during pregnancy, and is sometimes used as a medication to support early pregnancy). However, if you become pregnant you will be ineligible to continue the study, so should let us know as soon as you can.

In perimenopause, hot flushes and night sweats are variable, but commonly increase in frequency and intensity over time before they improve. The year after what is later known to be your last menstrual flow can be the most difficult time for hot flushes and night sweats. Because of this natural pattern, all women in the study may experience worse flushes over the three months—however, we expect that those taking placebo will do less well than those receiving progesterone.

Progesterone can also be used to treat heavy menstrual bleeding, and therefore you may find that your periods become lighter and shorter. However, in perimenopause, it is unlikely to make flow totally disappear. However flow may become so light as to be only spotting; alternatively, bleeding may not change at all. We expect that progesterone will also help with breast tenderness and bloating. No controlled trials have shown the effect of progesterone on large, symptomatic fibroids—thus we do not know whether fibroids will grow. If progesterone were to cause *asymptomatic* fibroids to grow, because most are very small, they are still not likely to become

symptomatic in this short a trial. We do expect that progesterone will help women with heavy flow.

There are no long-term results on the effects of progesterone alone on health (in menopausal or perimenopausal women), such as heart disease and breast cancer. In a similar, short-term trial of progesterone in menopausal women, we found no serious adverse effects. In the short term (minutes to hours), progesterone causes no negative and probably positive effects on forearm blood flow, a marker indicating normal heart and blood vessel function. In our randomized trial of progesterone for hot flushes in menopausal women, the heart disease risk factors we looked at were very similar in the progesterone and placebo groups, with a small decrease in high density lipoprotein (HDL) in the progesterone group.

In recent years, medical opinions have changed about whether hormone therapy is beneficial for menopausal women. The Women's Health Initiative found that, on balance, healthy menopausal women should not be given hormone 'replacement' therapy as a preventative therapy. Some people have attributed to progestin (synthetic derivative of progesterone) the early discontinuation of the Women's Health Initiative trial of combined estrogen-progestin therapy. It is generally agreed that progesterone is less likely to cause health risks than progestin, any potential negative consequences would require some years to emerge, and that any would be unlikely to arise from a three-month course of treatment.

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

You may not benefit directly from this study. Keeping the Daily Perimenopause Diary will help you to understand your own patterns, and may improve your understanding of your hot flushes and night sweats, as well as other perimenopausal changes. Many women have told us that this is helpful to them. If you receive the active medication, you will learn whether it may be helpful for you. If you receive the placebo, you will have a good measure of your current experiences, so that you can compare the effects of any therapy or lifestyle change you may choose to use following the trial. You will be able to learn which group you were in at the end of the study; this will help you to make decisions about your health care.

There are very few studies on therapies for hot flushes and night sweats in perimenopausal women. Therefore, this study will benefit other perimenopausal women in the future.

12. WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

If you choose not to participate in this study or to withdraw at a later date, the following treatment options may be available to you: A regular 20 minutes per day practice of deep relaxation, yoga-type breathing, mindfulness meditation, or the relaxation response have all been shown to be helpful for hot flushes in menopausal women. In addition, regular exercise, weight loss if overweight and stopping smoking all benefit menopausal hot flushes. These strategies are likely to be useful for perimenopausal hot flushes as well. Your physician may also prescribe progesterone

for you. You can discuss these options with your doctor before deciding whether or not to participate in this research project.

As mentioned earlier, there are no therapies, available in Canada, that are proven effective for **perimenopausal** hot flushes, although many physicians believe that oral contraceptives and menopausal type hormone therapy help. In a European study, however, an extract of rhubarb (called “resveratrol”) was more effective than placebo in perimenopausal women with hot flushes. Also, a very concentrated amount of sage extract may help as perhaps will soy, and vitamin E. Finally, hot flushes may be helped by a general attitude that they are a nuisance but we can cope with and live through them.

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If you choose to enter this study and at a later date a more effective treatment becomes available, it will be discussed with you. You will also be advised of any new information that becomes available that may affect your willingness to remain in this study.

14. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis. It is a legal requirement that these data cannot be destroyed.

You may learn which group you were in (whether progesterone or placebo) by contacting the research pharmacy. This information is available to you whether or not you complete the study. It is important that you do not let anyone running the study know this, however, until the study is complete. It will also help if you let the research staff know your reasons for stopping the study and in particular if it is because of side effects you believe the study drugs have caused. However, you are not required to provide any reason.

15. CAN I BE ASKED TO LEAVE THE STUDY?

You can be asked to leave the study if you become ineligible (for example, if you start taking hormonal birth control), if you are not taking the study medication, or if you are not completing the Daily Perimenopause Diary regularly.

If you are not able to follow the requirements of the study or for any other reason, the study doctor may withdraw you from the study and will arrange for your care to continue. On receiving new information about the treatment, your research doctor might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health.

16. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or her designate by representatives of Health Canada, and the University of British Columbia's Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a participant in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

We sometimes collaborate with researchers outside of Canada, for example, with a statistician who may help us with new analysis methods for hot flush and night sweat data from this study. Any study related data sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries [for example, the Patriot Act in the United States] dealing with protection of information may not be as strict as in Canada. However, all study related data that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information, to organizations located outside of Canada.

In most cases, your personal information or information that could identify you will not be revealed without your express consent. However, if as a result of your participation in this study, facts become known to the researchers which must be reported by law to public health authorities or legal authorities, then your personal information will be provided to the appropriate agency or authority.

Primary Care Physician(s) /Specialist(s) Notification

Please indicate, by checking the applicable box, whether you want us to notify your primary care physician(s) or specialist(s) of your participation in this study. This is not a consent to release medical information.

Yes, I want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study. My primary care physician(s) and/or specialist(s) name(s) is/are: _____

The name of the medical clinic I attend is: _____

Participant Initials: _____

No, I do not want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study.

Participant Initials: _____

I do not have a primary care physician or specialist.

Participant Initials: _____

The study investigator is my primary care physician/specialist.

Participant Initials: _____

I understand that if I choose not to advise my primary care physician(s) or specialist(s) of my participation in this study, there may be potential medical consequences which may affect my comprehensive medical care or treatment. I understand that the study investigator may not be responsible for these consequences.

You may wish to discuss the consequences of your decision with the study staff.

Disclosure of Race/Ethnicity

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. Providing information on your race or ethnic origin is voluntary.

17. AFTER THE STUDY IS FINISHED

Progesterone (as Prometrium) is available by prescription in Canada, and your doctor may choose to prescribe it for you after your participation in this study is completed. The research pharmacy can let you know which group you were in after you have completed or withdrawn from the study.

The study will run from 2011 until 2014. When we have study results (likely in 2015) we will hold a post-study gathering to share the results with you, the participants who made it possible.

18. WHAT HAPPENS IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities. Should you have a medical emergency, you may call 604-875-4111 and ask for the Endocrinologist on call. Please advise her/him that you are participating in this study.

19. WHAT WILL THE STUDY COST ME?

Study materials (e.g., Daily Perimenopause Diary) and study medications will be provided to you without cost.

As partial compensation and recognition of your time and expenses, you will be paid \$20 once each stage of the study. There are three stages to the study: initial enrollment, randomization to placebo or progesterone and the final visit, so the total possible compensation for the study is \$60.

20. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Christine Hitchcock at 604 875 5917 or the Principal Investigator, Jerilynn Prior, at 604 875 5927.

21. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns or complaints about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

22. PARTICIPANT CONSENT TO PARTICIPATE

- *I have read and understood the participant information and consent form.*
- *I have had sufficient time to consider the information provided and to ask for advice if necessary.*
- *I have had the opportunity to ask questions and have had satisfactory responses to my questions.*
- *I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives.*
- *I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.*
- *I understand that I am not waiving any of my legal rights as a result of signing this consent form.*
- *I understand that there is no guarantee that this study will provide any benefits to me.*
- *I have read this form and I freely consent to participate in this study.*
- *I have been told that I will receive a dated and signed copy of this form.*

SIGNATURES

_____ Printed name of participant	_____ Signature	_____ Date
_____ Printed name of principal investigator/ designated representative	_____ Signature	_____ Date