Brief Title: Ketone Pharmacokinetic Study in HFrEF

Official Title: Ketone Pharmacokinetic Study in Heart Failure With Reduced Ejection Fraction

NCT#: NCT05757193

Informed consent document date: 12/22/2023

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

CONCISE SUMMARY
This study is being conducted to test whether an over-the-counter ketone ester drink, DeltaG, is well tolerated in patients with heart failure on, and not on, a heart failure medication class called SGLT2 inhibitors. In this study, we are trying to find the best dose of DeltaG.

The study has a single visit. Participants will be served a light breakfast with the study drink, a physical exam will be conducted, and the study team will ask you questions about your demographics and medical background. The study team will draw blood intravenously up to eight times over the course of the half-day visit.

The greatest risk of this study involves bleeding and physical discomfort from the blood draw. Additionally, there is a chance of stomach irritability after ingesting the drink. There is also a potential loss of confidentiality.

If you are interested in learning more about this study, please continue reading below.

You are being asked to participate in this research study because you have heart failure. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

The research study is being conducted to test whether a ketone ester drink (DeltaG) is well tolerated in patients with heart failure (HF) on, and not on, a heart failure medication class called an SGLT2 inhibitor. In this study, we are trying to find the safest and most efficacious dose of DeltaG. This study is a single visit, during which we will collect data to determine the best dose of the ketone drink by drawing your blood and recording your vital signs for roughly four hours.

You are unlikely to benefit from this study since the study drink (DeltaG) lasts for a short time in the body. The most common risks of participation are related to the drink (DeltaG), which include bitter taste and stomach upset (nausea, diarrhea, constipation).

Your participation is voluntary; therefore, you can decline participation at any time. Any of your study information, including blood samples, may be sent to collaborators within and outside of Duke for analysis (including companies), though your name or other identifying information will not be included. The use of DeltaG in this study is experimental. DeltaG has not been approved by the Food and Drug Administration (FDA) for the purpose evaluated in this study.

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

Please note that there are other factors to consider before agreeing to participate, such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a study team member 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.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Senthil Selvaraj will conduct the study, which is funded by the National Institutes of Health and the American Heart Association. The sponsor of this study, Duke University, will pay to perform this research, and these funds may reimburse part of Dr. Selvaraj's salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, ***Dr. Selvaraj*** will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterward, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to test whether a ketone ester drink (DeltaG) is well tolerated in people with heart failure on, and not on, a heart failure medication class called an SGLT2 inhibitor. We are trying to determine the safest and most efficacious dose for patients like you.

Patients with heart failure have reduced ability to exercise. Ketones have been shown to improve exercise capacity in healthy volunteers. An infusion of ketones through an intravenous tube has also been shown to significantly improve heart function. This study aims to determine the best dose for patients with heart failure. DeltaG is available over the counter and has been given "generally regarded as safe" status by Food and Drug Administration.

The use of DeltaG in this study is investigational. The word "investigational" means the study drug or device or biologic is still being tested in research studies and has not yet been approved by the U.S. Food and Drug Administration (FDA) for this use.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 20 people will take part in this study at 1 center, and all participants will be from Duke.

WHAT IS INVOLVED IN THE STUDY?
If you participate in this study, you will be asked to come to the research center for one visit. During this visit, we will ask you questions to make sure you fit the criteria for our study. We will draw blood before a light breakfast and after the light breakfast. Then, you will receive the DeltaG drink once, and we will perform blood draws a total of eight times over four hours and check your vital signs frequently. You can request to leave the study at any time.

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

Procedures and Visit Schedule
Prior to this dose-finding study, our study team may contact you to discuss the study, ask you questions related to your health, and make sure you are eligible for the study.

Dose-finding study: *In-person visit at our research center. This visit will be approximately half a day. Please come fasting (nothing to eat for at least 8 hours).*
On this day, we will ask you about your heart failure symptoms, medical history, and medications. We will draw blood after we give you the DeltaG drink.

Here is a list of the events for this dose-finding study:

- *Review and sign this informed consent form.*
- *Meals* – a light breakfast will be served.
- *Vital Signs and focused physical exam* – We will check your blood pressure, heart rate, respiratory rate, and we may perform a physical exam.
- *Blood Draw* - We will draw blood from you. Blood will be drawn by inserting a needle into a vein in your arm and inserting an IV (intravenous) line. We will measure various substances in the blood that tell us, for example, about your sugar, acid-base status, and ketone levels. We may also perform other laboratory analyses from this blood (including, but not limited to, electrolytes, kidney/liver function tests, proteins, metabolites (for example, specific types of fat), and markers of heart or metabolic disease) on these blood samples pending sufficient funding. We will draw in total approximately 100 mL of blood (in comparison, blood donation generally involves 500 mL of blood).
- *Answer questions regarding your health* – We will ask you questions about your demographic information, symptoms, medications, and medical problems. We will also review your medical records.

The study chart below explains what is expected of you at the study visit:

Dose-finding study	• Read and sign this informed consent form (**ICF**). • If you are a pre-menopausal woman who has not had a hysterectomy, we will **confirm that you are not pregnant** using a urine pregnancy test. • Answer questions about your heart failure symptoms • Drink the study drink (DeltaG) • Have **blood drawn** through an intravenous line. • Record **vital signs** and may have a **physical exam** • Review your medications, medical history, and symptoms with the study team, and answer survey questions

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

Since we are doing this study on patients who are taking certain medications (SGLT2 inhibitors) and patients not on these medications, it is possible we may ask if you are interested in participating after holding this medication for at least 4 days prior to the visit. We would ask your provider permission as well for holding the medication. We may also ask you if you were interested in participating twice in this study (one time while taking the medication and once while holding the medication). If this were the case, we would obtain your consent again for this second time in the study.

After this, your participation in the research study will be over.

If you do not sign this consent form, you will continue to receive care, but not as a part of this study.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to participate in the study, you will be involved with this study for 1-2 visits.
You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled.

WHAT ARE THE RISKS OF THE STUDY?
Study Drug – Ketone ester ((R)-3-Hydroxybutyl (R)-3-Hydroxybutyrate)
Currently, we do not have much information regarding possible side effects of DeltaG in patients with heart failure on, and not on, a heart failure medication class called SGLT2 inhibitor. In studies of generally healthy individuals and one in patients with heart failure, DeltaG given as a drink was generally well tolerated.

DeltaG may cause some, all, or none of the side-effects listed below.

More likely
- Stomach ache
- Nausea
- Bitter taste

Less likely
- Vomiting
- Diarrhea or constipation
- Dizziness
- Headache
- Fatigue

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

In this study, you will only be given one dose of study medication on a study day, which may minimize the chances of significant side effects.

If you experience any side effects that you find too uncomfortable, you may withdraw from the study at any time.

Potential Drug Interactions and Instructions During the Study
There is not much information on DeltaG in subjects with heart failure, though it has been administered to patients with heart failure before. Certain medications that heart failure patients may be on (SGLT2 inhibitors, such as dapagliflozin, canagliflozin, and empagliflozin) also very mildly raise ketone levels, though levels are largely still within "normal" levels. Sometimes a very high level of ketones from SGLT2 inhibitors can cause acid to build up in the blood (called ketoacidosis), but this is very rare with SGLT2 inhibitors, and we do not believe this risk is increased by taking DeltaG. However, this is a potential risk and why we are starting this study with a lower dose to assess this risk and to choose the right dose of DeltaG.

We are trying to study the effect of DeltaG on patients taking SGLT2 inhibitors and patients not taking SGLT2 inhibitors. Therefore, if you are taking an SGLT2 inhibitor, we may ask your primary provider if it is ok for us to hold your medication for four days prior to the dose-finding study. This is similar to the time that a provider may ask you to hold this medication prior to a procedure. There is the potential risk of experiencing worsening heart failure symptoms after holding your SGLT2 inhibitor for four days, which include increased weight gain, swelling of legs, fatigue, and shortness of breath. If you experience these symptoms, please contact the study team for further recommendations.

For your safety, you must tell the study doctor or coordinator all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

Drug Interaction and Instructions Summary:

- Please continue taking your regularly scheduled medications. If your primary provider approves, we may ask you to stop taking your SGLT2 inhibitor for four days prior to your visit.

Other Possible Risks or Discomforts of Study Procedures

Blood Draw

- There may be minor discomfort or pain (sometimes accompanied by redness, swelling, and warmth to the area) from the needle used to place the intravenous line. Sometimes and intravenous line needs to be replaced (for example, it falls out). Some bleeding or bruising may occur. Fainting and infection at the site of the intravenous connection are both possible, although these occurrences are unlikely. You may develop inflammation in the vein where the intravenous

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

was placed (superficial phlebitis) or a clot in the vein. These problems generally resolve over time on their own after the needle has been removed.

- Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Holding SGLT2 inhibitor

- Some participants may be invited to participate in this study while holding it for a period of 4 days. While this is a short period of time, there may be a risk of increasing fluid retention (that may lead to, for example, leg swelling, fatigue, and shortness of breath). If this occurs, please alert the study team as well as your primary doctor, who may restart your SGLT2 inhibitor, and we may need to withdraw you from this study.

Confidentiality

- There is a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, and you may take a break at any time during the study. You may stop your participation in this study at any time.
- If any of your data (including but not limited to blood samples, vital signs, laboratory values, and medical history) are shared with other investigators (at Duke or elsewhere), we will make sure that no identifying information is included, and that all shared samples will be de-identified. De-identified data may be made publicly available. Any for-profit companies receiving your de-identified samples may ultimately discover products, drugs, tests, etc., as a result of this research and your samples. This discovery may lead to commercial products, and you would not receive compensation for this.
- *Genetic Information Non-Discrimination Act (GINA)*: The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law. The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:
    - Health insurance companies and group plans may not request genetic information from this research;
    - Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
    - Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

already-diagnosed genetic condition or disease. It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician. There may be risks, discomforts, or side effects from being in this study that are not yet known.

Reproductive Risks

- Pregnancy in women with heart failure is associated with an increased risk of complications for mothers and babies, including risk of maternal death of at least 10-20%. In addition, pregnancy affects how your body handles drugs and could affect the study results. Finally, the risks of this study drink to pregnant women, breastfeeding women, and fetus are unknown. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed), you will be asked to undergo a urine pregnancy test at least at the initial visit.
- Because of the risks of pregnancy in women with heart failure, you should already be using an effective birth control method to avoid an unplanned pregnancy. If you are asked to participate in a second visit, you should be sure to continue to use your birth control method. You will be tested for pregnancy again at the second visit.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are unlikely to benefit from participating in this research study. However, your participation will help us understand the effect of DeltaG on the body in heart failure. We hope that in the future the information learned from this study will benefit other people with your condition.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include **representatives from the Food and Drug Administration (FDA)**, Office of Human Research Protections (OHRP), the Duke University Health System Institutional Review Board (IRB), Duke Office of Clinical Research (DOCR), National Institutes of Health (NIH), American Heart Association (AHA), and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

Most tests done in research studies are only for research and would not be used to guide your healthcare. Some research results may be placed in your medical record (such as, but not limited to, basic laboratory

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

testing). However, if through testing we find out something that is clinically relevant to you, we will notify you regarding these results. We may also speak to your primary providers.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

Expiration date or event for the retention of records

The study results will be retained in your research record for at least six years after the study is completed. At that time, either the research information not already in your medical record may be destroyed, or information identifying you may be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this Study, some information may be inaccessible until the end of the study unless your physician(s) decide that it is necessary for your care.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You will not have to pay for any research procedures or tests that result from participating in this study.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans, and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable, depending on your type of insurance.

WHAT ABOUT COMPENSATION?
You will be reimbursed $50 for your expenses related to your participation (gas and time), which is described below.

You will receive financial compensation for your participation in this study. We will follow the following reimbursement scheme below:

- Completion of dose finding study: $50
- If we invite you to participate again in the study (holding your SGLT2 inhibitor medication if you are taking one): an additional $50

Your reimbursement will be given to you as a Greenphire clincard at the completion of each visit.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that Duke University is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction
For questions about the study or research-related injury, contact Dr. Selvaraj at 919-684-8111 during regular business hours and at [redacted] after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you email Dr. Selvaraj and let him know that you are withdrawing from the study. His email address is Senthil.Selvaraj@duke.edu.

We will tell you about the new information that may affect your health, welfare, or willingness to stay in this study.

The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons, why this might occur, include if the regulatory agencies think that the study drug might be associated with significant risks such as abnormal heart rhythms. If this occurs, you will be notified, and your study doctor will discuss other options with you.

Your information and samples will be de-identified. De-identified means that all identifiers have been removed. The information and samples could be stored and shared for future research in this de-identified fashion. Specifically, your de-identified data may be made publicly available for other researchers to analyze. 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 and samples only applies to the information and samples collected in this study.

A description of this clinical trial will be available on https://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.

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Selvaraj at 919-684-8111 during regular business hours and at [redacted] after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

OPTIONAL Blood samples for future research:

If you agree to have your blood samples taken for future research, they will be stored on Duke property with no identifying information that could link your sample to you on these specimens. We will use the amount of blood described in this consent form to store for future research purposes unrelated to the current purpose of the study. These samples will be maintained by Duke staff and processed by either a Duke or an external lab contracted through Duke. These samples will be kept indefinitely. Future researchers may have access to the data and blood samples, but no identifying information will be available to them or disclosed outside of DUHS.

Please initial next to the option you choose below.

_____ Yes. I agree to have blood collected for future research.

_____ No. I do not agree to have blood collected for future research.

SPACE INTENTIONALLY LEFT BLANK

Duke University Health System

Consent to Participate in a Research Study
Ketone Pharmacokinetic Study in Heart Failure with Reduced Ejection Fraction

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

If you agree to participate:

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time