Title: The Efficacy and Tolerability of Canagliflozin in Healthy Individuals
Comparing Dosing Protocols of Canagliflozin for use as a Gerotherapeutic

Protocol Number:
ALRx008

Test Drug: Canagliflozin, also known as Invokana.

Indication: For use in healthy, non-diabetic individuals (ages 18-85).

Study Design: Prospective, non-randomized trial to evaluate tolerability and efficacy in reducing baseline glucose and glucose spikes in non-diabetic individuals.

Site: This is a decentralized trial. Participants can be located in any of the 50 states of the USA. All participation will be via telemedicine using the AgelessRx website (agelessrx.com).

Sponsor Name, Address, and Telephone Number:

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Institutional Review Board of the Institute of Regenerative and Cellular Medicine
James P. Faber
Tel: (786) 271-2156
Email: jpfaber@ircm.org

Compliance:
The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

Date of Protocol: January 16th, 2023

Confidential Information
The information contained within this protocol is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of AgelessRx.

1. Signature Page

I have read this clinical protocol and confirm that to the best of my knowledge it accurately describes the design and conduct of the study titled “The Efficacy and Tolerability of Canagliflozin in Healthy Individuals: Comparing Dosing Protocols of Canagliflozin for use as a Gerotherapeutic”.

Sajad Zalzala, MD

Date 01/17/2024

2. Synopsis

Name of Sponsor/Company: AgelessRx

Name of product: Canagliflozin (trade names: Invokana)

Title of study: The Efficacy and Tolerability of Canagliflozin in Healthy Individuals Comparing Dosing Protocols of Canagliflozin for use as a Gerotherapeutic

Objectives:

Primary: To measure the effects that canagliflozin intervention has on reducing average glucose in healthy individuals.

Secondary: To assess the tolerability and side effects and urinary glucose excretion following the pulsatile dosing protocol.

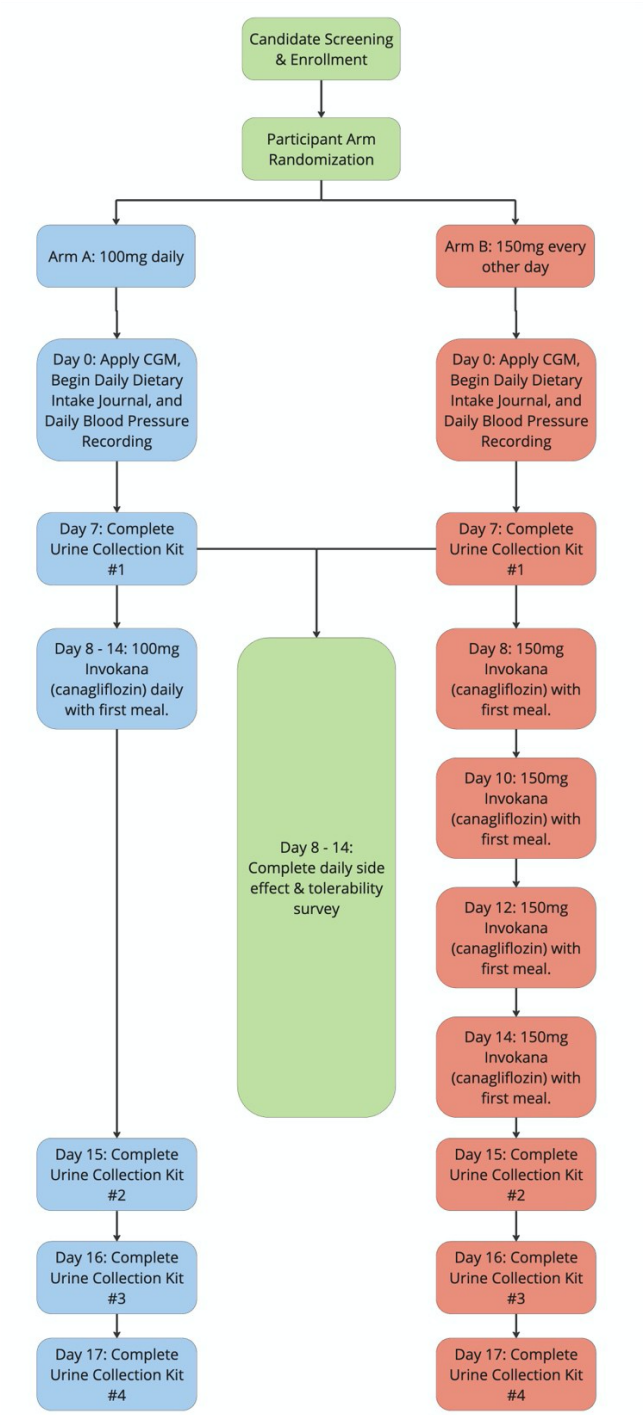
Methodology:

1. Candidates will be offered participation through word of mouth and AgelessRx platform.
2. Once screened and enrolled, participants will be randomized into one of two arms (A and B) and provided with all items included in the materials list below.
3. **Arms A & B:**
    a. Day 0: Participants will attach a continuous glucose monitor (CGM) and follow instructions for calibration period.
    b. Day 1 – 14: Participants will take morning blood pressure readings, and keep dietary intake journal via Lifesum.
    c. Day 7: Participant completes Urine Collection Kit #1
4. **Arm A:**
    a. Day 8 - 14: Participants take 100mg Invokana (canagliflozin) with first meal daily.
    b. Day 15: 24h after final dose, Participant completes Urine Collection Kit #2
    c. Day 16: 48h after final dose, Participant completes Urine Collection Kit #3
    d. Day 17: 72h after final dose, Participant completes Urine Collection Kit #4
5. **Arm B:**
    a. Day 8 - 14: Participants take 150mg Invokana (canagliflozin) with first meal daily, every other day for a total of 4 doses.
    b. Day 15: 24h after final dose, Participant completes Urine Collection Kit #2
    c. Day 16: 48h after final dose, Participant completes Urine Collection Kit #3
    d. Day 17: 72h after final dose, Participant completes Urine Collection Kit #4

Number of subjects planned: Up to 20 healthy individuals via telehealth administration, 10 individuals in each Arm.

Diagnosis and main criteria for inclusion: Subjects will be healthy and of any sex, any ethnicity, and any age from 18-85. Participants must be approved by AgelessRx Medical Team for use of canagliflozin. They also require a CGM-compatible mobile device (defined here)
Test product, dose, and mode of administration (proposed): The tablets will be from the brand Invokana and have a dosage of 100 mg or 300 mg per tablet. Investigational drugs are to be administered orally. Investigational drugs will be provided by Curexa Pharmacy, 3007 Ocean Heights Avenue, Egg Harbor Township, NJ 08234
Duration of treatment: 7 days
Criteria for evaluation: Efficacy: • CGM data • Urinary glucose
Safety: • Tolerability • Adverse events • Blood pressure
Statistical analysis: Demographic and baseline characteristics will be summarized using descriptive statistics. CGM readings will be analyzed using analysis of variance. Evaluation will be performed by research coordinators/MDs.

3. Study Design



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5. List of Abbreviations

Abbreviation	**Definition**
ADR	Adverse Drug Reaction
AE	Adverse event
SAE	Serious Adverse event
CGM	Continuous Glucose Monitor

6. Background and Rationale

6.1 Glucose Spikes

Excessive refined carbohydrate intake can lead to an excess of glucose in the blood. The pancreas works to stabilize blood sugar levels by secreting a surge of insulin to help move glucose into our cells or storage. However, even after excess glucose has been cleared, our insulin levels remain high. This leads to an overcorrection and subsequent low blood sugar. Unstable blood sugar is linked to depressed and anxious mood, "brain fog," impaired cognitive performance, disturbed sleep, chronic pain, and poor workout performance. Conversely, stable blood sugar can boost our energy levels, mood, productivity, and overall well-being.[2]

Glucose variability is not only a problem for individuals with diagnosed health conditions relating to glucose. According to a 2018 study, "16 out of 20 participants who were classified as normal on standard clinical tests experienced severe post-meal glucose spikes that reached into the prediabetic range 15 percent of the time"[3]. Additionally, a 2009 study of glucose spikes studied more than 15,000 healthy, non-diabetic individuals. It found that elevated 2-hour postprandial glucose increased the risk of cardiovascular and all-cause death significantly[4].

Excessive post-meal blood glucose spikes are an independent risk factor for a host of chronic conditions, including diabetes, cardiovascular disease, stroke, kidney failure, cancer, retina damage, and cognitive decline. Eating to promote stable blood sugar and developing metabolic flexibility is critical to supporting your long-term health and wellbeing[5].

6.2 Canagliflozin

Canagliflozin is an SGLT2 inhibitor. It is a compound also known under the name Invokana. Canagliflozin is used (with diet and other medications) to treat type 2 diabetes (a condition in which the body does not use insulin normally and therefore cannot control the amount of sugar in the blood). Canagliflozin works by blocking SGLT2, a protein that helps the body reabsorb glucose from urine to the bloodstream. The body instead excretes glucose through urine. [1]

Clinical studies

Canagliflozin Tablets were studied as monotherapy and as combination therapy to metformin, insulin, or other treatments. The treatment effects on HbA1c levels and one-hour postprandial glucose levels are summarized for four placebo-controlled, double-blind, randomized studies conducted in the United States. The placebo-subtracted treatment differences, which are summarized below, were statistically significant for both variables in all of these studies.

Study 1: (n=584) This study showed that canagliflozin caused a significant reduction in blood sugar soon after taking canagliflozin. This was true at both doses of 100 mg canagliflozin as well as with 300 mg of canagliflozin. Hba1c levels dropped by 0.8 mg/dl with the 100 mg treatment and by 1.0 mg/dl with the 300 mg treatment. [1]

Study 2: (n=20) Canagliflozin reduced postprandial plasma glucose by 35% and insulin excursions by 43% in this study ($P < 0.001$ for both). It also increased urinary glucose excretion (UGE_0–6h, 18.2 ± 5.6 vs. <0.2 g; $P < 0.001$). It reduced blood glucose by increasing glucose excretion. [6]

Study 3: (n=1450) Canagliflozin at 100 mg and 300 mg reduced A1c levels by −0.65% and −0.74%, respectively, over a treatment period of 104 weeks. Also, it reduced systolic blood pressure by -2.0 mmHg with the 100 mg dose and by -3.1 mmHg with the 300 mg dose. [7]

Study 4: (n=4401) Canagliflozin was generally well tolerated[8]. Adverse events related to the kidneys were lower with canagliflozin treatment of 100 mg, with an incidence of 60.2 per 1,000 vs an rate of 84.0 per 1,000 of the control group. [9]

6.3 Current standard of care and alternative treatments for glucose spikes

Current standard of care for glucose control in diabetics revolves around the use of diet, and exercise, in combination with different medicines and molecules, such as Metformin, Insulin, Sulfonylureas, SGLT-2 inhibitors, and acarbose. In healthy, non-diabetic individuals, the main way to mitigate blood sugar spikes is to rely on diet and exercise. Non-diabetic individuals have to find ways to substitute sugars or carbohydrates from their diet to prevent spikes. Similarly, they exercise in order to have normally-functioning glucose disposal, or stay well hydrated by drinking water after consuming starchy meals.[10] Glucose spikes often go untreated, and are common in healthy, non-diabetic individuals after high carbohydrate intake.

6.4 Rationale and Hypothesis

Canagliflozin is a prime candidate to reduce glucose spikes and blood sugar. It has consistently acted to treat type 2 diabetes and has been shown to improve biomarkers such as fasted glucose and glucose spikes.

The current FDA-approved use of the drug is for use together with diet and exercise to treat type 2 diabetes. Canagliflozin is sometimes used in combination with insulin or other diabetes medications taken orally. It is routinely prescribed at equal or higher doses than the ones proposed in this trial.

AgelessRx Trial doses: 100 mg and 150 mg doses, taken every day and every-other day, respectively.

FDA-approved dose: Maximum recommended dose: 300 mg once daily.

Some possible side effects at the FDA-approved doses include hypoglycemia, indigestion, nausea, UTI, increased urination or thirst, hypotension, ketoacidosis, dehydration, and headache. The doses we propose have potential for some side effects, though the drug is generally well tolerated.

This trial will use a lower dose than the maximum one recommended by the FDA. We are using a maximum of 150 mg in one day vs the maximum of 300 mg each day recommended by the FDA. At this smaller dose, side effects are less common[8]. This dose has been shown to be generally safe.

Our hypothesis is three-fold:

1. Canagliflozin can be used safely and is well tolerated at doses of 100 mg per day or 150 mg every two days in healthy, non-diabetic individuals.

2. Usage of canagliflozin at these doses can effectively reduce glucose spikes (and their detrimental effects) and blood sugar levels measured by CGM in a healthy population.

3. Usage on alternate days will be effective as measured by our endpoints.

7. Objectives

7.1 Primary Objective

To measure the effects that Canagliflozin intervention has on blood glucose at the tested doses. This will be measured by observing glucose spikes following a high-carbohydrate meal at the tested doses, as well as by studying baseline glucose levels with and without canagliflozin.

7.2 Secondary Objective
To assess the tolerability and side effects of the dosing protocol, and measure urinary glucose excretion.

8 Experimental plan

8.1 Study Design
This study is designed to mitigate the effects of glucose with intermittent oral Canagliflozin for healthy, non-diabetic volunteers of any sex who enroll in the study. The volunteers can be within 18-85 years of age at the time of enrollment. Participants will provide informed consent via AgelessRx EMR. If eligible, prescriptions will be provided online through the AgelessRx website (www.agelessrx.com). Participants will be randomized into two arms: Arm A will take 100 mg of canagliflozin each day for a total of 7 doses, while Arm B will take 150 mg of canagliflozin every other day for a total of 4 doses. Participants in Arm B will also be provided a pill cutter to use throughout the trial on the 300mg tablet.
All participants will begin the trial on the day that they apply a continuous glucose monitor (considered Day 0) and will be asked to take daily blood pressure reading. After one week of baseline readings, both arms will start their canagliflozin dosing protocols.
Participants will be asked to complete 7 total surveys to outline side effects and tolerability, one each day starting after their canagliflozin consumption.
Participants will be asked to complete a dietary intake journal through Day 0 – Day 14. Lifesum (https://lifesum.com/) should be used to track Carbohydrate/Protein/Fat consumption. Participants will share their dietary intake journal twice over their participation (Day 7 & Day 14).

8.2 Cost of Participation
This trial will be sponsored under the organization AgelessRx. There will be no cost to the participant to participate.

8.3 Number of Centers and Subjects
We will recruit up to 20 healthy participants to participate in the study. Online prescriptions will be provided by Dr. Sajad Zalzala via the AgelessRx website (www.agelessrx.com). Our partner pharmacy with the ability to ship to most states nationwide will provide the prescriptions and CGMs to participants. Efficacy testing will be performed by AgelessRx. To measure glucose, the Abbott Laboratories Freestyle Libre CGM (https://www.freestyleprovider.abbott/us-en/freestyle-libre-2.html) will be used. For urinalysis, Access Medical Labs Glucose, Urine (https://www.rupahealth.com/lab-tests/access-medical-labs-glucose-random-urine#description) will be used.

8.4 Estimated Study Duration
We anticipate the study will last a maximum of 90 days.

9 Subject Selection

9.1 Number of Subjects
Up to 20 individuals

9.2 Inclusion Criteria
1. Age 18-85
2. Any sex
3. Any ethnicity
4. Interest in taking Canagliflozin
5. Approved by the AgelessRx Medical team to take Canagliflozin
6. Willing and technically able to use and operate a CGM
7. Own a CGM-compatible phone

8. Relatively good health with only well-managed chronic diseases (hypertension, coronary artery disease, type II diabetes, etc.) clinically stable
9. Adequate cognitive function to be able to give informed consent

9.3 Exclusion Criteria

1. Diabetes of any type
2. Taking metformin or any other glucose lowering medication
3. Other diabetes medication
4. Active malignancy of any kind
5. Clinically relevant renal or kidney disease or dysfunction
6. History of eating disorder
7. Any diuretic
7. Taking any medication, or has any medical condition, that might interfere with the action of canagliflozin or the CGM sensor

9.4 Withdrawal

Participants are free to withdraw from the study at any time. They can do so by notifying the Principal Investigator through email or phone call. Participants can provide consent whether or not to allow use of data obtained up to that moment.

10 Schedule of Assessments and Procedures

10.0 Patient Recruitment

Candidates will be offered the opportunity to participate in this interventional trial after approval of canagliflozin through the AgelessRx platform and expressing interest via screening questionnaire.

10.1 Screening

Candidates will be offered the opportunity to participate in this trial after approval of canagliflozin prescription through the AgelessRx platform. Patients must proceed through medical intake, consent to participate, consultation with the AgelessRx medical team (synchronously or asynchronously, depending on the regulations of the state in which the candidate resides), and approval before receiving their treatment. Medical intake will be reviewed by the AgelessRx medical team and consent responses will be reviewed by the research coordinator. Once the candidate has been approved for their canagliflozin prescription and the patient has expressed interest and consented to participation, the AgelessRx research coordinator will contact the candidate for additional instruction. The medical intake and consent built into the patient process will include inclusion/exclusion screening criteria and will serve as a screening tool for medical and research personnel. The consent language built into the patient intake workflow can be found in Appendix A. Identity validation will occur prior to product intake submission and will be verified following consent completion, as a photo of self and I.D. are required before the patient may proceed. Informed consent will be captured via free text name entry within the consent questionnaire.

10.2 Enrollment

Participants will be enrolled in the study for a total of two weeks. After the two weeks, participants will be free to use the trial drug off-label as they choose.

10.3 Safety and efficacy evaluations

The primary endpoint, average glucose, will be assessed by examining blood glucose (mg/dL) area under curve as measured by CGM. Glucose data on days without canagliflozin treatment will serve as a control.

The secondary endpoints of safety and tolerability and urinary glucose excretion will also be assessed. Safety and tolerability will be measured by adverse event reporting, blood pressure monitoring, and by comparing treatment tolerability survey results with control tolerability results through subjective surveys. Urinary glucose excretion will be measured by at-home glucose testing strips.

11 Investigational Product

11.1 Investigational Drug

Canagliflozin is an SGLT2 inhibitor. It is known under the name Invokana, when mixed with other compounds. It is chemically known as (2S,3R,4R,5S,6R)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl] -4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol. It has a molecular weight of 444.52 g/mol and is an off-white powder. It is used to treat type 2 diabetes mellitus (a condition in which the body does not use insulin normally and therefore cannot control the amount of sugar in the blood). It works by inhibiting a sodium-glucose pump in the kidneys, SGLT2, leading to increased glucose excretion through urine. This helps reduce blood glucose levels as glucose is not reabsorbed into the blood.

11.2 Control Drug

No placebo will be used in this trial.

11.3 Dosing and Administration

11.3.1 Dose Escalation, Dose Adjustments, Stopping Rules

Participants will receive 100 mg tablets or 300 mg tablets, broken in half. There will be no dose escalation in this study. Dose adjustments or discontinuation of the drug can be made based on adverse events in a participant, which will be discussed in a phone call between the participant and Research Coordinator.

11.3.2 Packaging and Labeling

Trial medication and CGM Freestyle Libre 2 will be dispensed by Curexa Pharmacy 3007 Ocean Heights Ave, Egg Harbor Township, NJ 08234, United States.

11.3.3 Storage

Tablets should be stored at room temperature, away from heat and light. Tablets are dispensed in a tight, light-resistant labeled container.

11.4 Concomitant Medications

If participants fit eligibility criteria but are on other medications, they should continue to take those at the prescribed dosages. They will be instructed to tell their other physicians, medical providers, and pharmacists of their enrollment in the trial. Any changes to concomitant medications or any planned surgery should be discussed with the PI immediately.

12 Adverse Event Reporting

12.1 Adverse Events Definitions

Adverse drug reaction (ADR): a noxious and unintended reaction to a drug at doses normally used in humans for prophylaxis, diagnosis, therapy of diseases, or for the modification of physiological function where a causal relationship is at least reasonably possible.

Adverse event (AE): an adverse occurrence experienced by a study subject during the course of the clinical trial that is not necessarily associated with the drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not related to the investigational product. When an AE has been determined to be related to the investigational product, it is considered to be an adverse drug reaction.

12.2 Serious Adverse Events

Serious adverse events (SAE): any AE that results in death, is life-threatening, requires inpatient hospitalization, is persistent, or causes significant disability/incapacity, or causes a congenital anomaly or birth defect.
Adverse events will be graded according to the system below:

1. Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated (e.g. headache, nausea, abdominal discomfort).
2. Grade 2: Moderate; minimal, local or noninvasive intervention (e.g. vomiting, diarrhea, shortness of breath).
3. Grade 3: Severe; or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling (e.g. dehydration, hypotension).
4. Grade 4: Life-threatening ; urgent intervention indicated (e.g. respiratory failure, myocardial infarction, liver failure).
5. Grade 5: Death related to an AE.

12.3 Reporting of Adverse Events

12.3.1 Routine

The principal investigator will be notified about any adverse events. Furthermore, this information will be obtained through monitoring forms sent out to participants.

The Principal Investigator will document this information in the participant's medical record. Participants will be asked to report any serious adverse event immediately to the Principal Investigator. This can be done by email or phone (after hours phone number is available).

AEs will be documented using standard AE reporting (FDA regulations 21CFR314.80 and 21CFR213.32(s)). Both expected (already known) and unexpected AEs will be reported.

12.3.2 Expedited

Serious adverse events that occur while the research participant is actively participating in the research study will be reported to the IRB within 48 hours for the duration of the study (until study is closed at the IRB).

13 Statistical Analysis

Demographic and baseline characteristics will be summarized using descriptive statistics. Blood tests will be analyzed using analysis of variance. Evaluation will be performed by research and medical teams.

14 Ethics

14.1 Ethical Conduct of the Study

The study and any amendments will be reviewed by an Institutional Review Board (IRB). The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study will be conducted in accordance with good clinical practices (GCP).

14.2 Participant Information and Consent

Informed consent will be obtained for all subjects enrolled in the study.
Participants will receive a digital PDF version of the informed consent documentation associated with the study (Appendix A). Participants will have the opportunity to ask questions before signing. Participants will respond to individual lines with Yes or No to indicate each section was read and understood, and then sign it electronically.
A study coordinator will ensure the participants have completed the consent form and have agreed to understanding the study and implications of being a participant. It will be stressed that:
1) No benefits of any kind can be expected from participation in this trial
2) The subjects may withdraw from the trial at any time without a penalty of any kind
3) There may be risks associated with participating in the trial

Consent will be documented by a free text first and last name field confirming the participant understands the study. Identity will be validated by way of state-issued ID upload alongside an image of the participant. All participants will be provided a PDF version of the consent form for their reference and storage.

14.3 Study Participant Confidentiality

All study records for analysis will be de-identified, so that records cannot be directly linked to the participant and are only linked to the participant via coded identifiers. Data will be stored on a password-protected HIPAA-compliant cloud service.

15 Administrative Procedures

15.1 Modifications to the Protocol

Modifications to the protocol will be added to the Clinical Study Protocol and communicated with the IRB.

15.2 Plans for Dissemination of Findings

We intend to disseminate the findings primarily in four ways:
1) Publications in peer-reviewed medical journals
2) Lectures at non-scientific public events
3) Announcements via the AgelessRx website
4) Outreach to various media outlets

16. Reference List

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10. Suh, Sunghwan, and Jae Hyeon Kim. "Glycemic Variability: How Do We Measure It and Why Is It Important?." Diabetes & metabolism journal vol. 39,4 (2015): 273-82. doi:10.4093/dmj.2015.39.4.273

Appendix

Appendix A: Informed consent forms

Title of Study:

The Efficacy and Tolerability of Canagliflozin in Healthy Individuals

Comparing Dosing Protocols of Canagliflozin for use as a Gerotherapeutic

Principal Investigator:

Dr. Sajad Zalzala

Sponsor:

AgelessRx

Purpose of the Study: I understand that the purpose of this study is to measure the effects that canagliflozin intervention has on reducing average glucose in healthy individuals**.**

(Yes/No)

Participation: I understand that participation in this study will last 2 weeks. During the 2-week of participation, I will be asked to take 150mg Invokana (canagliflozin) a total of four times or 100mg Invokana (canagliflozin) a total of 7 times, complete four side effect and tolerability surveys, complete morning blood pressure recordings, and wear a continuous glucose monitor for the study duration.

(Yes/No)

Canagliflozin: I understand that Canagliflozin is an SGLT2 inhibitor. It is a compound known under the name Invokana, used to treat type 2 diabetes by increasing urinary glucose secretion. (Yes/No)

Am I eligible?: I understand that if I am interested in this study, the study coordinator will assess my eligibility following the completion of this form. There are no restrictions in ethnicity, gender, socioeconomic status, educational status, sexual preference, religious preference, or political views in this study. (Yes/No)

What are the possible benefits of participating in the study?: I understand that AgelessRx cannot promise any benefit for participating in this study. There will be no financial benefit to participating in this study. I will be provided with the results of the study.

(Yes/No)

What are the possible risks of taking part in the study?: I understand that there are risks of side effects from taking canagliflozin, including hypoglycemia, indigestion, stomach pain, nausea, urinary tract infections, and headache.

(Yes/No)

How will information be kept confidential?: I understand that health information will be stored in AgelessRx's secured database and will be made available only to study collaborators. Study staff will protect your personal information closely. No one will be able to connect my responses and any other information that identifies me. Federal or state laws may require AgelessRx to show information to university or government officials (or sponsors), who are responsible for monitoring the safety of this study. Directly identifying information (e.g. names, addresses) will be safeguarded and maintained under controlled conditions. I will not be identified in any publication from this study. Should my information be re-identified, this information will only be made available to AgelessRx research staff, the FDA, or the IRB.

(Yes/No)

What is the cost to participate in the study? I understand that there is no cost required to participate in the study. All costs of trial materials will be covered by AgelessRx.

(Yes/No)

What happens next if I decide to participate in the study?: I understand that if I am selected to participate in the study, the study coordinator will reach out to enroll me and order my study materials. (Yes/No)

Where does this study take place? I understand that this study is a virtual trial. Participants can be located in any of the 50 states of the USA. All participation will be via telemedicine using the AgelessRx website (agelessrx.com).

(Yes/No)

How can I withdraw from the study?: I understand that if I decide that you would like to withdraw, I can reach out to the study coordinator at any time.

Andy Nyquist
(650) 272-3169
research@agelessrx.com
(Yes/No)

Data-sharing: I understand that de-identified data from this study may be shared with the research community at large to advance science and health. AgelessRx will remove or code any personal information that could identify me before files are shared with other researchers to ensure, by current scientific standards and known methods, that no one will be able to identify me from the information we share. Despite these measures, I acknowledge that AgelessRx cannot guarantee the anonymity of my personal data.
(Yes/No)

Future Use of Data: I understand that identifiers might be removed and the de-identified information or biospecimens may be used for future research without additional consent.
(Yes/No)

Information about the results: I understand that information derived from my specimens may be used to generate commercial profit. I will not share in any commercial value or other compensation from products developed using this information.
(Yes/No)

Research Funding: I understand that funding for this study has come entirely from AgelessRx. No government grants were used to fund the study.
(Yes/No)

Voluntary participation and responsibilities of the volunteer: I understand that taking part in this research study is voluntary. If I choose to take part in this research, my major responsibilities will include completing multiple questionnaires and completing one week of control days and one week of treatment days. On the treatment days, I will take up to 150 mg of canagliflozin, as directed. I have the right to stop at any time. If I decide not to participate or if I decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which I am otherwise entitled.

The AgelessRx investigator may take me out of the research study without my permission. Some possible reasons for this are side effects from medications, my own compliance with the study requirements, my use of habit-forming medications or recreational drugs, my development of an unrelated illness, a car accident or other accident, or my having a major surgery. Also, the IRCM IRB may end the research study early. If my participation in the research ends early, I may be asked to perform final testing at that time. If I will be participating in another clinical trial with the same investigators or at the same study sites, or elsewhere, while in this research study, I should discuss the procedures and/or treatments with my physician or the investigators. This precaution is intended to protect you from possible side effects from interactions of research drugs, treatments, or testing.
(Yes/No)

Contacting the research team: I understand that I have the right to ask any questions I may have about this research. If I have questions, complaints, or concerns or believe I may have developed an injury related to this research, contact the AgelessRx Research team at (650) 272-3169.
Should I wish to contact an impartial third party not associated with this study, I may contact James P. Faber, secretary of the Institutional Review Board (IRB) of the Institute of Regenerative and Cellular Medicine (IRCM), which reviewed this study for ethical compliance: jpfaber@ircm.org or (786) 271-2156.
(Yes/No)

Consent to Participate: I understand that by entering my first and last name here you agree that you received this information, have asked the questions you currently have about the research, and have received answers to those questions. I will receive a copy of the consent form for future reference.

_____

Participant First and Last Name Date

Appendix E: Declaration of Helsinki

This informed consent document has been created using the guidelines established by the National Institutes of Health, National Center for Complementary and Integrative Health, 9000 Rockville Pike, Bethesda, Maryland 20892. These guidelines were based on the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, in Jun, 1964; and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment
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12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of
the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.