

STUDY INFORMATION SHEET

A Randomised, Double-Blind, Placebo-Controlled Trial Investigating the Effects of Vanizem® (*Aframomum melegueta* seeds extract) on Stress, Anxiety, Sleep, and Mood in Adults with Mild-to-Moderate Stress.

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Background

Aframomum melegueta (*A. melegueta*), a member of the ginger family, is commonly known as grains of paradise, alligator pepper, or melegueta pepper. In West Africa, it is used as a spice in cooking and in traditional African medicine for the treatment of various health conditions. Preclinical studies have demonstrated that *A. melegueta* has neuroprotective, antidepressant, and anti-stress effects. A small trial conducted on an *A. melegueta* extract, known as Vanizem®, in adults showed positive effects on self-reported mood and sleep. Therefore, the aim of this study is to investigate the effects of Vanizem® on self-reported stress, general mood, sleep, and fatigue in adults experiencing mild to moderate stress. Furthermore, to help understand how Vanizem® works, changes in blood and saliva markers associated with mood, sleep and brain activity will be examined over time.

This study will be conducted by Dr Adrian Lopresti and Dr Stephen Smith (Clinical Research Australia).

Information about the funding source and declaration of interests

This study is funded by Nektium Pharma SL, the company that produces Vanizem®. However, this study is being independently managed by Clinical Research Australia (CRA) without external influence from the study sponsor.

What does participation involve? (see study flow chart on page 3)

This study will comprise several steps as outlined below:

Step 1: Completion of initial online screening

This questionnaire takes approximately 10 minutes to complete. It provides us with information relating to the eligibility criteria. If, based on the screening questionnaire results, you are assessed as 'likely' eligible, you will be contacted for a phone interview. Ineligible volunteers will be informed by email that they do not fulfil the eligibility criteria.

Step 2: Phone Interview for an assessment of eligibility

If you are potentially eligible to participate in the study, you will be interviewed by a researcher. The interview will be conducted over the phone (approx. 20 minutes). The purpose of this interview is to obtain relevant background information (e.g., medication use, current treatments, stress levels and causes, general health, etc.) and assess other relevant eligibility criteria. We will also provide you with further details about the study. If you meet our eligibility criteria and agree to participate in the study, you will proceed to the next step.

Step 3: VISIT 1 (Day 0, Baseline): Face-to-face assessment (total time approx. 60 mins)

The face-to-face assessment will comprise the following:

- a. Measurement of vital signs and anatomical measurements: A researcher will measure your sitting blood pressure, height, and weight.



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- b. **Blood collection:** A researcher will collect a blood sample from you. This blood sample will be used to measure the following:
 - i. **Safety markers:** liver function, renal function, complete blood count, blood lipids, and thyroid activity
 - ii. **Outcome makers:** these include markers of inflammation, neurotransmitter activity, and proteins involved in neuroplasticity
- c. **Heart rate measurement:** We will place a heart rate chest monitor on you and measure your heart rate at rest for 5 minutes.
- d. **Completion of self-report questionnaires:** You will complete a series of questionnaires.
- e. **Provision of a 28-day supply of the study capsules:** You will be given one bottle containing capsules with either Vanizem® or a placebo.
- f. **Provision of saliva collection kit:** We give you tubes to collect a saliva sample at your home. These collections will occur at 9 pm on days 0 and 27. We will provide you with instructions on the collection of your sample
- g. **Provision of Gift Voucher.** You will be given a \$30 gift voucher.

PLEASE NOTE: We will obtain the results of your safety blood makers within 48 hours after collection. In the unlikely event that any of these markers are **significantly** outside the normal range, we will contact you immediately and may need to withdraw you from the study.

Step 4: DAY 0: Collect a saliva sample

At 9 pm, after visit 1, you will need to collect a saliva sample. This involves collecting 5mls of saliva in a collection container. You will need to store this in your freezer until you return for your second visit. Instructions on collecting your saliva will be provided.

Step 5: DAY 1: Start taking your capsules

In this study, we will be using a randomised, double-blind, placebo-controlled design. This means that half of the participants will be placed on placebo capsules and the other half on capsules containing Vanizem®.

Neither you nor the investigator will know which group you have been placed in. This random allocation is crucial for us to accurately assess the true effects of Vanizem®.

You will be required to take **ONE** capsule, **ONCE** daily in the morning with food. It is extremely important that you take these capsules every day

* Placebo involves providing a substance with no known treatment effects. In this case, the placebo will contain maltodextrin (a plant starch).

Step 6: DAYS 1 TO 28: Daily Mood and Sleep Record (Online): Every morning between 7:00 and 8:00 a.m., you will receive a notification on your phone to complete questions about your mood and sleep. You will click on the link and complete these questions. They will take less than 1 minute to complete

Step 7: DAY 3: questionnaires (online): You will complete questionnaires online, which will take approximately 5 to 10 minutes

Step 8: DAY 7: questionnaires (online): You will complete questionnaires online, which will take approximately 10 to 15 minutes

Step 9: DAY 14: questionnaires (online): You will complete questionnaires online, which will take approximately 10 to 15 minutes

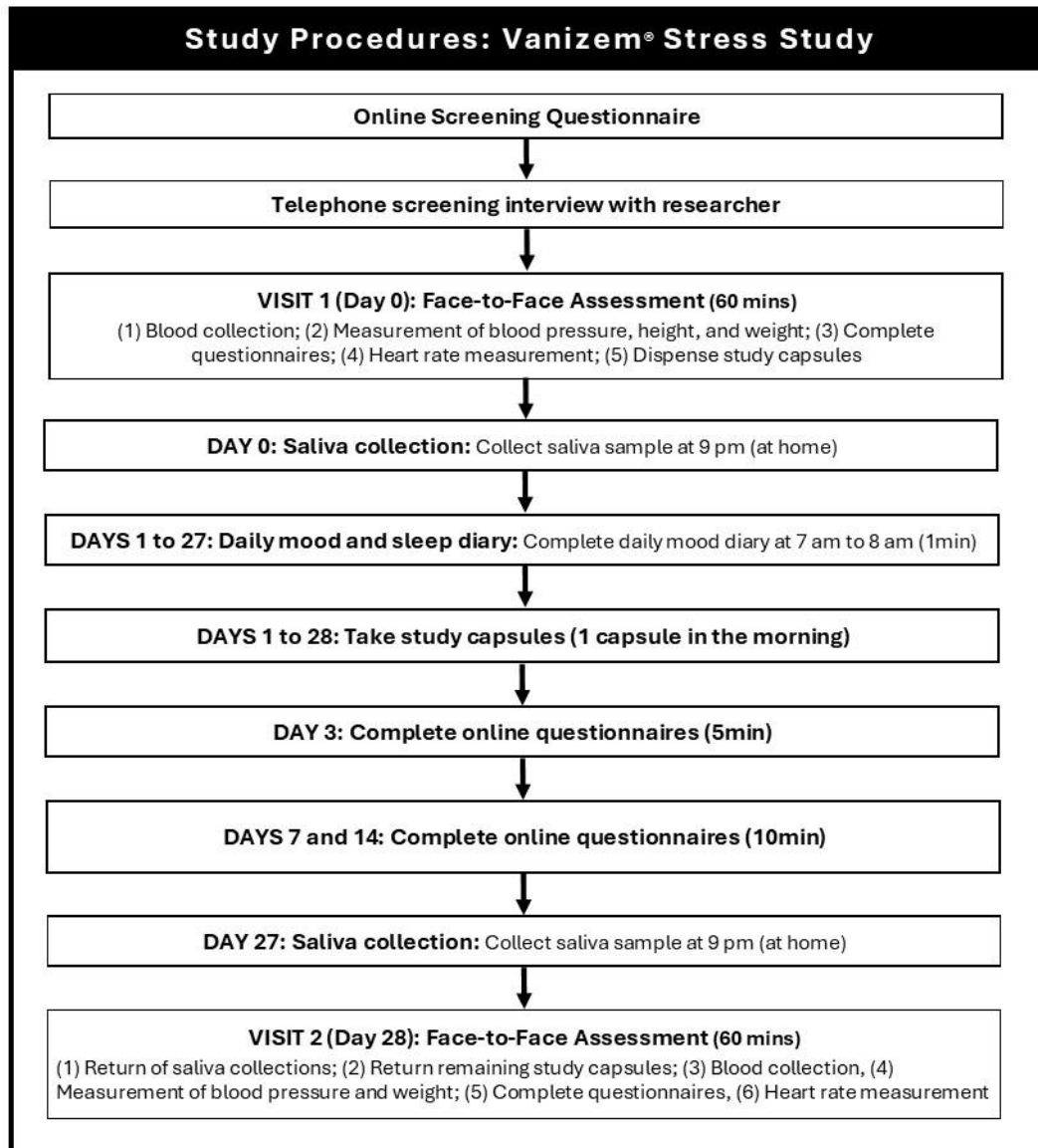
Step 10: DAY 27: Collect a saliva sample

At 9 pm, the evening before your second visit, you will need to collect another saliva sample.

Step 11: VISIT 2 (Day 28): Face-to-face assessment (total time approx. 60 mins)

The face-to-face assessment is similar to visit 1 and will comprise the following:

- a. You will need to return your saliva collections
- b. You will need to return your study bottles/ capsules
- c. Measurement of vital signs and anatomical measurements: A researcher will measure your sitting blood pressure and weight.
- d. Blood collection: A researcher will collect a blood sample from you.
- e. Heart rate measurement: You will have your resting heart rate measured for 5 minutes while at rest.
- f. Completion of self-report questionnaires: You will complete several questionnaires.
- g. Provision of Gift Voucher. You will be given a \$150 gift voucher



Compensation for participating in this study

To compensate participants for travel costs and time associated with participating in this study, you will receive a \$30 gift voucher at visit 1 and a \$150 gift voucher at visit 2.

At the end of the study, volunteers in the placebo group will also be offered a complimentary 28-day supply of Vanizem® to try.

Criteria for inclusion/ exclusion in this study

To be included in the study, the following inclusion criteria must be met:

1. You are aged 18 to 60 years
2. You are experiencing self-reported stress and score within the range required on our questionnaire

3. You have been a non-smoker for at least 12 months
4. You have a body mass index between 18 and 35 kg/m²
5. You have no plan to commence new treatments over the study period.
6. You understand, are willing and able to comply with all study procedures.
7. You are willing to provide a personally signed and dated informed consent form detailing all pertinent aspects of the trial.

If any of the exclusion criteria below are met, you will not be suitable for participation in this study:

1. You have a diagnosis of a medical condition, including but not limited to diabetes, hypertension, cardiovascular disease, adrenal disease, gastrointestinal disease requiring regular use of medications, biliary disease, thyroid disease, cancer/malignancy, renal disease, hepatic disease, endocrine disease, respiratory disease, neurodegenerative disease, or chronic/acute pain condition.
2. You have had past gastrointestinal surgery that may affect the absorption of the investigational product
3. You have a current diagnosis of a psychiatric disorder, other than mild-to-moderate depression or anxiety symptoms
4. You have abnormal blood makers, comprising fasting glucose, thyroid function, liver function, or renal function.
5. In the last 3 months, you have regularly taken any pharmaceutical medication (excluding contraceptive medication or the occasional use of analgesics of not more than twice weekly) or intend to start during the study period.
6. In the last 3 months, you have regularly taken any over-the-counter vitamin or herbal supplement, or intend to start during the study period.
7. You are engaged in night-shift work, irregular shift work, or have experienced circadian rhythm disruption (e.g., jet lag) in the last month.
8. You are planning a major lifestyle or dietary change during the study duration
9. You have an alcohol intake greater than 14 standard drinks per week
10. You have a current or 12-month history of regular illicit drug use
11. You are pregnant, breastfeeding, are less than 3 months postpartum, or intend to become pregnant during the study period.
12. In the last year, you have had surgery that continues to affect your general health or daily function, or have a planned surgery in the next 2 months
13. You have participated in any other clinical trial in the last month

Voluntary participation and withdrawal from the study

It is essential that you understand your involvement in this study is entirely voluntary. While we appreciate your participation, we respect your right to decline. There will be no consequences to you if you decide not to participate, and this will not affect any future treatment/service. If you decide to discontinue participation at any time, you may do so without providing an explanation. If you withdraw, any assessments already conducted may continue to be used for analysis.

Please note that if you choose to commence treatment to reduce your stress levels, improve your mental health, or require medical treatment for any other condition during the study, this may result in your withdrawal from the study. Your health is the utmost priority, and your choice/need to commence new treatment before completing this study is respected and supported.

Your privacy

Your privacy is of the utmost importance to us. Your participation in this study and any information provided will be treated in a confidential manner. Your name and identifying details will not be used in any publication arising out of the research. Following the study, the data will be stored in a de-identified format in a locked cabinet in the Investigator's office and will be retained for statistical analysis and potential future publication. Re-identified codes will be retained for 6 months in case they are needed and will then be destroyed.

Possible benefits

Chronic, high stress has a significant negative effect on both mental and physical health. Therefore, identifying strategies to help reduce stress and mitigate the negative effects of chronic stress on the body is important. If found to be effective, Vanizem® will present as a natural option for adults to help support them during times of stress.

Possible risks

Participation in this study carries minimal risk, and numerous measures will be in place to minimise the likelihood of potential risks. Vanizem® is available in the international market for commercial use. It is well tolerated, where no serious adverse effects have been reported. *A. melegueta* also has a long history of traditional oral medicinal use, where it has been used for the treatment of multiple health ailments. Previous clinical trials on Vanizem® have also confirmed that it is well-tolerated at the doses to be used in this study. However, anecdotal reports from consumers indicate that the most common side effects are mild stomach irritation or discomfort. This is likely due to the vanilloid content of *A. melegueta*, which is a spice. To avoid this, Vanizem® will be taken with food.

In this study, we will collect a blood sample from your vein (venepuncture). Although venepunctures are very safe, there is a possibility of bruising at the site of the needle puncture. This usually appears within 24 hours and may range in size from a small spot to a large purple bruise. While bruising can be unsightly, it is not dangerous and typically disappears over a few days. Very rarely, a small artery that contains blood at a much higher pressure than in veins will lie unusually close to, or underneath, a vein. In this situation, the artery may be accidentally punctured during venepuncture. Bruising on the lower arm may develop over the next 2 to 3 days. Again, this is not dangerous and will gradually disappear over a couple of weeks. Although extremely rare, some people may have a small branch of one of the sensory nerves in the arm running over the surface of a vein. Rarely, the needle will hit this tiny nerve on the way into the vein. This may cause a sharp, electric-shock-type pain. This may be all that occurs, but in some cases, a tingling type of pain may persist for 1 to 4 weeks as the nerve heals. This is inconvenient and may be unpleasant, but it eventually subsides. Another rare complication is the formation of a small clot (or thrombus) in the vein at the site of the venepuncture. This is noticed as a small firm lump just under the skin at the venepuncture site. The lump may be tender, and it will typically subside over a couple of weeks. Finally, although extremely rare, an infection can occur at the site of puncture. Please notify us immediately if this occurs. To minimise all these risks, blood collections will be collected by a qualified and experienced phlebotomist using current best practices.

What to do if you experience significant side effects

If you experience any significant illness, injury, or side effect that has commenced since starting your capsules, please contact Dr Adrian Lopresti or Dr Stephen Smith immediately (contact details are below). You may be asked to stop participating in the study and to seek medical advice.

Dr Stephen Smith: Ph: 9448 7376 | Mob: 0412 813 518 | Email: steve@clinicalresearch.com.au

Dr Adrian Lopresti: Ph: 9448 7376 | Mob: 0411 969 797 | Email: adrian@clinicalresearch.com.au

Feedback on study results

It is estimated that the results of this study will be finalised in late 2026. A summary of the results obtained from all participants in this study will be emailed to you when they have been published in a peer-reviewed journal (usually 6 to 12 months after the completion of the study).

Questions

If you would like to discuss any aspect of this study, please contact the principal investigator, Dr Adrian Lopresti, on 08 9448 7376 or email adrian@clinicalresearch.com.au

This study has been approved by the National Institute of Integrative Medicine (NIIM) Human Research Ethics Committee (HREC) (Trial Reference Number: 0165E_2026). If you have any reservations or complaints about the ethical conduct of this research and wish to talk with an independent person, you may contact the NIIM Research Ethics Office (Tel. 03 9804 0646) or email hrec@niim.com.au. Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.