THIS IS AN IMPORTANT DOCUMENT – KEEP FOR FUTURE REFERENCE

PARTICIPANT INFORMATION AND CONSENT FORM

Sponsor / Study Title:	**Graminex LLC / "A randomized, triple-blind, placebo controlled, parallel clinical trial to investigate the effect of pollen extracts on menopausal symptoms in healthy women"**
Protocol Number:	**24GXCFG01**
Principal Investigator: (Study Doctor)	**David Crowley, MD**
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You are invited to participate in a clinical research study. Participation in this study is strictly voluntary. To make an informed decision about participating in this study, it is important that you understand the potential risks and benefits of the study. This process, known as informed consent, ensures you have all the information needed to decide. This consent form outlines the study's purpose, procedures, potential benefits, risks, and how your medical information will be handled.

Take your time to thoroughly read all the details about the study, and do not hesitate to ask any questions you may have regarding the information given and about the study. Study staff will answer all your questions. You have access to this form and can review it at your leisure before deciding.

You should not sign this form until you fully understand the information provided, feel comfortable with your decision to participate, and have had all your questions about the study answered to your satisfaction. You will be provided with a signed copy of this form and are expected to keep it for your record. Once consent has been obtained, the study assessments will proceed.

If you wish to contact the study staff, please use the phone number or email address provided at the top of this page.

Background And Purpose

Menopause is a natural biological transition in the life of a woman and is diagnosed by the absence of a menstrual cycle for 12-months. Commonly reported menopausal symptoms include hot flashes, night sweats, mood disturbances, and poor sleep quality. A greater severity of these symptoms is associated with poor quality of life, lower levels of work productivity, and increased risk of heart, blood vessel, and cognitive (mental) health disorders.

Hormone replacement therapy, antidepressants, and anticonvulsants are some of the treatment options available for the management of menopausal symptoms, however they have been associated with side effects. Therefore, there is a need for alternative safe and effective strategies for the management of menopausal symptoms.

The purpose of this study is to examine the effects of *Graminex Water Soluble Pollen Extract (WSPE)* and *Graminex Lipid Soluble Pollen Extract (LSPE)* on menopausal symptoms in healthy women over a 36-week period. Pollen extracts similar to the study products, made from various grasses, have previously been shown to help improve menopausal symptoms and have been generally well-tolerated. These products are currently marketed as dietary supplements.

Study Population

This study will include approximately 120 healthy females between 45-60 years of age who are experiencing menopausal symptoms.

How Long Is the Study?

If eligible and enrolled in the study, your participation in this study will last approximately 252 days.

Important Things to Note

- For your safety, you cannot join this study if you have **asthma** and/or have any allergy (including **bee products** or **pollen**), sensitivity, or intolerance to the study products or placebo ingredients.
- To determine your eligibility to participate in this study, detailed information about your lifestyle, medications, and medical history will be collected. This information will help determine if you meet the necessary inclusion and exclusion criteria for this study.
- By signing this consent form, you are not guaranteed to be enrolled in the study. Your participation depends on meeting the study's specific eligibility criteria, which will be determined through a series of questions and assessments.
- This study will use competitive enrollment. This means when the target number of participants begin the study (120), all further enrollment will be closed. Therefore, it is possible that you could be in the screening phase, ready to begin the study, and be discontinued without your consent if the target number of participants have already begun the study. If this occurs, you will not be eligible for study compensation.
- If you voluntarily consent to participate in this study, you must agree and be willing to complete all study assessments, procedures, visits, and agree to maintain your current lifestyle as much as possible throughout the study, including diet, exercise, medications, dietary supplements, and sleep.

What Will Happen During the Study?

The following provides an overview of the study assessments, procedures, and schedule of study visits.

Assessments and Procedures:

Randomization – Visit 1 (If eligible)
Randomization means you will be assigned by chance (like drawing names from a hat) to a study group. If eligible, you will be randomized to 1 of 3 groups:

- Graminex WSPE®
- Graminex LSPE®
- Placebo

This is a *triple-blind study*, so neither you, the study staff, or the researchers analyzing the data will know which group you have been randomized to. Neither you nor the study staff will be able to pick which

group you are in, ensuring the integrity of the study. However, if it becomes necessary for your health, the study staff can access this information.

A *placebo* is an inactive substance that looks like the study product but has no active/medicinal ingredients. It is used in research to help determine whether the study product has real effects beyond what might happen by chance or expectation. Using a placebo ensures the study results are reliable by reducing bias, as neither participants, study staff, or researchers will know who is receiving the study product.

Menopause Rating Scale (MRS) – This questionnaire will assess menopausal symptoms and symptom severity (Visits 1, 2, 3, 4, 5).

Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short-form 8b – This questionnaire will measure sleep disturbance over the past 7 days (Visits 1, 2, 3, 4, 5).

Study Diary – You will complete a daily online study diary throughout the study to record study product use, any changes in health or medication use, and frequency of hot flashes and night sweats.

Compliance Calls – Study staff will contact you to review any changes in lifestyle including, diet, physical activity, and sleep (Day 21, 63, 126, 210 (± 2 days)). Compliance means you have been completing study activities and taking the study product as directed.

Schedule of Study Visits:

Visit 1 – Screening/Enrollment *Some portions of this visit may occur virtually prior to coming into clinic*
After informed consent is obtained, the screening assessments will include: • Review of lifestyle, medications, medical history, and current health status • Weight and height (Body Mass Index (BMI) calculation) • Blood pressure (BP) and heart rate (HR) measurements • MRS and PROMIS Questionnaires • Review any changes in health If you meet all necessary criteria, you will be enrolled and randomized into the study. • Study product, study diaries and instructions will be provided • A compliance call will be scheduled for Week 3 (Day 21 ± 2 days)
Visit 2 – (Week 6, Day 42 ± 2 days), Visit 3 (Week 12, Day 84 ± 2 days) and Visit 4 (Week 24, Day 168 ± 2 days)
• Return all unused and opened study product packaging, along with completed study diaries • Review of medications, any adverse events, and study diaries • Returned study product will be reviewed for a compliance calculation (confirm you have taken the study product as directed) • BP and HR measurements • Weight (BMI calculation)

• MRS and PROMIS Questionnaires • New study product and study diary will be provided • A compliance call will be scheduled for Week 9 (Day 63 ± 2 days), Week 18 (Day 126 ± 2 days) and Week 30 (Day 210 ± 2 days)
Visit 5 (End of Study visit, Week 36, Day 252 ± 2 days)
• Return all unused and opened study product packaging, along with completed study diaries • Review of medications, any adverse events, and study diaries • Returned study product will be reviewed for a compliance calculation (confirm you have taken the study product as directed) • BP and HR measurements • Weight (BMI calculation) • MRS and PROMIS Questionnaires

Medications, Supplements, And Food/Drinks

If you are taking any prescribed medications, you must agree to maintain you dosing regimen during the study, unless otherwise recommended by your general/nurse practitioner. If they recommend any medication or dose changes, please notify the study staff immediately. You should not discontinue your regular medications unless explicitly instructed by your general/nurse practitioner. Stopping regular medications without medical advice to join this study may worsen your health. If you stop your regular medications, inform the study staff immediately.

- If you are taking any prescribed medications and/or treatments which may affect the study outcomes, you may only be assessed for eligibility if you have been taken off these therapies by your general/nurse practitioner. The study doctor will recommend an appropriate washout period prior to enrollment in the study.
- If you use any over-the-counter medications, supplements and/or foods and drinks which may affect the study outcomes, you must be willing to stop taking them and agree not to consume these items during the study. The study doctor will recommend an appropriate washout period prior to enrollment in the study.

Washout Period: This is a period of time recommended by the study doctor to allow restricted substances (such as medications, supplements, foods, or drinks) to clear from the body before the study begins. If you have recently taken or stopped any restricted substances or participated in activities that conflict with the study, a washout period may be required before enrollment.

Study Product Information

The study product and placebo will be in a capsule form.

The Graminex® study products contain a standardized extract consisting of **rye pollen (*Secale cereale*).**

Study Product: Graminex WSPE® (Water Soluble Pollen Extract Capsules)

Medicinal Ingredient	Quantity per capsule (Qty)
Graminex Water Soluble Pollen Extract	150 mg

Non-medicinal ingredients: gelatin, microcrystalline cellulose, maltodextrin, stearic acid, titanium dioxide, silicon dioxide

Study Product: Graminex LSPE® (Lipid Soluble Pollen Extract Capsules)

Medicinal Ingredient	Quantity per capsule (Qty)
Graminex Lipid Soluble Pollen Extract	36 mg

Non-medicinal ingredients: gelatin, microcrystalline cellulose, maltodextrin, silicon dioxide, stearic acid, titanium dioxide

Placebo Ingredients: gelatin, microcrystalline cellulose, maltodextrin, silicon dioxide, hydroxypropyl cellulose, calcium stearate, titanium dioxide

Directions:

- You will take one capsule twice a day with breakfast and dinner for the duration of the study starting on Day 1 (the day after Visit 1)
- If you forgot to take the product, take it as soon as you remember on the same day
- Do not exceed two capsules per day
- You will save all unused and open study product packaging and return them to the clinic at each study visit

Alternative Treatments

You do not have to participate in this study to obtain relief for your menopausal symptoms. You can continue on any supplements or medications you are currently taking or speak with your doctor about other alternatives.

Additional Safeguards

If you need regular medical care for current medical conditions, you should continue with this medical care unless otherwise instructed by your regular physician or other healthcare professional. For your safety, you must discuss your current medical care with the study staff, as well as changes in medical conditions during the study. In addition, all new medications including supplements and natural health products (NHPs) that are taken during the study must be reported to the study staff.

Risks To You

It is possible that you could have problems or side effects from the study product that nobody knows about yet. There may be unknown risks with taking the study product. Potential side-effects of taking the study product may include:

- Gastrointestinal/Abdominal discomfort (such as pain, bloating, nausea, vomiting, heartburn)
- Allergic skin reactions

Could I Have an Allergic Reaction?

It is possible for people to have allergic reactions to the study product. If you have a serious allergic reaction, you could die. Please read the study ingredients carefully to make sure you are not allergic to any of them. Some effects of an allergic reaction that could be a sign of a life-threatening (anaphylaxis) include:

- Rash
- Difficulty of Breathing
- Wheezing
- Sudden drop in blood pressure (making you feel dizzy or lightheaded)
- Swelling around the mouth, throat, or eyes
- Fast pulse
- Sweating

If you have any of the above-listed effects or any other side effects during the study, you should get medical help or go to the emergency room immediately and then contact the study staff. Please also refer to section "Whom to Contact About This Study" for instructions on what to do in case of an emergency.

Contact the study staff if you have questions about the signs or symptoms of any side-effects you read about in this consent form. Please inform the study staff right away if you experience any side-effects, problems with your health or the way you feel during the study, and whether you think these problems are related to the study products or not.

Potential Risks From E-Consent

You may receive a link via email/text message to download a PDF copy of this signed consent form. There may be risks of loss of privacy and confidentiality if the PDF copy of this consent form is viewed and/or stored on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Also, the PDF copy of the consent may not be able to be permanently removed from a PED.

Withdrawal From the Study

- Your participation in this research study is strictly voluntary. You have the right to choose not to be in the study or leave at any time, for any reason, without affecting your relationship with the study doctor or study staff and without penalty or loss of benefits to which you are otherwise entitled.
- If you discontinue the study for whatever reason, you are expected to return all study materials, such as study product, to the clinic.
- You may be asked to undergo some final visit procedures. These may include returning to the clinic to complete any end-of-study assessments or questionnaires.
- If the study doctor or study staff finds out any related information that may greatly affect your well-being (for example, information related to your health), they will share it with you immediately.

The Sponsor has the right to stop the study at any time.

The study doctor may also stop your participation in the study at any time without your consent, but you will be informed about the reason. Reasons for this may include, but are not limited to:

- Missing scheduled study visits
- Not taking study product as directed
- Not completing required assessments or procedures
- Development of medical conditions or serious side-effects that may pose a health risk to you or the study outcomes
- The need for restricted medication(s) during the study

New Findings

Any significant findings that become available during the study which may influence your continued participation in the study will be disclosed to you as soon as possible.

Benefits

Your menopausal symptoms may or may not improve by your participation in this study. While there may be no immediate benefit to you, the results of this study will provide some of the required scientific evidence for the study products in this clinical research study. Your participation in this study supports the research that is required to ensure the science behind the study products.

Costs To You

- All the tests, study products, examinations, and medical care required as part of this study are provided at no cost to you, the public health plan, or your private medical insurance. All costs will be paid for by the Sponsor of this study.
- You, the public health plan, or your personal medical insurance (if any) should continue to pay for expenses for your current medical care and/or prescriptions. These expenses will not be paid as part of your participation in this study.
- The Sponsor of this study is paying your study doctor for the time, effort, and expenses to conduct this study.

Compensation For Participation

For your time and participation in the study, you will be compensated a total of $800 if you complete the entire study and all associated requirements.

You will receive your compensation after completion of the study on a Clincard, which can be used like a prepaid Mastercard. It can be used anywhere that accepts Mastercard, or the funds can be withdrawn from an ATM (ATM fees apply). Processing times may apply before funds become available on your Clincard.

If you are enrolled (randomized and received study product), the compensation breakdown is as follows:

- Visit 1 (Screening/Enrollment)*: $100
- Visit 2: $125
- Visit 3: $150
- Visit 4: $175
- Visit 5: $250

* Please note, if you complete visit 1 and are not enrolled into the study for any reason, you will not be compensated for this visit.

Once enrolled, for any case in which you or the study doctor determine you cannot complete all the study visits and assessments, you will receive compensation for the visits you have completed. An early termination visit will be requested where you will bring back all study-related materials and may be requested to complete some visit assessment and procedures if you consent to doing so. If you complete the early termination visit, you will be compensated $50.

Compensation And Treatment for Injury

- In case of an injury or illness suffered while, and solely as a result of participating in this study, you will receive appropriate medical care. The Sponsor will cover necessary medical costs not covered by

the provincial health plan or your private medical insurance (if any). By signing this form, you are not giving up your legal rights, nor releasing the study doctor or Sponsors from their legal and professional obligations.

- Be aware that the provincial health plan or your health care payer/insurer might not cover the costs of study-related injuries or illnesses.

Confidentiality Of Records

- Staff at KGK Science (the contract research organization managing this study) will keep all your medical information confidential to the extent permitted by law.
- All research data (health information, past medical history, and test/procedure results from this study if applicable) will be kept in a locked file. Forms on which your information is entered will not contain your name (except for the study intake form and/or external requisitions if applicable)
- Any of your personal information that is stored electronically will be password protected, accessible only to authorized personnel and coded wherever possible. Electronic data may be stored on secure servers which are physically located in Canada and/or the United States.
- You will not be identified in any publication that might result from the study. Unless required by law, only the following may have access to confidential study data (not your personal information) at the study site:
    - The study doctor and study staff
    - The Sponsor (including its monitors and auditors)
    - Members of the Research Ethics Board - Univo REB (an independent ethics committee that reviews the ethical aspects of studies to help ensure that the rights and welfare of participants are protected and that the study is carried out in an ethical manner)
    - Government regulatory authorities including Health Canada and other foreign regulatory agencies.
- While the Sponsor will not have access to your personal identifying information, the study doctor, study staff, monitors, auditors, REB, and regulatory authorities may review study records, which could include your personal identifying information (such as the signed consent form) for compliance and verification purposes.
- Study records will be kept by the sponsor as required by Canadian clinical trial regulations (currently a minimum of 15 years)
- Information from this study will be submitted to the Sponsor. Information sent from the study site will not contain your name.
- You have the right to check your study records and request changes if the information is incorrect.
- While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.
- As part of this research, you may be required to use one or more of the following: a phone or web app/ site, an electronic study diary (eDiary), or a device that tracks information about you. While using these, information about you may be collected and shared with the researchers or people outside of the study. This data might include personal health information, location, call logs, text message history, web browsing history, or social media use. A complete description of the data collection and sharing for an app, eDiary, or device can commonly be found in the Terms of Use, End User License Agreement, or Privacy Policy associated with the device. If you would like to read these documents, request a copy or instructions about how to access this information from the study doctor.

- While the Terms of Use, End User License Agreement, or Privacy Policy may include statements limiting your rights if you are harmed as a result of your use of the app, eDiary, or device in this study, you do not release the investigator, sponsor, institution, or agents for responsibilities from mistakes. You also do not waive any of your rights as a research study participant.

By signing and dating the consent form, you give your consent to collect, use and disclose your health information as described above.

A description of this clinical trial will be available on https://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Future Contact

By participating in this study, you agree that the study staff may contact you in the future should additional information be needed. This contact would only occur if more data were required after you have completed the study, or the study has concluded/expired. Any additional information gathered will be handled with the same confidentiality and privacy protections outlined in this consent form. You may choose not to provide additional information if contacted in the future, without any penalty or effect on the care or benefits you receive.

Whom To Contact About This Study

You can contact the study staff via email or by telephone listed on the first page of this document during the study if you experience any medical problems, suffer a research-related injury, or have questions, concerns, or complaints about the study, such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The study doctor's or study site's decision to withdraw you from participation;
- Results of procedures, if applicable

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study and please inform the KGK Science study staff.

A research ethics board (REB) is an independent committee that helps to protect the rights and welfare of research participants. If you have any questions about your rights and welfare as a research participant, or have concerns or complaints regarding this research study, please contact Univo REB at (919) 910-7743 or via email at info@univo-group.com.

Voluntary Consent to Participate

By signing and dating this document I agree that I have been provided enough time to read and consider whether to participate. I have reviewed and understand all pages of the consent form and information it contains regarding the study in a language I understand. I have been given the opportunity to ask all my questions regarding the study with answers to my satisfaction. I understand that I may consult with the study staff, should anything become unclear or if I have further questions.

I volunteer to be in this study at my own free will and without being pressured by the study doctor or the study staff knowing I have the opportunity to leave at any time without giving a reason and without affecting my health care. I understand that if I choose to withdraw from the study, I must notify the study staff. The risks involved with participating in this study are clear to me. I agree to follow the study instructions provided to me by the study staff and understand I may not participate in another study while I am enrolled in this study.

It is clear to me that my data derived from this study will be kept anonymous and may be reviewed by the Sponsor, their agents, Research Ethics Review Board, Health Canada and other foreign regulatory agencies. I understand that all my personal information will be treated as strictly confidential, except where disclosure is required by law, and will not be made publicly available; however, absolute confidentiality cannot be guaranteed.

I know that the study product is for my use only. I will not share it with anyone, and I will store it in a safe place away from children, pets, or others for whom it is not intended.

By signing and dating this document, I do not waive any of my rights under the law or release the study doctor or Sponsor from their legal and professional obligations.

I understand that I am expected to keep a copy of this signed and dated consent form for my record.

IN THE EVENT THAT ELECTRONIC CONSENT IS NOT AVAILABLE:

By signing this informed consent document, you acknowledge that you have read and fully understand all pages of the information presented in it, had enough time to consider this information, had an opportunity to ask questions, and voluntarily agree to be in this study.

_____
Printed Name of Participant

_____ _____ _____AM/PM
Signature of Participant Date (MMM,DD,YYYY) Time (HH:MM)

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FOR PERSON EXPLAINING CONSENT

I attest that the participant had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be in this study.

_____
Printed Name of Person Explaining Consent

_____ _____ _____AM/PM
Signature of Person Explaining Consent Date (MMM,DD,YYYY) Time (HH:MM)

FOR ELECTRONIC CONSENT:

For electronic consent, your name, digital signature, date, and time of consenting will be added below by the consenting software. By adding your electronic signature, you consent to the material provided as if you were physically signing a hard copy of this document. By signing this informed consent document, you acknowledge that you have read and fully understand all pages of the information presented in it.

Participant

I voluntarily agree to participate in this study
↓