Evaluating the Benefits of Physiologic Insulin Delivery

Informed Consent Form

NCT04416737

June 14, 2022

Are you participating in any other research studies? _____ Yes _____No

• Your consent is being sought for research participation that is completely voluntary

• The purpose of this research is to understand the effects of intraperitoneal insulin administered into the deep upper and lower abdomen compared to subcutaneous delivery. If you are willing and able, we will ask you to come to our Clinical and Translational Research Unit (CTRU) for 3 visits, separated by at least 1 week. At each visit you will be injected with insulin in a different body location, blood will be collected through an intravenous catheter and dextrose infused for low blood sugar.

• We are asking for your time and there may be financial hardship if you miss work. Injection and catheter placement carry common risks of discomfort, bleeding, bruising and infection. All insulin injections come with the possibility of hypoglycemia, allergic reactions, hypersensitivity, injection site reactions, lipodystrophy, and weight gain. During the experiment, we will be causing hypoglycemia for a brief period to test if your body produces glucagon when insulin is injected into the peritoneum. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. We will be performing the test under very controlled conditions and will give you IV dextrose to rapidly increase the blood sugar back to normal.

• Use of continuous glucose data will provide you individualized information about glucose response to intraperitoneal and subcutaneous insulin. The data on subcutaneous insulin may allow you optimization the active insulin time for pump therapy. The data we obtain could also suggest if your glucagon production could be restored when insulin is delivered in a more physiologic manner.

• You do not have to participate in this research study to be treated for your diabetes. The alternative is not to participate.

• You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

- If you are coming in-person to research visits, you are required to be fully vaccinated—2 doses (1 for Johnson and Johnson), 2 weeks out and to

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provide proof of your vaccination (e.g., CDC COVID-19 Vaccination Card, e-Health record, etc.) to the researcher prior to study participation. Alternately, you can provide a negative COVID test within 72 hours of your visit.

PURPOSE OF RESEARCH

You are invited to participate in a research study of the effects of intraperitoneal insulin administered into the deep upper and lower abdomen compared to subcutaneous delivery. We hope to learn the speed of absorption of intraperitoneal insulin Fiasp and whether it can restore glucagon production. The insulin is FDA-approved but has not been extensively tested in the peritoneal space. You were selected as a possible participant in this study because you have type 1 diabetes and are using an insulin pump (which can be suspended) and continuous glucose monitor (CGM).

If you decide to terminate your participation in this study, you should notify Rayhan Lal, MD at 650-725-6549 or inforay@stanford.edu.

This research study is looking for 15 people in good health with type 1 diabetes using an insulin pump and CGM. Enrollment will occur only at Stanford University.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 12 months; each participant will come in for 3 visits separated by at least 1 week. There is a gap of 1 week to allow the body to reset itself after a controlled low blood sugar and so that the effects of one injection does not influence the others.

PROCEDURES

If you choose to participate, the Protocol Director and his research study staff will collect some baseline data including your name, age, gender, race/ethnicity and diabetes duration. A physical exam will be performed including vital signs, height, weight and BMI. We will record the value of the most recent hemoglobin A1c if performed in the last 6 months, and will record glucose management indictor (GMI) or a calculated equivalent if a recent HbA1c is not available. All participants who are female will receive a urine pregnancy test. During this initial visit we will perform an ultrasound to make sure it is safe to perform the intraperitoneal injection. If this is normal, you be randomly assigned to receiving the injection in the upper peritoneum or lower peritoneum first.

You will be asked to not eat anything after midnight the night prior to the first visit so that you have no carbohydrates in your system. Approximately 1 hour prior to the visit we will ask you to suspend insulin delivery so that you have very little subcutaneous insulin on board at the time of the procedure. Two IVs will be placed: (1) for blood draws that measure insulin, glucose and glucagon and (2) for dextrose administration. Ultrasound of the injection site will be performed to pick a safe site in the upper or lower belly. While we do not expect the procedure to be painful, you can choose if you would like a local anesthetic injected first. We will perform the insulin injection under ultrasound guidance. Approximately 0.25 units/kg Fiasp will be administered through the needle and the needle immediately removed. Following injection, blood will be collected through the IV and measures will occur every 5 minutes for either 150 minutes or until blood glucose concentration stabilizes. If blood sugar drops to 50mg/dL or below, dextrose will be administered through the IV. After 150 minutes or a stable glucose trajectory, you will be done with blood tests and can restart your pump. The data from your CGM will also be downloaded.

At least 1 week later, the same study will be performed but using the other area of the abdomen.

A final visit will occur at least 1 week later. At this visit the two IVs will again be placed. This time for the purposes of comparison, standard subcutaneous insulin will be administered. Using a standard insulin syringe approximately 0.25 units/kg Fiasp will be injected. Following injection, blood samples will be taken every 15 minutes for the lesser of either 6 hours until blood glucose concentration stabilizes. If blood sugar drops to 50mg/dL or below, dextrose will be administered through the IV. After 6 hours or a stable glucose trajectory, the trial is complete and you can restart your pump. Once again, your CGM data will be downloaded. You will be contacted by e-mail or telephone within 7 days of this final visit.

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The samples of blood needed for each set of tests is minimal (less than half a tablespoon). In total for each visit, we will require less than 7 tablespoons blood. This research will not include whole genome sequencing.

Participants of Childbearing Potential

If you are a participant who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Future Use of Private Information and/or Specimens

We are not storing blood and samples will not be saved for future research. Your information and/or specimens will not be used or distributed for future research studies even if all identifying information is removed.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Ask questions as you think of them.

- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Rayhan Lal, MD at 650-725-6549.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

<u>Study Participation</u>
Participation includes travel to Stanford and possible missed work which may pose a hardship. Any clinical research may involve risks to the subject, which are currently unforeseeable.

<u>Invasive Testing</u>
Injection and catheter placement carry common risks of discomfort, bleeding, bruising and infection. All such procedures will be carried out by experienced providers, to decrease the risk of these complications.

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Insulin
As with all insulin adverse reactions include: hypoglycemia, allergic reactions, hypersensitivity, injection site reactions, lipodystrophy, and weight gain.

Hypoglycemia
During the experiment, we will be causing hypoglycemia for a brief period to test if your body produces glucagon when insulin is injected into the peritoneum. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. We will be performing the test under very controlled conditions and will give you IV dextrose to rapidly increase the blood sugar back to normal.

Hyperglycemia
Since we are asking you to suspend insulin delivery before each study visit, there is a chance of time limited high blood sugar. This relatively short period is not associated with diabetic ketoacidosis or long-term complications.

POTENTIAL BENEFITS

Use of CGM data will provide you individualized information about glucose response to intraperitoneal and subcutaneous insulin. The data on subcutaneous insulin may allow you optimization the active insulin time for pump therapy. Additionally, it is believed that those with long-standing type 1 diabetes do not produce much glucagon in response to low blood sugar. The data we obtain could suggest if glucagon could be restored when insulin is delivered in a more physiologic manner.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not have to participate in this research study to be treated for your diabetes. The alternative is not to participate. Your decision not to participate in this research study will have no effect on your current treatment or any other future treatment you require.

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PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

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

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

The purpose of this research study is to obtain information on the safety and effectiveness of intraperitoneal injection of ultra-rapid acting insulin; the results will be provided to the sponsor (the National Institute of Health), the Food and Drug Administration (FDA) and other federal and regulatory agencies as required. The FDA, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or specimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena,

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unless you have consented for this use. Information, documents, or specimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institutes of Health which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you 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.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child abuse and neglect, or harm to self or others.

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Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of this study is to evaluate the effects of intraperitoneal insulin administered into the deep upper and lower abdomen compared to subcutaneous delivery. We hope to learn the speed of absorption of intraperitoneal insulin Fiasp and whether it can restore glucagon production. Because the results of these studies may be altered by other health conditions, we request access to your health records to screen for these health problems.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary

to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

Rayhan Lal, MD
Stanford University, Department of Endocrinology
453 Quarry Road,
Palo Alto, CA 94304

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, health information relevant to the study, past medical history and laboratory results. Personal information such as your name, date of birth, gender, race/ethnicity, date of diagnosis, weight and height may be used.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director: Rayhan Lal, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

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Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on January 1, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

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FINANCIAL CONSIDERATIONS

Payment/Reimbursement
You will not be paid to participate in this research study.

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
The NIH is providing financial support and/or material for this study.

Consultative or Financial Relationships
Dr. Bruce Buckingham is a paid advisor to Novo Nordisk, the company whose products may be used in this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

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You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Rayhan Lal, MD at 650-725-6549. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and

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- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent