Monell Center Research Study Summary for Potential Subjects

Protocol Title: Sensory analysis and taste modulation of KE drinks
Principal Investigator: Paul M. Wise, Ph.D. 267-519-4799
Emergency Contact: 24 hour access number: 267-519-4900

You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to better understand the bad taste of ketone ester (KE) drinks and find ways to make KE drinks taste better. Ketone esters are chemicals that cells in your body can use for energy. Your body produces KE by breaking down fat, particularly during a low carbohydrate ("ketogenic") diet or heavy exercise. We are studying liquids that contain artificially produced ("exogenous") KE. Some athletes use KE drinks to enhance performance. We are inviting you to participate because you are a healthy adult between the ages of 21 and 45.

If you agree to join the study, we will first train you to recognize various kinds of tastes (for example, bitter, sweet, and salty) by tasting examples, and how to rate the strength of these tastes. Next, participants will rate how KE solutions (KE mixed in water) taste. Finally, participants will rate the taste of KE solutions with and without various flavor modifiers, which may or may not change how the KE solutions taste.

In total, all the activities listed in the paragraph above should require 7 or 8 study visits to the Monell Center over 3 or 4 weeks. However, we will study many flavor modifiers over the course of about a year, so you may be eligible to participate in more study visits over a longer time if you chose (but you are not required to do so, and can stop at any time).

You will NOT receive any direct benefit by participating in the study. A highly likely risk is that many liquid samples will taste bad (perhaps very bad, with an aftertaste that can linger). We will instruct participants to drink (swallow) KE solutions. We do this because taste or feel in the back of the throat may be important in how people experience the flavors. The United States Food and Drug Administration (FDA) allows KE drinks to be sold to consumers in the USA, but some people report feeling nausea or indigestion after drinking KE drinks. These feelings tend to pass fairly quickly. There is also a chance of experiencing stronger feelings of nausea associated with disgust from very unpleasant tastes. Those these feeling should also pass quickly, but if you find any samples too unpleasant to tolerate, you are encouraged to stop rather than toughing it out.

Since the procedures do not diagnose or treat any illness or condition, you lose nothing if you decide not to participate. Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

MONELL CHEMICAL SENSES CENTER RESEARCH SUBJECT INFORMED CONSENT AND FORM

Protocol Title:	**Sensory analysis and taste modulation of KE drinks**
Principal Investigator:	Paul M. Wise, Ph.D. Monell Chemical Senses Center 3500 Market Street, Philadelphia, PA 19104 267-519-4799
Emergency Contact:	24 hour access, call 267-519-4900

Why am I being asked to volunteer?

You are being invited to volunteer for a research study. You are being asked to volunteer since you meet the requirements for enrollment into this study, namely, that you are a healthy adult between the ages of 21 and 45 and weigh at least 100 pounds. Your participation is voluntary, which means you can choose whether or not you want to volunteer. If you choose not to volunteer, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with others. Take all the time you need to make your decision. Take the form home with you for further study and research if you want. You may find some of the language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to volunteer, you will be asked to sign this form and be given a copy of this form.

What is the purpose of this research study?

Ketone esters (or KE for short) are chemicals that cells in your body can use for energy. Your body produces KE by breaking down fat, particularly during a low carbohydrate ("ketogenic") diet or heavy exercise. We are studying drinks that contain artificially produced ("exogenous") KE. Some athletes use these drinks to enhance performance. However, KE drinks taste very bad to most people.

We are interested in better understanding the bad taste of KE drinks and finding ways to make KE drinks taste better.

This study is being done in collaboration with HVMN, the company who makes and sells the KE drinks. This company will supply us with the same KE they use in their marketed products, which we will mix with filtered water to create liquid samples for tasting in this study. The work is funded by the US Department of Defense though a Small Business Technology Transfer (STTR) grant. Monell is a sub-contractor under this grant, hired to do flavor research on the KE drinks. HVMN may eventually benefit financially from knowledge gained in this study. The Monell Center is not affiliated with HVMN, but could benefit financially if the work results in patents. Dr. Paul Wise, the principle investigator of the study, and the study team do not expect to personally benefit financially. Research participants will NOT receive payments or royalties beyond compensation for their time (see "Will I be paid for being in this study?" below).

How long will I be in the study? How many other people will be in the study?

If you agree to volunteer, you will be asked to participate in at least seven (7) study visits of up to 90 minutes each. We would like you to complete these seven sessions within 3 to 4 weeks if your schedule permits, but if you have trouble scheduling the sessions within a month it is OK to complete the sessions over a longer period. In addition, we will test a number of flavor modifiers over the course of about a year, and you may be eligible to participate in more study visits over a longer period if you wish to do so (but you are not required to do to and you can stop any time). In total, we expect up to about 40 people to participate over the course of about a year.

What am I being asked to do?

Study visit 1 (about 60 minutes):

- Read, discuss, and (if you agree) sign this consent form.
- If you or someone in your family is an employee of the Monell Chemical Senses Center, you will be asked to complete an additional consent form.
- Complete questionnaires to provide contact information, basic information including date of birth, gender, and race/ethnicity, and information on smoking and eating habits. We will also ask some general health questions to decide if you qualify to participate.

- If you seem to qualify based on health questions, we will weigh you using a medical scale. To be eligible, you must weigh at least 100 pounds (45.4 kilograms).
- If you are qualified, we will then ask you to do some training. We will ask you to taste and discuss various samples (mostly liquids) to demonstrate sensations we will later ask you to rate (for example, bitter, sour, astringent). You will be instructed to NOT swallow any of these samples, but spit them out and rinse your mouth with water after each one. We will also train you in the use of scales used to rate taste sensation. Some training may be done in a small group (with up to 5 other participants). All other activities in the study visit will be private.

Study visit 2 (about 60 minutes):

- We will continue with the training, and do some practice ratings of various liquid samples to determine if you have mastered the concepts learned during training. Some people may require an additional training session to master all concepts. If so, that additional training would require another study visit. Training may be done in a small group (with up to 5 other participants).

Study visits 3 through 7 (up to 90 minutes each):

- Taste 12-15 liquid samples over the study visit, with breaks of about 5 minutes between samples.
- We will ask you to rate the flavor of the samples. We will also ask you to rate how you feel (for example, if you feel any nausea) between samples.
- Some samples we will instruct you to swallow. Each sample will be about 5 ml (or about a teaspoon). We will keep the total amount of ketone ester swallowed below a single serving size as the product is sold.
- For some samples, we will instruct you to wear plastic nose clips (similar to those used to pinch the nose shut for swimming) to block aroma from reaching the nose.

Further study visits (optional)

- Same as study visits 3-7 (above). If more than one month has passed between your first set of visits, we will ask you review this consent form again (and sign again if you agree). We may also ask you to do a training refresher session. Again, all these visits would be strictly optional.

Note: Some taste testing may be done in small groups (up to 6 people present in the room).

We expect you 1) to attend sessions as scheduled, 2) not to eat, drink anything except for water, or smoke for at least one hour before the start of each session, 3) not to wear strong personal fragrances or perfumes to the session, 4) to speak up right away and tell study staff if any procedure is too uncomfortable for you, or if you have any concerns, and 5) to follow all instructions.

What are the possible risks or discomforts?

We know of no likely risks of serious harm from tasting the liquid samples we will present. Anything we ask you to swallow will be approved for use in foods and drinks. Other samples may contain chemicals that are NOT approved food additives, and we will instruct you NOT to swallow those samples, but rather spit them out and rinse with water after tasting. **It is important that you follow instructions on which samples to swallow and which to spit out to reduce possible risk of harm.** The model ketone ester drinks to be used in this study will contain ketone esters dissolved in filtered water to levels at or below levels found in marketed products. Some flavor modifiers we plan to test do not dissolve well in water. To dissolve them in model drink samples, we may use a small amount of ethanol (the kind of alcohol in beer, wine, and distilled spirits) and/or a small amount of food-grade surfactant (an ingredient which helps dissolve substances which don't easily go into water). If we use alcohol, the amount we ask you to consume in a visit will be less than you might find in a non-alcoholic beer (NA, or "near beer"), and comparable to what you might get in a piece of ripe fruit. This should not affect most people, but if you are allergic to or sensitive to alcohol you should NOT participate.

- We'll record some personal information about your health, as well as your social security number for the purpose of recording payment. If this information is revealed, it might affect your social relationships, employment opportunities, or health/life insurance options. If your personal information is revealed, you might also be at risk of identity theft. We will do everything we can to make sure your information remains confidential, but you should consider this risk.
- Many of the samples will taste bad to most people. Samples might taste bitter, sour, oily (fatty), or astringent (dry). If you find any of the samples too unpleasant, please tell the study staff right away. You can stop participating any time you wish.
- The United States Food and Drug Administration (FDA) permits the sale and consumption of KE drinks which contain the same ketone esters we will use in this research study, at the same levels. However, some people report

feeling mild to moderate nausea or indigestion after drinking KE drinks. These feelings tend to pass fairly quickly, but they may happen more often if people do not exercise after drinking (and participants in the study will NOT exercise during the study visits). Also, tasting very unpleasant samples can cause disgust and nausea, occasionally strong nausea for some people. Again, if any samples are too disgusting for you to tolerate, you are free to stop at any time. The decision to stop or not will be up to you, but if samples you taste are too punishing we encourage you to stop rather than trying to tough it out. You will be compensated for all sessions or partial sessions completed, and you will still be welcome to participate in any other Monell studies for which you otherwise qualify.

- Some people report feeling less hungry on study days during which they drink KE drinks. Many people report reduced appetite on a "keto" diet, and there is some evidence that the artificially produced ketone esters might have a similar effect for a short period (i.e., during a study day). Some people also report feeling more energetic and focused for a couple of hours after drinking KE drinks.

Risks might be greater if you have food allergies, diabetes, or another metabolic issue. If so, you should NOT participate. Also, for small people (less and 100 pounds), amounts consumed might be closer to a maximum single serving, so if you are lighter than 100 pounds you should NOT participate. Since some samples may contain trace amounts of alcohol, if you are allergic to or sensitive to alcohol, you should NOT participate. One bitter chemical we will ask you to taste and spit out (not swallow) is 6 n-propylthiouracil (or PROP), which is a medicine for treating over-active thyroid. The drug can have serious side effects, including fatal liver damage. The amounts we will use for bitter taste samples will be very small compared to what patients take to treat thyroid problems, but if you are unusually sensitive to PROP, accidentally swallowing a taste sample could possibly increase your risk. PROP also has dangerous interactions with some prescription drugs (including some blood thinners, beta blockers, digitalis, and theophylline). If you take these or any other medications (except for birth control), you should NOT participate.

- Although we know of no special risks to unborn or nursing babies, it would be best to avoid participating if you are nursing, pregnant, or believe you might become pregnant during the study to avoid any possible added risk to unborn or nursing babies. If you are able to become pregnant, you are asked to use a medically accepted method of birth control (pill, implant, etc.) while you participate in the study.

Again, we emphasize that If any procedure causes you discomfort, please tell the study staff right away. Testing can be paused, or stopped

completely, at any time if you choose. You can withdraw from the study without losing any compensation earned, and you will still be eligible to participate in any other Monell study for which you would otherwise qualify.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You will not receive any benefit. Society in general can benefit from increased understanding of how make performance supplements taste better. The knowledge gained could also help us understand how to make medicines or nutritional supplements taste better.

What other choices do I have if I do not participate?

The only alternative to participation in this study is not to participate.

Will I be paid for being in this study?

You will receive $25 for each session, paid by check. If all seven study visits are completed, then you will receive a check for $175 after the last visit is complete. If you chose to participate in additional sessions, you will be paid at the same per session rate. If you chose to stop participating, you will be paid for all sessions completed up to the time you leave the study. We collect social security numbers (or IRS-issued taxpayer ID numbers) as part of the payment process (using an Internal Revenue Service form W-9). If you are paid more than $600 in one calendar year, Monell will issue a 1099-MISC to you and the IRS.

If you are a non-resident alien without a social security or IRS-issued taxpayer ID number, you may still be eligible to receive compensation. If you are a citizen of a country that has a tax treaty with the United States, you will need to fill out an IRS form 8233 instead of a W-9. If you a citizen of a country that does not have a tax treaty with the United States, you will need to fill out a form W-8BEN instead of a W-9 and Monell will be required to withhold 30% of your total compensation to be paid to the United States Internal Revenue Service.

If you are unwilling to fill out the required tax forms and/or agree to withholding (if required), then you may still be eligible to participate in the research study **but we will not be able to pay you** for participating.

If you are a member of the United States military or an employee of the United States Federal government, we cannot compensate you while you are on duty. During non-duty hours, many Federal employees (civilian and uniformed) may be compensated for participation in research studies. However, some may be prohibited from accepting compensation without prior approval from their agency and others may be required to report their participation to their supervisors. **If you are a member of the US military, or another Federal Employee, we suggest that you consult your supervisor if you have any questions about the policies of your agency. If you do choose to participate, please understand that we can only compensate you for participation while you are on leave or off duty.**

Will I have to pay for anything?

There are no costs to participate.

Will I receive the results of research testing?

No, but please note that the results would not tell participants anything about their health in any case.

What happens if I am injured or hurt during the study?

If you are injured during the study, you should go to the nearest emergency room. There are no plans for the Monell Chemical Senses Center to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study (Paul M. Wise, Ph.D.) as soon as possible. The researcher's name and phone number are listed in this consent form. You may also use the Emergency contact number listed on page one of this form.

Also, any injury related to this research study must be reported to the US Department of Defense within 30 days.

When is the study over? Can I leave the study before it ends?

This study is expected to end after all participants have been evaluated, and all information has been collected. This study may also be stopped at any time by the Monell Chemical Senses Center, the Food and Drug Administration (FDA), The U. S. Office of Human Research Protections (OHRP), or representative of the US Department of Defense.

In addition, the Principle Investigator may end your participation in the study if the Principle Investigator feels that 1) continued participation may be dangerous to your health or safety, or 2) you have not followed study directions (in particular, if you swallow samples we instruct you to spit out, you will be removed from the study). Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.

You are free to leave the study anytime, for any reason. Withdrawal will not interfere with your future interactions with this institution.

How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. Paper records with personal information will be kept in a locked room, on a locked floor, in a locked building. Computer records with personal information will be kept on secure servers protected by passwords.

However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If the taste test results of particular people are presented, the results will identify people only according to a random code number (for example, KE0241). The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. Members of the Monell Chemical Senses Center Human Subjects Committee may access your records to make sure the study was done properly. The company who makes the ketone ester drinks (HVMN) might need to access your records for oversight of the project. Representatives of the US Department of Defense, the project funder, might need to review your research records. Finally, the United States Food and Drug Administration (FDA) may review your research records.

Will information about this study be available to the public?

We may make a description of this study available on www.ClinicalTrials.gov. If so, no personal health information or information that can be used identify you will be posted.

A summary of results will be shared with HVMN, the company that makes and sells the ketone ester drinks, and with the US Department of Defense. We also plan to publish results in scientific journals and/or present results at scientific meetings. Results shared outside the study team in this way will have all identifiable information removed so no one will be able to identify particular participants. If individual participant results are published or presented, your results will be identified using a random ID code (for example, KE0241) rather than your name or initials.

Future Use of Data

Your information will be de-identified. De-identified means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected in this study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form (Paul M. Wise, 267-519-4799). If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614. You may also report concerns regarding the research to the United States Special Operations Command Human Research Protection Office by calling (813) 826-7498 (hrpp@socom.mil).

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When you sign this form, you are volunteering to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the Monell Chemical Senses Center to use your personal health information collected about you for research purposes within our institution. You are also allowing the Monell Chemical Senses Center to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Please Print)	Signature	Date