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Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Consent Approval Date: 03/25/2019

Protocol Number: 2015P000064

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
12/09/2019
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Memory Advancement by Intranasal Insulin in Type 2 Diabetes (MemAID)
PRINCIPAL INVESTIGATOR: Vera Novak, PhD
PROTOCOL NUMBER: 2015P000064

INTRODUCTION:

You are invited to take part in a research study about the effects of insulin on memory, daily functionality and walking speed in people with diabetes. You are being asked to take part in this study because you have type 2 diabetes mellitus, or because you are a non-diabetic volunteer. Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand.

- Your participation is voluntary;
- A research study includes only people who choose to take part;
- You may or may not benefit from participating in the study. However, your participation may help others in the future as a result of knowledge gained from the research;
- You may leave the study at any time;
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at Beth Israel Deaconess Medical Center.

Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of this form to keep for your records.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC AND INVESTIGATORS

This study is being conducted by Vera Novak, Ph.D. and is funded by the National Institutes of Health (NIH). The sponsor agency in this study National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is paying Beth Israel Deaconess Medical Center (BIDMC) and the Principal Investigator, Dr. Vera Novak, to perform this research. BIDMC or Dr. Novak does not have any

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additional interests in this research project or in the funding agency. BIDMC has also received supplemental in kind contribution for safety substudy from Medtronic, Inc. and of Novolin® R insulin from Novo Nordisk, Inc. One of our co-investigators, Dr. Mantzoros is a paid consultant for Novo Nordisk, Inc. Harvard Medical School (HMS) participates in neuropsychological training. The Brigham and Women's Hospital (BWH) participates as the second study site.

WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, concerns or complaints about this research or experience any problems, you should contact Dr. Vera Novak at 617-632-8680. In case of medical emergency, you should contact the investigators (pager 617-632 7243x ID 34257) and the study clinicians (Dr. Lioutas, Dr. Peter Novak, Dr. Buss or Dr. Mateo) will be contacted. For BIDMC-scheduling call 617-632-8883 or 617-632-8859. Dr. Peter Novak is the Principal Investigator and the study clinician for the BWH participants (617-983-7580 or for emergencies call 617-540-8541), for BWH-scheduling call: 617-632-8884.

PURPOSE

Type 2 diabetes mellitus accelerates brain aging, alters cerebral blood flow regulation and increases the risk for dementia and Alzheimer's disease. Previous studies have shown that insulin sprayed into the nose may improve memory in older non-diabetic adults and in people with mild problems of reasoning and memory when used once daily over up to a one month period. <u>These studies have shown that insulin sprayed into the nose is safe and not associated with major side effects and did not affect sugar levels in the blood.</u>

The purpose of this study is to find the long-term effects of daily administration of 40 International Units (IU) of Novolin® R insulin administered as intranasal spray as compared to placebo (sterile saline) on cognition and memory in people with type 2 diabetes mellitus, and non-diabetic controls over 24 weeks of treatment and 24 weeks of follow-up. The insulin or placebo (sterile saline) will be sprayed into the nose once daily. We are interested to see whether intranasal insulin can improve memory and cognition and blood flow in the brain in the diabetic group as compared to placebo and to the non-diabetic group over a long-term period. We will use a ViaNase device (nasal spray device), manufactured by Kurve Technology, Inc. to effectively deliver the insulin/placebo into the nose. This device is listed by the Food and Drug Administration [FDA] as a noninvasive device.

The use of intranasal insulin to improve cognition and blood flow in the brain is investigational. The use of insulin for improvement of blood flow and memory is still being tested in research studies. The Food and Drug Administration [FDA] has not approved insulin use for such purposes. This investigational agent, insulin, has been approved by the FDA for use in other diseases or conditions, but we do not yet know if it is useful or safe as a treatment for cognitive decline and impairment of blood flow. In addition, we hope to learn what kinds of side effects will be caused by insulin sprayed into the nose,

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and how severe those side effects will be. This means that you may experience the side effects listed in the Risks section of this consent form.

STUDY PARTICIPANTS

You have been asked to be in the study because you have type 2 diabetes or as a non-diabetic volunteer, and you meet other criteria for this study. We anticipate that we will screen 800 subjects by phone and enroll 360 subjects (sign consent form) in order to meet our enrollment goal to complete treatment in 210 subjects upon the trial's completion: 120 diabetics (60 in DM-INI, 60 DM-placebo) and 90 non-diabetics (45 control-INI, 45 control-placebo) across all study sites. Approximately 600 people will take part in this study at BIDMC and 200 will take part at BWH.

Procedures that will be done at the Beth Israel Deaconess Medical Center:

BIDMC participants will complete all visits at the BIDMC Clinical Research Center. BIDMC participants may complete the study at BWH if needed.

Procedures that will be done at the Brigham and Women's Hospital:

Participants enrolled at the BWH will complete all visits at the BWH Center for Clinical Investigations. Laboratory samples collected from the BWH site will be stored at the BIDMC Clinical Research Center (CRC) laboratory. BWH diabetics may participate in MRI substudy at BIDMC.

DESCRIPTION OF STUDY DETAILS

If you agree to be in this study, you will be asked to read and sign this consent form. According to Good Clinical Practices, all procedures will be explained to you and all of your questions will be answered. You can opt out from participating in the study at any time. After you sign the consent form, the following things will happen as outlined below and in the **Table 1**:

The **MemAID** study will require 24 weeks of treatment and 24 weeks of long-term follow-up, and it includes 12 visits (V1-V12). There is one screening visit (V1). There are eight assessment visits: V2-baseline assessment, V2-intervention 1-beginning of treatment, V4- intervention 2, V6- intervention 3, V8-intervention 4-end of treatment; V9-treatment 5 is a "virtual visit" and only short phone call assessment, V10-post-treatment 6, V11- post-treatment 7, V12-post-treatment 8. There are three short follow-up visits during the treatment period V3, V5, V7. You may be allowed to skip some assessment visits (V4, V6, V10 and V11) and some follow-up visits (V5 or V7) for significant reasons. If you choose to skip a visit during the treatment period, your medications will be mailed to you and you will be asked to bring all medications vials and study materials (home calendar of device usage) for your next visit. You will be asked to continue using the device daily and call investigators if you have any questions or device problems. However, not more than 8 weeks may elapse between in-person visits during treatment period. Meals will be provided for all assessment visits and as needed. Transportation assistance will be provided, as needed.

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Magnetic Resonance Imaging (MRI) substudy: In 40 diabetic participants, MRI will be done at the BIDMC Center for Magnetic Resonance Imaging at baseline and before the end of treatment. **You may choose not to participate in the MRI substudy and still participate in the MemAID.**

Health management: Your primary care provider will manage your health/diabetes during the course of the study. We will send pertinent medical information (e.g. medical history, medication list, laboratory results, ECG etc.) to your primary care provider. We may request additional information regarding your health status and/or medication list.

Data and samples: Laboratory samples collected from the study will be stored at the BIDMC Clinical Research Center (CRC) laboratory and at the MemAID study freezers at the Department of Neurology at the BIDMC. The information about data from all study participants will be stored centrally at the BIDMC and the secured Science Trax Servers.

Criteria for participation for the two study groups:
Participants will be between the ages of 50 to 85 years, men and women of any race. They should be able to walk for 6 minutes. Diabetic group will include participants with type 2 diabetes mellitus who are being treated with oral or injectable agents. Control group will be similar in age as diabetic group, with a normal fasting glucose (<126 mg/dl) and HbA1c (<6.5%).

You cannot participate in this study if you have any of the following conditions:
1. Type 2 diabetes treated with subcutaneous insulin
2. Type 1 diabetes mellitus
3. Intolerance to insulin
4. History of severe low blood sugar. After enrollment, participants who have more than one asymptomatic and/or symptomatic episode of hypoglycemia (glucose < 54 mg/dL) through the entire duration of the study during home measurements using finger stick or on plasma glucose measurements will be excluded.
5. Acute medical condition that required either hospitalization or surgery within the past 6 months (e.g. severe hypoglycemia, malignancies, myocardial infarction, stroke).
6. Liver or renal failure or transplant.
7. Dementia (MMSE scores ≤20).
8. Current recreational drug or alcohol abuse.
9. Serious systemic diseases that would interfere with conduction of clinical trial.
10. MRI substudy: claustrophobia, implants and body proportions incompatible with 3 Tesla MRI.
11. All women in the study are required to be post-menopausal or practice adequate birth control.

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If you qualify to take part in this research study, you will undergo the following procedures:
Table 1: Research Procedures and Study Timeline

Weeks	Visits	Procedures
Week 0	**Visit 1 Screening** 120 mins	• Consent form explanation, medical history and medication review • Vital signs and ECG • Blood Draw • Physical Examination • Mini-Mental State Examination • Meal <u>MRI substudy (only):</u> MRI safety checklist; head circumference and shoulder width measurements.
	MRI Substudy 90 mins	Selected subjects will have a magnetic resonance imaging (MRI) scan within 2 weeks before Visit 2.
ENROLLMENT, RANDOMIZATION -BASELINE, START OF TREATMENT		
Week1	**Visit 2 Baseline** **Intervention 1** 240 min	**<u>Baseline Assessment</u>** • Vital signs, height, weight and hip-waist ratio, blood draw • Medical history and medications update • Appetite scale • Meal • Cognitive and walking test (6 min normal and 6 min dual-task walk. **<u>Intervention Assessment 1</u>** • Teaching session: Review of study procedures, glucometer and finger stick training, intranasal insulin device training. • First intranasal insulin/placebo administration • Blood draw • Cognitive and walking test (6min normal and 6 min dual-task walk) • Meal Study team will call participant one week after Visit 2 to follow-up.
Week 4	**Visit 3 Follow-up 1** 45 min	• Vital signs • Medical history and medication review • Cleaning of the nosepiece and device • Medication refill & new calendars • Adverse events monitoring and compliance checks
Week 8	**Visit 4 Intervention 2**	• Vital signs, height, weight and hip-waist ratio, blood draw • Medical history and medications update • Appetite scale • Intranasal insulin/placebo administration

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	180 min	• Meal • Cognitive and walking test (6min normal and 6 min dual-task walk) • Medication refill & new calendars • Adverse events monitoring and compliance checks
Week 12	**Visit 5** **Follow-up 2** 45 min	Follow-up procedures are the same as Visit 3.
Week 16	**Visit 6** **Intervention 3** 180 min	Assessment procedures and fasting blood draws are the same as Visit 4.
Week 20	**Visit 7** **Follow-up 3** 45 min	Follow-up procedures are the same as Visit 3 and 5.
Week 24	**Visit 8** **Intervention 4** 180 min	Assessment procedures and fasting blood draws are the same as Visits 4 and 6. Final review of study documentation.
		MRI Substudy: Second MRI. Additional 60 mins duration.
END OF TREATMENT- START OF LONG TERM FOLLOW-UP		
Week 25	**Visit 9** **Phone Interview** **Post-treatment 5** 20 min	**Post-treatment Assessment 5** **Phone Call (Mail these forms on a prepaid envelope given in Visit 8)** • Medical history and medication review • Functional assessment forms (GDS, WHODAS) • Glucose finger sticks value
Week 32 **Week 40** **Week 48**	**Visit 10** **Post-treatment 6** **Visit 11** **Post-treatment7** **Visit 12** **Post-treatment 8** 180 min	• Vital signs and blood draw • Dietitian assessment • Meal • Cognitive and walking test (6min normal and 6 min dual-task walk) • Adverse events monitoring
STUDY COMPLETION		

INTERIM VISIT: You may also be asked to come on a separate visit if the study procedures cannot be completed during any of the study visits for any reason. For example, if you are not able to come fasting for your first visit or other study visits, we will ask you to come back for an extra visit; or any scheduling issues for physical exam, MRI studies, walk test, cognitive tests or other reasons. In case of an emergency some functional assessments might be completed over the phone.

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VISIT 1: SCREEENING (Week 0)
This visit will take about 120 minutes. You will be asked to read and sign this informed consent. Screening procedures will be used to determine if you are eligible to participate in this study. Medical history and medications will be assessed. You must bring all your medications in their original bottles.
Visit procedures: vital signs, ECG, height, weight, waist and hip circumference (HCW).
Mini-mental state examination (MMSE*):* You will complete a short task evaluating your mental status.
Laboratory tests: You have to come after about 8 hours of fasting. Three teaspoons of blood, approximately 15 ml, will be drawn and about 5 teaspoons of urine will be collected for routine laboratory tests of kidney function. Routine blood testing includes an evaluation of blood sugar, lipids, and blood cell counts and C-peptide for insulin-treated diabetic subjects. You may be asked to come for an additional visit for the blood test in case you cannot come fasting.
Physical and neurological exam will be done by a study physician or a Clinical Research Center physician. Toronto neuropathy scale will be completed. You may have to come for an interim visit, if there is a scheduling conflict, or the physician needs to further evaluate your health status.

MRI substudy: If you have diabetes and want to be in the MRI substudy, you will be asked to complete the MRI safety checklist. Your shoulder width and head circumference will be measured. You cannot have MRI if you have any metal implants or devices not compatible with 3 Tesla MRI.

Medications: Bring all your medications with you in the original bottles for each visit.

Fasting blood draws & and holding blood sugar control medications: Visits V1, V2, V4, V6, V8, V10, V11, V12) require that you'll come after about 8 hours of fasting. You will be given a meal after blood draw is completed.

Control group: If you are a control and you are not taking any sugar control medications, you will take your medications as prescribed.

Diabetic group: If you have diabetes and you take sugar lowering medications, fasting may increase the risk of low blood sugar (hypoglycemia). If you take your sugar control medications in the morning, you will be asked to hold your morning dose of sugar control medications before the visits that require you to come fasting (V1, V2, V4, V6, V8, V10, V11, V12). Bring your medications with you to each visit, and you will take them after the fasting blood draw. Meals will be provided after blood draws.
If you cannot come fasting for these visits (e.g. scheduling or other reasons), you will take all your medications including sugar control medications as usual. You will be asked to come early morning another day (within few days before or after the visit) for an interim visit for fasting blood draws.

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Glucose monitoring and symptoms of low blood sugar (hypoglycemia):
Glucose levels will be monitored during the study. You will continue your usual daily activities and treatments. You will have to measure fasting glucose with a finger stick once a week and keep a detailed diary of low blood sugar level episodes and physical activities. If you experience symptoms of hypoglycemia, such as being shaky, sweaty, dizzy, anxious, irritable, confused, very hungry and nauseated, very sleepy – not at bed time or loss of consciousness), you will also be asked to take a finger stick to make sure your blood glucose is within normal limits. You cannot participate in the study if you have a history of severe symptoms due to low blood sugar or low glucose levels during home monitoring. If your glucose levels are low or you experience symptoms such as shaking, sweating, headache, or confusion etc., an emergency protocol will be initiated.

You need to complete Visit 2 within the 3 months after the screening Visit 1. It is important to keep your appointments on time or within 2 weeks of the original scheduled visit (Visits 4, 6, 8, 10, 11, 12). Please contact the study team immediately if you need to reschedule any of your visits. You will be asked to come to BIDMC Research Center or to BWH Clinical Research Center (BWH participants) for these visits.

VISIT 2 (Week 1): BASELINE AND INTERVENTION 1- BEGINNING OF TREATMENT:
This visit will take about four hours. You have to come after about eight hours of fasting. Bring all your medications in original bottles. You will receive meals and snacks, and you can take breaks.

Visit procedures: vital signs, physical and neurological exam by study physician (if not done before), medical history review, medication review, HWC and VAS for appetite feelings. A blood draw to measure: fasting glucose, insulin and metabolic panels, and endothelial and DNA (ApoE4) markers. A whole blood sample for ApoE4 makers can be also taken at other visits if not done at V2.

Baseline Assessment: You will be asked to complete a neuropsychological assessment, 6-min normal walking and performance of a dual task (6-min walking while counting backwards), 30-second balance test with eyes open, 30-second balance test with eyes closed, functional measures and depression scale. Neuropsychological testing will be done using a computer system (Cambridge Cognition computerized system CANTAB), and will include testing of word memory and visuospatial learning, recognition and memory and depression and functional measures.

Teaching session: The study team will review procedures and you will receive instructions on how to administer the study drug using the ViaNase device, how to measure glucose using a study glucometer and a finger stick, and how to fill out home calendars. The study glucometer will be provided.

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Intervention Assessment 1 TREATMENT BEGINS:
You will take the first dose of insulin/placebo yourself under supervision of the study staff. You will spray insulin/placebo twice into each nostril, alternating the nostrils, which will take about one minute. The following procedures will be repeated again after the nasal spray: blood draws for glucose and insulin, neuropsychological, depression, functional assessments, normal walk, walk with a counting backwards, balance test with eyes open and with eyes closed.
You will use intranasal insulin/placebo at home once daily for a maximum of 168 days.
You will use insulin/placebo daily in the morning before breakfast and write down the time of nasal spray on the home calendar. Once a week you will measure your fasting glucose using a finger stick. A week after V2 the study team will give you a call to check compliance and assess any problems with device usage and other study procedures.

MRI substudy: A subset of 40 diabetic participants will also complete a MRI scan at baseline (within two weeks days before V2) and at the end of intervention (during or within two weeks days before V8.). You cannot participate in this substudy if you have metal implants or pacemakers, or exceed body proportions parameters. You will be asked to lie down on an imaging table that will slide into the magnetic field. An MRI imaging coil, which is made from special wires that are covered in plastic, will be placed around your head. Foam pads will be placed around your head to limit head movement during the scan. During the scan, you will be asked to lie still on your back for up to 80 minutes and stay still when the images will be acquired which takes from 2-15 minutes. You will hear a loud knocking or hammering noise while the MRI is taking pictures, but the process itself will be painless. You will be given disposable earplugs to use to help make the noise less noticeable. During the procedure, you will be in constant contact with the MRI technician through an intercom. If at any time during the scan you feel too uncomfortable to continue, no matter what the reason, the procedure will be immediately stopped and you will be removed from the magnet (MRI scanner).

Carbon dioxide re-breathing and hyperventilation: You will be asked to breathe a mixture of air and carbon dioxide to increase your carbon dioxide level above normal. Then you will be asked to breathe faster.

Genetic testing: This study will obtain blood samplessamples(V2 or other visit) from participants to measure apolipoprotein E4 (ApoE4), a genetic marker which researchers have found to increase the risk of developing Alzheimer's disease. There are no clear-cut tests to diagnose Alzheimer disease during life. Some doctors may use the ApoE4 test with other clinical information to help in the diagnosis of Alzheimer disease in adults who have dementia. In this study we are doing the test for research only. This study is not designed to diagnose Alzheimer's disease and we will not provide the results of The ApoE4 testing to you or your primary care provider. The blood samples will be stored and we will do all testing at the end of the study. If you have questions about Alzheimer's disease we

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will encourage you to talk with your primary healthcare provider.
Are you interested in having ApoE4 measured? YES ☐ NO ☐

VISIT 3 (Week 4): FOLLOW-UP 1
This visit will take about 45 minutes. Visit will include: vital signs measurement, glucose measurement using a finger-stick, drug inventory and refill, compliance checks, adverse events monitoring, device testing and further re-training on device usage.

VISIT 4 (Week 8): INTERVENTION ASSESSMENT 2
This visit will take about three hours. Visit will include: vital signs measurement, medical history, medication review, fasting glucose, insulin and metabolic panels, endothelial markers, HWC, visual analog scales (VAS) for appetite feelings; drug inventory and refill, compliance checks, and adverse events monitoring.
You will be asked to complete a neuropsychological assessment, 6-min normal walk and performance of a dual task (a 6-min walk while counting backwards), 30-second balance test with eyes open, 30-second balance test with eyes closed, functional measures and depression scale.

VISIT 5 (Week 12): FOLLOW-UP 2
This visit will take about 45 minutes. The visit will include: vital signs glucose measurement using a finger-stick, drug inventory and refill, compliance checks, adverse events monitoring.

VISIT 6 (Week 16): INTERVENTION ASSESSMENT 3
This visit will take about three hours. Visit will include: vital signs measurement, medical history, fasting glucose, insulin and metabolic panels, HWC, VAS for appetite feelings; drug inventory and refill, compliance checks, and adverse events monitoring.
You will be asked to complete a neuropsychological assessment, 6-min normal walk and performance of a dual task (6-min walk while counting backwards), 30-second balance test with eyes open, 30-second balance test with eyes closed, functional measures and depression scale.

VISIT 7 (Week 20): FOLLOW-UP 3
These visits will take about 45 minutes. Visits will include: vital signs, glucose measure using a finger-stick, drug inventory and refill, compliance checks, adverse events monitoring.

VISIT 8 (Week 24): INTERVENTION ASSESSMENT 4 – END OF TREATMENT
<u>This is the most important assessment visit that needs to be completed.</u> This visit will take about three hours. This the end-of treatment visit and the last day that you will take the nasal spray. <u>Visit procedures:</u> vital signs, medical history, fasting glucose, insulin and metabolic panels, endothelial markers, urine creatinine and microalbumin, HWC, VAS for appetite feelings; drug inventory, compliance checks, and adverse events monitoring.

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You will be ask to complete a neuropsychological assessment, 6-min normal walk and performance of a dual task (6-min walk while counting backwards), 30-second balance test with eyes open, 30-second balance test with eyes closed, functional measures and depression scale.

If you participate in MRI substudy, you will also complete an MRI scan at this visit (or within 10 days before this visit).

VISITS 9-12: POST-TREATMENT ASSESSMENTS 5-8 - LONG-TERM FOLLOW-UP
PHONE CALL "Visit 9" (Week 25): This assessment will be done over the phone and it will take about 30 minutes. The phone interview will include: medical history review, medication review, functional and depression scales, glucose measurement using a finger stick, VAS for appetite feelings. You will be asked to fill out the forms prior to the interview and mail the forms and glucometer to the investigators.

Visit 10, 11, 12 (Week 32, 40 and 48)-END OF STUDY
These visits will take place at weeks 25, 32, 40, and 48, and will last about 3 hours each at the Clinical Research Center. Visits procedures: fasting blood draws for glucose, insulin and fructosamine, and at V12 also urine creatinine and microalbumin and endothelial function markers; medical history review, HWC, VAS for appetite feelings, vital signs measurement, glucose measure using a finger-stick, neuropsychological assessment, 6-min normal walk and performance of a dual task (6-min walking while counting backwards), functional measures and depression scale.

RISKS AND DISCOMFORTS
As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

- Intranasal insulin or placebo: You may spend time and experience side effects taking a drug that may not provide you with any health-related benefits.
- Hypoglycemia symptoms: being shaky, sweaty, dizzy, anxious, irritable, confused, very sleepy – not at bed time or loss of consciousness
- Risk of hypoglycemia: Previous studies reported that intranasal insulin has minimal effects on peripheral glucose levels. You will be asked to monitor your blood sugar at home and those with hypoglycemic events during monitoring will be excluded. Fasting blood glucose will be sampled before the visits and monitored during the study to minimize the risk of hypoglycemia. Appropriate clinical measures will be administered if hypoglycemia is detected. These studies reported that blood sugar levels were not affected by insulin administration at the dose that will be administered into the nose in one session and over a one month period.
- Several study visits require that you come fasting. Sugar control medications including insulin may increase the risk for hypoglycemia if you are fasting. Therefore, you may be asked to hold

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your sugar control medications before those visits and you will take your usual prescribed dose after the fasting blood draw is completed. You will be provided a meal after a fasting blood draw.

The studies have also shown that intranasal insulin administrations is safe and is not associated with major side - effects.

The insulin administered into the nose may cause some, all or none of the side-effects listed below:

- You will be instructed not to inhale insulin.
- Side effects reported were mild. More common side effects may include: lightheadedness or dizziness, headache, nose bleed, mild nose irritation or running nose, sneezing (to insulin or placebo), weakness, upper respiratory tract infection/flu like symptoms, fall, rash, other unspecific effects, or allergic reaction to other ingredients in insulin/placebo.
- Less common effects were headache and low glucose level.
- Other possible adverse effects may include: allergic reaction, local allergic reaction to insulin or other substances in insulin/placebo preparation, skin thickens at administration site, swelling, vision changes, low potassium in blood.

Since the combination of insulin and its delivery is so new, there may also be other side effects that we cannot predict, because of our very limited experience with this combination of insulin and nasal delivery. Participants will be evaluated by the study physicians and treatment will be stopped if medically indicated.

Glucose monitoring using a finger sticks: You will be required to measure fasting glucose once a week using a finger sticks, and may experience discomfort, pain and rarely, infection at the site. Insulin-treated diabetics will measure glucose using finger stick five times per day for two weeks.
Weight and body mass: INI may be potentially associated with reduced food intake. Therefore, body weight, waist and hip circumference will be monitored during study visits.
Visual Analogue Scale (VAS): You will be required to complete a scale regarding your appetite feelings; the use of VAS may cause minimal risk, including mental stress or exhaustion. Rest will be given if necessary, and testing will be stopped upon your request.
Blood drawing*:* There are risks and discomforts when drawing blood from a vein. These include the possibility of pain or bruising at the site of the blood draw; occasional lightheadedness; and rarely, infection at the site of the blood draw.
Cognitive Tests: Some tests may cause frustration or anxiety. If you are feeling overwhelmed, the administrator will stop testing.
Walking tests: The proposed walking tests will be conducted at preferred speed and for relatively short duration (six minutes). Physical activity associated with these tests is therefore low to moderate intensity, and potential risks include strains, sprains, muscle soreness, and light-

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headedness. In rare instances, more serious side effects such as an injurious fall may occur.
Walking: Gait speed will be measured during a 6-minute walk at participant's preferred speed in an unobstructed hallway with a cognitive challenge (a dual task counting backwards subtracting seven).
Balance: Balance will be measured during two 30-second trials. You will stand still first with eyes open and then with eyes closed. The research assistant will accompany participants to minimize the risk of falling during walk and balance tests using Mobility Lab System (APDM, Inc. Portland OR).
Other adverse effects: Unknown adverse effects may occur, and therefore we will ask you to keep detailed diaries of all potential adverse events.

MRI sub-study: Magnetic Resonance Imaging at 3Tesla is a method of taking pictures of the brain and of the blood flow in the brain, using a large magnet and radio signals. It allows examination of your brain without exposing you to X-rays. All studies performed under this protocol will not exceed the FDA guidelines for magnetic resonance in any way. Therefore, the risks assumed by you are the same as in any noninvasive protocol involving whole body MRI. Patients with metal implants and pacemakers and those who do not meet body proportion requirements are excluded from the study, because of physical risks related to imaging subjects with such devices. You must tell the investigators about any operations you have had and any metal you may have in your body, so it can be decided if it is safe for you to proceed with the scan. We will also require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects will be allowed into the magnet room at any time. During the MRI session, the scanner will generate loud beeping and clicking noises. The expected discomforts during MRI are dizziness, claustrophobia (fear of small places), and annoying beeping and clicking sounds generated by the scanner. You will be given earplugs to minimize discomfort from the noise. You will be in constant two-way contact with the technologist and may ask that the scan be stopped because of noise or for any other reason. If you feel the need to be removed from the MRI scanner at any time, the scan will be stopped immediately. Hyperventilation and CO_2 breathing will be used to test vasodilatation and vasoconstriction reserves.
Hyperventilation: Hyperventilation is a standard clinical procedure that may be associated with a transient dizziness and tingling in the fingers due to decline of CO_2, but symptoms disappear after the end of hyperventilation.
CO_2 rebreathing may be associated with discomfort from the cannula or mask, shortness of breath and potential risk of panic attacks. You may need a medical evaluation at that time. If you tell us that you wish to be removed from the scanner, we will end the study.

EARLY TERMINATION
Your participation in the trial can be terminated at any time for non-compliance or inability to follow study procedures and/or serious adverse events.

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LOSS OF CONFIDENTIALITY

There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information. However, if your participation becomes known, it could create a problem or hardship for you depending upon the type of information disclosed.

PSYCHOLOGICAL STRESS

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 the study at any time.

CERTIFICATE OF CONFIDENTIALITY

The National Institutes of Health has issued a Certificate of Confidentiality for this research. This adds special protection for the research information and specimens that may identify you. The researchers may not disclose information or specimens that may identify you, even under a court order or subpoena, unless you give permission. However, a Certificate of Confidentiality does not prevent researchers from disclosing your information or specimens if required by law (such as to report child abuse, communicable diseases or harm to self or others); if you have consented to the disclosure (such as for your medical treatment); or for use in other research as allowed by law. In addition, the Certificate cannot be used to refuse a request if a governmental agency sponsoring the project wants to audit the research. By signing this form, you are giving your consent to the disclosure of your information or specimens for any purpose you have agreed to in this informed document and for any purpose permitted without additional authorization in the BIDMC Notice of Privacy Practices. Any research information that is placed in your medical record would not be covered under this Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your involvement in this research. If others obtain your written consent to receive research information or specimens, then the researchers are permitted, but not necessarily required, to disclose that information.

CONFIDENTIALITY

Information learned from your participation in this study and from your medical records may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, the National Institutes of Health, accreditation agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the Beth Israel Deaconess Medical Center with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical records may be used for research purposes and may be published; however, you will not be identified by name in such publications.

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POSSIBLE BENEFITS

Although there may not be any direct benefit to you from participating in this research study, your participation may contribute to a better understanding of diabetes and its complications in the brain and the effects of insulin on blood flow regulation and cognition, which may help future patients. intranasal insulin has been previously shown in prior studies to improve memory. However, this result cannot be guaranteed. The investigators do not expect to cure your disease or condition with the study treatments.

OTHER AVAILABLE OPTIONS

Taking part in this study is voluntary. You may choose not to participate in this study. This is study may provide information that may lead to future novel applications of intranasal insulin for blood flow impairment in diabetes. You may choose to participate in clinical studies treating diabetes. Information about these studies is available on National Institutes of Health and American Diabetes Association Web Sites. Though the MRI images obtained will be helpful for research, they cannot be used in place of a standard clinical MRI. Though genetic testing for ApoE4 will be obtained, it is not for diagnosis, and these tests cannot be used in place of standard clinical evaluations for diagnosis of cognitive impairment or dementia. If for any reason, you desire a clinical evaluation of your brain, your memory or mental status, you will have to arrange it separately in consultation with your physician.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study. Instead of being in this study, you have the following options:

- There is no therapy to treat mild memory impairment in diabetics at this time. You will, however, be provided with care to help you feel more comfortable. It is important to note that it is possible to get treatment for cognitive impairment at this institution or other locations even if you do not take part in the study.

This research study is not meant to diagnose or treat medical problems not stated in this informed consent form. Participation in this research study does not take the place of routine physical examinations or visits to your regular doctor.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY

Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not

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participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.
If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at Beth Israel Deaconess Medical Center.

INVESTIGATORS RIGHT TO STOP THE STUDY

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU

COSTS COVERED BY STUDY

You will not be charged for laboratory tests, MRI and other tests that are part of this research study. However, you and your insurance company will be charged for other tests, procedures or medications of this study that are considered standard treatment for your medical condition- for example cost of medications or other medical procedures that you will need to treat your medical conditions while participating in this study.

PAYMENTS TO YOU:

The total payment for this study remains the same but payment schedule has changed. Therefore, you will receive the same total amount (up to $1000) upon completion of all study procedures:

1. Visit 1 (Screening): $20
2. Visit 2 (Baseline/Interv1): $150
3. Visits 3-5, 7: (Follow - up visits): $50 per visit
5. Visits 4, 6, 8, 10, 11, 12 (Functional assessments): $110 per visit
6. Visit 9 (phone interview): $20
7. Interim visit: $20 for completion
8. MRI substudy: $50 each scan ($100 total)
9. If you skip V4,V5,V6, V7 and use the study medication as prescribed, and bring the vials and home glucose calendar to your next visit, you will be compensated with $50 for the skipped visit.

Parking vouchers and MBTA tickets, other transportation (Uber, Lyft, etc.) will also be either provided or reimbursed. Lyft concierge service can be used upon request and approval. Taxi fare will be paid for but only in special circumstances.

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It may take up to eight weeks for you to receive payment by check.
Any payments made to you may be taxable income. This does not include any payments you may receive to reimburse (pay you back) you for certain expenses like parking fees or travel. We are required to obtain your name and social security number for preparation and submission of Internal Revenue Service (IRS) Form 1099-Misc. You may receive an Internal Revenue Service Form 1099 from BIDMC if you receive more than $600 in one calendar year for taking part in one or more research studies at BIDMC. Questions about your own tax status should be referred to your personal tax advisor.

COST OF RESEARCH RELATED INJURY:
If you are injured as a direct result of your participation in this study, you should contact the Investigator at the number provided under the section "Who to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. We reserve the right to bill your insurance company or the sponsor (NIH), if appropriate, for the care you get for the injury. We will try to get these costs paid for, but you may be responsible for some of them. You may be responsible for all co-payments and deductibles required under your insurance. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

OTHER IMPORTANT INFORMATION
A description of this clinical trial is available on www.ClinicalTrials.gov (NCT0421556) 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.

USE OF YOUR TISSUE FOR COMMERCIAL DEVELOPMENT
As part of this research program, samples of your tissue and information about your medical history may be provided to other researchers and/or outside collaborators without identifying you by name. They may use your tissue and information in other scientific research, product testing or commercial development. It is unknown whether a product will ultimately be developed from any such work that may be performed. In signing this consent form, you are acknowledging and voluntarily consenting to the possibility that your tissue may be used for commercial purposes. You also understand and agree that tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. Beth Israel Medical Deaconess Medical Center has no program to compensate you in the event product testing or commercial development takes place.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION
As part of this study, we will be collecting, using and sharing with others information about you. Please review this section carefully as it contains information about the federal privacy rules and the

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use and disclosure of your information.

PROTECTED HEALTH INFORMATION [PHI]
By signing this informed consent document, you are allowing the investigators and other authorized personnel to use [internally at BIDMC and BWH] and disclose [to people and organizations outside the BIDMC and BWH workforce identified in this consent] health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information, the results of any laboratory tests, as well as any new information generated as part of this study. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC WHO WILL SHARE AND USE YOUR PROTECTED HEALTH INFORMATION
Your Protected Health Information may be shared with and used by investigators listed on this consent form as well as the supporting research team [i.e. research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, administrative assistants]. Your Protected Health Information may also be shared with the members and staff of the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, which is responsible for reviewing studies for the protection of the research subjects.

PEOPLE/GROUPS OUTSIDE OF BIDMC WITH WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE SHARED
We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this study:

- The funding source of this study National Institutes of Health and their clinical research organizations.
- Laboratories not affiliated with BIDMC that are involved in conducting tests related to the research
- Statisticians and other data monitors not affiliated with BIDMC
- The members and staff of any other IRBs (beyond the BIDMC Committee on Clinical Investigations) that oversee the research
- Centralized data collectors
- Your health insurance company
- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Data and Safety Monitoring boards that oversee this study (if applicable)

Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to

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others and use your information without being subject to penalties under those laws.

WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION

The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document. We also shall use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION

Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization Vera Novak, Ph.D. at Division of Neurology Beth Israel Deaconess Medical Center, 185 Pilgrim Road Palmer Bldg. 127, Boston MA 02215. Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

REFUSAL TO SIGN

Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI

If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS

You may contact the Human Subjects Protection Office at (617) 975-8500 in the event that you would like to obtain information or to offer input about the research study or Dr. Peter Novak [617] 424-4101 for BWH participants. This office is independent of the investigator or investigator's

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research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO).

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

Signature of Subject or Legally Authorized Representative (Parent if the subject is a minor) — Date

_____

Relationship of Legally Authorized Representative to Subject

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/Co-Investigator's NAME

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BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
12/09/2019
APPROVAL EXPIRATION DATE

HE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____

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