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Memory Advancement by Intranasal Insulin in Type 2 Diabetes (MemAID) Randomized Controlled Clinical Trial: Design, Methods and Rationale

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Abstract

Background—Type 2 diabetes mellitus (T2DM) accelerates brain aging and increases the risk for dementia. Insulin is a key neurotrophic factor in the brain, where it modulates energy metabolism, neurovascular coupling, and regeneration. Impaired insulin-mediated brain signaling and central insulin resistance may contribute to cognitive and functional decline in T2DM. Intranasal insulin (INI) has emerged as a potential therapy for treating T2DM-related cognitive impairment.

Methods/Design—Ongoing from 2015, a prospective, two-center, randomized, double-blind, placebo-controlled trial of 210 subjects (120 T2DM and 90 non-diabetic older adults) randomized into four treatment arms (60 T2DM-INI, 60 T2DM-Placebo, 45 Control-INI, and 45 Control-Placebo) evaluating the long-term effects of daily intranasal administration of 40 International Units (IU) of human insulin, as compared to placebo (sterile saline) over 24 weeks and 24 weeks of post-treatment follow-up. Study outcomes are: 1) long-term INI effects on cognition, daily

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functionality, and gait speed; 2) identifying a clinically relevant phenotype that predicts response to INI therapy; 3) long-term safety.

Conclusion—This study addresses an important knowledge gap about the long-term effects of intranasal insulin on memory and cognition in older people with T2DM and non-diabetic controls, and may provide a novel therapeutic target for prevention and treatment of cognitive and functional decline and dementia.

Trial Registration—NCT02415556

Keywords

Intranasal insulin; type 2 diabetes mellitus; cognition; memory; gait; balance; functionality; randomized controlled clinical trial

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for accelerated brain aging, dementia, and stroke [1]. T2DM affects 25% of adults older than 65 years (≈ 422 million) globally [2]. This population has a high prevalence of cognitive dysfunction, impaired executive function, worse self-management, and a greater risk of falling [3]. Currently, there are no therapies available for T2DM-related cognitive impairment.

Brain insulin resistance has emerged as a key feature of neurodegenerative diseases, mood, and cognitive disorders [4]. Previous studies have shown that T2DM is associated with brain insulin resistance, impaired vasoreactivity, regional hypoperfusion [5], microstructural abnormalities, altered functional connectivity [7], and atrophy in fronto-temporal regions [8] that manifest as functional and cognitive deficits [9].

Brain insulin receptors are abundant within neurons, astrocytes, and capillaries [10], where they regulate regional perfusion [11], neuronal homeostasis [12], and signaling within memory [13] and energy metabolism networks [14,15]. Neuro-protective effects of insulin include upregulation of regional brain activity and cerebral blood flow in the neurovascular unit [11,16], modulation of serotonergic and monoaminergic pathways, increased gamma-Aminobutyric acid (GABA) uptake by astrocytes, and protein synthesis [4].

Intranasal insulin (INI) has emerged as a potential treatment for amnesic cognitive impairment [17–19]. INI delivery bypasses the blood-brain barrier and is effectively delivered to central insulin receptors, thus avoiding systemic hypoglycemia [20]. Preliminary studies suggest that INI may acutely improve functional connectivity [7], neurovascular coupling, regional vascular tone, and neuronal activity [21].

The Memory Advancement by Intranasal Insulin in Type 2 Diabetes –MemAID– is a randomized controlled clinical trial that aims to determine the effects of INI on memory, cognitive function, and daily functionality; identify a phenotype and long-term trajectory predicting clinically relevant response to INI treatment; and determine the long-term safety of INI. Our primary hypothesis is that diabetic subjects treated with INI will perform better on outcomes of memory and cognitive function, have faster dual-task walking speed, and

better daily living functions, as compared to placebo-treated diabetic subjects. We also hypothesize that in the control group, subjects with INI would perform better on these outcomes than the placebo-treated control subjects; although, the INI beneficial effect is expected to be higher in the diabetic subjects. We intend to determine long-term trajectories of INI-responses during treatment and follow-up, and to identify a phenotype that is predictive of a clinically relevant response to INI therapy based on glycemic control, insulin resistance, endothelial, and genetic markers. Findings obtained from this study will ascertain the long-term safety of INI regarding glycemic control, vital signs, body mass, appetite feelings, and food intake. The MemAID trial will provide proof-of-concept for the efficacy and safety of INI and will lay the groundwork to potential treatment of T2DM and age related cognitive decline. In this paper, we describe the study design, data collection procedure, and method of analysis.

2. RESEARCH DESIGN

2.1. Design and setting

This two-center, prospective, randomized, double-blind, placebo-controlled trial involves 210 older adults (120 T2DM and 90 controls) randomized into four treatment arms (60 T2DM-INI, 60 T2DM-Placebo, 45 Control-INI, and 45 Control-Placebo). We will evaluate the long-term effects of daily administration of 40 international units (IU) of insulin (Novolin® R, Novo Nordisk, Bagsværd, Denmark) administered as intranasal spray versus placebo (sterile saline) over 24 weeks of treatment and 24 weeks of post-treatment follow-up throughout twelve study visits Figure 1. We will assess whether INI/placebo improves cognition, daily functionality, and walking speed (Aim 1); identify a phenotype and predictors of response to INI treatment (Aim 2), and determine safety of long-term INI usage (Aim 3).

The trial is conducted by the Syncope and Falls in the Elderly (SAFE) Laboratory at the Clinical Research Center at Beth Israel Deaconess Medical Center (BIDMC) and the Center for Clinical Investigation at Brigham and Women's Hospital (BWH) (Boston, MA). The BIDMC Committee of Clinical Investigation and Harvard CEDE Review reviewed and approved the study procedures. Informed consent is required from all subjects prior to their participation in this study.

This study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (1R01DK103902), approved by the Food and Drug Administration Investigational New Drug Application (FDA-IND-107690), registered at clinicaltrials.gov (NCT02415556), and World Health Organization international trial registry (UTN-U111-1175-1588).

2.2. Participant recruitment and eligibility

We intend to screen up to 800 subjects over the phone; and enroll (sign informed consent) 360 subjects (200 diabetics and 160 controls) between July 2015 and December 2019 to allow for attrition during the longitudinal study. We plan to screen 360 subjects (visit 1), have 210 subjects completing treatment (visit 8) and 168 subjects completing the follow-up (visit 12).

Out of the 210 subjects, we aimed to have 120 T2DM subjects and 90 non-diabetic subjects. Participants are recruited using advertisement in local community newspapers, radio, Facebook, SAFE- laboratory recruitment repository, BIDMC, BWH and Joslin Diabetes Clinics, ClinQ BIDMC database, and ResearchMatch database. ResearchMatch is a national volunteer registry that was created by several academic institutions, and supported by the U.S. National Institutes of Health.

Table 1 lists the inclusion and exclusion criteria. Several retention strategies have been implemented to improve subject participation and reduce dropout rates. These include 24/7 accessibility of the investigators, reminder letters, flexibility with visit scheduling, ability to skip follow-up and/or assessment visits, transportation to BIDMC, traveling expense reimbursement, and financial incentives for completing the visits.

2.3. Randomization and power analysis

The randomization was done for each of the two sites (BIDMC, BWH). Within each site, a subject was randomized to one of the four treatment arms (T2DM-INI, T2DM-Placebo, Control-INI, and Control-Placebo). Block randomization was used with three block sizes: 4, 8, and 12. The size of the block is randomly determined by uniform distribution (e.g. if the random variable is less than 1/3, block size of four was selected, between 1/3 and 2/3, block size of eight was selected, and greater than 2/3, block size of twelve was selected). We expect the distribution of subject-specific confounding variables to be similar across groups. The principal investigator, study physicians, study staff, participants, and their health care providers are blinded to the randomization. The principal investigator and the study physicians review eligibility, adverse events, outcomes, and provide approval for enrollment. The study staff conducts the study procedures. The randomization code was generated by the study statistician (L.N.) and is given to BIDMC and BWH study pharmacists.

For the power analysis, at the design phase, we used simulation to create data for linear mixed effects model since we have longitudinal data for each subject. We assumed a compound-symmetry structure for the variance-covariance matrix of the data, and simulated the data based on assumed magnitudes of the within-subject, and between-subject variance components. The primary comparison was between the INI group and placebo group of the diabetic group, so the power was based on the desired effect size on this comparison. We based our initial power analysis on the treatment efficacy in diabetic group (the difference between INI-treated vs. placebo treated diabetics) at the end of treatment. We focused power analyses on null hypothesis for Brief_Visuospatial_Memory_Test_total_recall because we used this variable in our pilot study [11] and it is known to be correlated with CANTAB cognition tests. For our gait outcome, we used our data showing the diabetics have slower normal and dual task walking and estimated a faster walking speed in INI-treated diabetics. For functional outcomes we used the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)[22].

We used simulation and linear mixed effects models with linear contrasts in our computation of the power analysis. With a total sample size of N=500 (125 per group, 4 groups), results showed a power of 0.93, type-I error of 0.05, and an effect size of at least 20% of the standard deviation. We expect an attrition rate of up to 20% at week 18 as a conservative

estimate. Considering this, the power was 0.87 at our original N=400. In June 2017, the power analysis for Aim 1 was revised based on data from 42 enrolled diabetic subjects. The sample size was decreased to N=360 (signed informed consent form) where results showed a reduced power of 0.83 and type I error of 0.05.

For analysis of aims 1 and 2 we expect 210 subjects to complete treatment. We estimate that with an attrition rate of 20% during the follow-up, 168 subjects will also complete the post-treatment follow-up. Aim 3 evaluates long-term INI safety. The safety sub-study was designed to consecutively enroll 20 insulin-treated diabetic subjects who would measure finger-stick glucose five times per day for one week during baseline and during the first week of INI/placebo treatment to evaluate the effects of INI on glycemic control and hypoglycemic states. Due to a high dropout rate, it was stopped for futility by the Data and Safety Monitoring Board (DSMB) in July 2017.

2.4. Experimental measures

2.4.1. Neuropsychological assessment—Neurocognitive function is assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd, Cambridge, UK) which provides multiple validated parallel versions of the same test to minimize practice effects with a complex repeated measures design [23,24]. Outcome measures include visuospatial memory and learning [25,26], retention of spatial information in the working memory [27], attention and general cognitive performance [28], and immediate and delayed verbal memory [11]. The Wechsler Test of Adult Reading (WTAR™) IQ test is a well-normed measure of premorbid verbal IQ, which provides a correlate of verbal intelligence [29]. The Mini Mental State Examination (MMSE) is administered at visit 1 to screen for clinically significant dementia [30] using age- and education- adjusted norms.

2.4.2. Gait assessment—Gait speed and step characteristics are measured with a Mobility Lab System (APDM, Inc., Portland, OR) during 6-minute walking at usual speed and 6-minute walking at a usual speed with a dual-task (counting backwards subtracting seven). Balance is measured with the same system for 30 seconds while standing with eyes open and 30 seconds while standing with eyes closed.

2.4.3. Functional measures assessment—The Geriatric Depression Scale (GDS) is a self-reported measure of overall mood, activity, sadness, and worry. The outcome measure is a total score (up to 30 points) that reflects level of depression [31].

The WHODAS 2.0 is a short, easy-to-administer, and widely used self-reported questionnaire that measures daily function and disability and is valid across a broad age range and across all diseases [32]. WHODAS 2.0 provides standardized disability levels and profiles in the following domains: Cognition (understanding and communicating), Mobility, Self-care (hygiene, dressing, eating, staying alone), Getting along (interacting with other people), Life activities (domestic responsibilities, leisure, work, and school), and Participation (joining in community activities).

2.4.4. Laboratory measures—Blood panels are collected during assessment visits (visits 1, 2, 4, 6, 8, 10, 11, 12) for measurement of: fasting serum glucose, hemoglobin A1c (HbA1c), fructosamine, insulin, complete blood count, lipid panels, genetic markers (Apolipoprotein E4), and markers of endothelial function that have demonstrated relationship to gray matter atrophy and cognition [8] (soluble intracellular adhesion molecule, vascular adhesion molecule, C-reactive protein, and matrix metalloproteinase 1–10). Insulin resistance will be quantified using an updated HOMA-2 model [33]. Urine samples are collected during visits 2, 8, and 12 to measure creatinine and microalbumin.

2.4.5. Visual Analog Scale—Appetite feeling is assessed at visits 2, 4, 6, 8, 10, 11, and 12. Subjects are asked to rate their appetite feeling on a 10-cm visual analog scale before meal and INI/placebo, before meal and after INI/placebo, and after meal and INI/placebo.

3. PROTOCOL

The study involves 12 visits over a 48-week period: 24 weeks of intervention and 24 weeks of post-treatment follow-up Figure 1. Screening procedures include a phone call screen and an on-site screening visit. On-site screening visit 1 comprises the informed consent process, a comprehensive review of medical history, vital signs, electrocardiogram, metabolic panel (fasting glucose, HbA1c, lipids, complete blood count panel), height, weight, measurement of waist and hip circumferences, physical and neurological examination, MMSE, and Toronto Clinical Neuropathy Score. The intervention period has four assessments (visits 2, 4, 6, 8) and three follow-up visits (visits 3, 5 and 7). Participants administer INI/placebo once daily before breakfast and measure fasting glucose using finger-stick once a week and/or whenever symptomatic for hypoglycemia. Visit 2 combines baseline assessment, WTAR™, a teaching session on device usage, safety and compliance measures, the first INI/placebo administration, and the first INI/placebo assessment. Assessment visits include INI/placebo refills, medical history updates, medication reconciliation, measurement of vital signs, weight, waist and hip circumference, appetite feelings, fasting laboratory measures, functional, cognitive, and gait measures, adverse event and compliance monitoring. Follow-up visits include vital signs, compliance checks, INI/placebo refills, and adverse event monitoring.

The follow-up period has four assessments (visits 9, 10, 11, 12), which consist of the same procedures as the treatment period visits (excluding drug-related procedures). Visit 9 is a phone interview one week after finishing the intervention period and includes completion of functional measures and appetite visual analog scale.

3.1. INI/placebo administration

Insulin/placebo is delivered using the ViaNase™ electronic atomizers (Kurve Technology, Inc. Lynnwood, WA, USA), which allow precise electronic dosing for each administration. The device targets delivery into the olfactory region in the upper nasal cavity. Subjects are provided with a ViaNase™ device in order to administer 40 IU (0.4mL) human insulin (rDNA origin) or placebo (0.4 mL bacteriostatic Sodium Chloride 0.9% solution) intranasally once daily before breakfast for 24 weeks. Devices are calibrated to dispense 0.1

ml over 20 seconds in a single dose, which is administered twice into each nostril, alternating sides, over two minutes.

BIDMC and BWH research pharmacy package insulin/saline into sterile vials, perform sterility procedures, and dispense vials according to the randomization code. Subjects receive three identical 10-mL vials containing 100 units/mL of insulin (Novolin® R Novo Nordisk Bagsværd, Denmark) or sterile saline. Each vial is used over a two-week period and is refrigerated between administrations.

3.2. Compliance monitoring

Study compliance is assessed at each visit during the intervention period. The remaining volume in the provided vials is compared to the expected volume usage. Participants are required to record daily medication usage and annotate any new events in the study-provided calendars.

Device and drug volume usage greater than 109 days (65%) is considered as compliant with INI/placebo usage.

3.3. Safety monitoring

A DSMB has been established to monitor progress, adverse events, and safety of the MemAID trial. Adverse events, defined as any new medical condition after the screening visit, are evaluated by the clinical research center nurses at each visit. Whenever an adverse event is reported, study physicians evaluate the subject during the visit, assess the possible relationship of the adverse event to INI/placebo, and determine medical follow-up and administrative reporting procedures.

We aim to determine the long-term safety of intranasal insulin and its potential effects on glycemic control. We conducted a safety sub-study that consisted of continuous glucose monitoring (Medtronic IPro2) (Medtronic, Northridge CA, USA) for one week during baseline and during the first week of INI/placebo usage. Twenty consecutively enrolled diabetic subjects were required to self-monitor blood glucose using finger-stick glucose five times a day, and complete a detailed monitoring log of medications, meals, and activities. This sub-study was terminated by the DSMB in July 2017 due to futility and a high dropout rate (57%) in the subcutaneous insulin-treated T2DM group.

3.4. Data monitoring and management

MemAID StudyTRAX® is a web-based relational database that we have used to enter study data. All data is hosted and managed on StudyTRAX® (<https://www.studytrax.com/>) servers that are fully compliant with the Health Insurance Portability and Accountability Act, automatically updated, and maintained. The hosted solution is secured with 256-bit encryption and a dedicated firewall. Data is protected from hardware failure through geographically redundant storage backups. Data is entered into the StudyTRAX® system by our research staff at BIDMC. StudyTRAX® technical staff is available to help implement dynamic, on-demand, study reports. Questionnaire forms, assignment of variable names and coding, and a data entry system with error checks (i.e. range and logic checks) are provided

by the electronic platform. Audit trails and electronic signatures are enforced to make sure data modifications are tracked. Medical history and experimental measures (neuropsychological and gait assessments, functional and laboratory measures, and visual analog scales) are captured and analyzed electronically. This database system is used to generate reports to track subject enrollment, provide descriptive statistics of data variables, and allows data tracking for assessment of study compliance. The study staff is assigned different levels of access privilege to prevent unauthorized use of data. Variables in the database can be downloaded to validated analysis software (Statistical Analysis System-SAS) for further analysis. The download procedure and conversion of StudyTRAX[®] data to SAS have been automated by our team. The conversion software in StudyTRAX[®], captures the clinical data and converts them in SAS for further reporting and analysis by our analysts and statistician. The statistical analyses are fully coded and automated in SAS for monthly reporting of study progress, and exploratory analyses. These analyses consist of the progress for each aim, data distributions, missing data amount and reasons, outlier analyses, study compliance (amount of medication taken and returned), and number of missed visits.

4. ANALYSIS PLAN

Linear mixed models will be used to analyze the longitudinal data collected during treatment and post-treatment assessment visits. We will evaluate the long-term trajectory of the main outcomes (cognition, gait speed, and functionality), the longitudinal relationship among the main variables, and the time point when the maximum effect of treatment is reached during the study.

Furthermore, we will explore the potential confounders such as baseline differences in cognition, years of education, and potential effects of age, sex, and race to determine response to INI therapy.

4.1. Analysis for Aim 1

We will use summary measures of gait testing, functionality, and the computerized CANTAB cognitive tests to determine whether T2DM treated with INI have better memory, daily living functionality, and faster dual-task gait speed than the placebo treated and control groups. The primary time point of interest for assessing INI treatment efficacy is the fourth assessment (visit 8), which is the end-of-treatment date (week 24). We will compare each of the outcome variables among the four groups: T2DM-INI, T2DM-placebo, control-INI, control-placebo and across each of the eight assessment visits.

4.2. Analysis for Aim 2

The outcome of a positive response to INI therapy will be a binary variable. We define a positive response to INI therapy as 1.5 increase score in cognitive variables of interest at the end of treatment. We will include variables that may be predictive of response to therapy such as: demographic characteristics (age, sex, and adiposity), glycemic control measures (fasting glucose, insulin, HbA1c, and diabetes duration), endothelial function markers, and genetic markers.

We expect T2DM and control subjects to have a positive response to INI therapy and show improvement in the main outcome measures. Our modeling approach will enable us to identify a clinical phenotype predicting a clinically relevant response to INI therapy and identify the time-dependent trajectories of INI effects of cognitive and functional outcomes during the treatment and duration of these effects during the follow-up period.

4.3. Analysis for Aim 3

We will evaluate five continuous outcome variables at all assessment visits to determine the long-term safety of intranasal insulin. Included variables are fasting glucose, HbA1c, and number of hypoglycemic episodes to determine effect over glycemic control, insulin resistance as measured by the Homeostatic Model Assessment (HOMA-2), and blood pressure. All measures will be assessed by the linear mixed effects model and we do not expect significant differences from the placebo treated groups.

5. DISCUSSION

MemAID will determine the long-term effects of INI on cognition and memory in T2DM and non-T2DM adults; identify a clinical phenotype that is likely to respond to INI therapy, and ascertain its long-term safety. Findings obtained in this study will allow us to determine the role of INI in prevention and treatment of DM-related effects in the brain, including neuronal damage and cerebrovascular diseases. The study population will allow us to evaluate INI effects over a wide range of fasting glucose and insulin resistance measurements. Thus, we can address an important, understudied area: the long-term trajectory of the effects of INI on cognition in older diabetic people vs. normal aging.

INI therapy has emerged as a novel approach for treating cognitive impairment. The chronic administration of a low dose of INI has been found to improve delayed memory and preserve general cognition as compared to acute administration of higher INI doses [16]. A pilot placebo-controlled study has shown that following INI administration, functional connectivity between hippocampal and default mode network regions modulating cognitive functions has increased in older T2DM adults to the levels similar to healthy participants [7]. Trials using 40 IU of rapid-acting or regular INI for eight weeks improved declarative memory in healthy adults when compared to placebo [34]. Increasing evidence has supported the positive effects of the long-term administration of INI on cognition in the cognitively impaired elderly in which heterogeneous medical conditions exert a detriment on their brain health [35,13,36].

Consistent with our previous studies [5,8,11,7], we anticipate accelerated progression of cognitive decline, increased depression scores [8], decreased gait speeds [37], and decreased functionality in the placebo-treated T2DM subjects. We are investigating whether INI can reduce cognitive decline and/or improve functionality. The 24-week treatment and post-treatment follow-up periods are intended to investigate the changes in the baseline health of the four treatment groups and determine whether there will be changes related to INI treatment or aging per se.

The broad inclusion criteria favor enrollment of a diverse T2DM and non-T2DM population and warrant generalization of results. The non-T2DM group will serve as a reference model of aging and includes people with cardiovascular risk factors and pre-diabetes. Lenient criteria for MMSE permit inclusion of T2DM and non-T2DM older adults with mild cognitive impairment while excluding those with dementia. The 24-week treatment period extends beyond previous studies [38,35,13,17,19], and will enable to identify clinical factors that affect responses to therapy as well as potential duration of the effects.

Evidence supporting the safety of delivering insulin to the brain through INI is growing [18,39,40]. A recent article [40] reviewed more than 1900 people exposed to INI and determined that acute and chronic administration of INI appears to be safe. No treatment-related serious adverse events have occurred in clinical studies. Daily administration of 40 IU of INI during eight [34] and sixteen weeks [17] was not found to significantly change circulating blood insulin, blood glucose levels [40], heart rate, or blood pressure [34]. Furthermore, recent studies have shown that chronic administration of low dose INI may have a better safety profile than administration of higher doses [16]. The ancillary safety sub-study of MemAID was terminated due to futility and a high participant dropout rate, highlighting the challenges that investigators face when including long-term follow-up periods in interventional studies.

The long-term trajectory effects of INI on cognition in older diabetic and non-diabetic adults are yet to be demonstrated. Elucidating the potential protective neurological effects of INI, which may be exerted on the reward system and centrally-controlled body weight management, will provide a better understanding of the role of insulin in the brain. At the date of writing this manuscript, clinicaltrials.gov showed at least thirteen active clinical trials using INI as an intervention [41]. The Study of Nasal Insulin to Fight Forgetfulness -SNIFF trial-(NCT01767909) is the largest randomized controlled clinical trial to date and has finished recruitment, results are not available yet. Information obtained from this study will provide further understanding of the role of INI therapy in improving memory in adults with mild cognitive impairment or Alzheimer's disease, which are prevalent diseases in the elderly.

Potential limitations in MemAID include challenges in recruitment and retention of participants during the treatment and post-treatment follow-up periods. Dropout rate has been higher than the expected 20% attrition rate, most likely owing to the characteristics of the participants. Older diabetic subjects have multiple comorbidities, polypharmacy, and limited ambulation posing a challenge for long-term follow-up in interventional studies. In our experience, the most common baseline health factors associated with study dropout have been chronic pain and musculoskeletal issues. We have found that the time point with the highest dropout rate is just after the visit 2 in which the intervention begun. The most commonly cited reasons of consent withdrawal are personal and family issues, new jobs, and/or home relocation.

We have implemented procedures to optimize recruitment and retention during the trial to facilitate subject participation. These incentives have had a positive effect on participant's

retention and highlight the importance of continuous re-evaluation of subject enrollment and retention strategies in clinical trials.

In conclusion, INI has been shown to improve performance in cognitive domains related to verbal and declarative memory in different populations including healthy [35,28] and cognitively impaired older adults [42]. Insulin is a well-studied hormone with millions of patient-year exposure and its intranasal administration has emerged as a novel, feasible, and safe approach for treating disorders that involve abnormal insulin signaling within cognitive reward networks such as obesity, Alzheimer's Disease, mild cognitive impairment, and T2DM. This translational study lays the groundwork for larger trials that will lead to better understanding and treatment of T2DM-related cognitive decline. MemAID will help determine the safety of prolonged INI treatment, the best outcome domains, and the best patient characteristics to be used in future studies. This study may reveal a novel therapy for insulin-resistance-related cognitive decline in obesity, T2DM, and Alzheimer's disease.

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Figure 1: Study roadmap and interventions

After completing phone screening, subjects complete on-site screening. Intervention period visits happen every four weeks; follow-up period visits happen every eight weeks. V2 includes two assessments: baseline and intervention. Visit 9 is a phone call.

Abbreviations: V, Visit number; MMSE: Mini Mental State Examination; WHODAS 2.0: World Health Organization Disability Assessment Scale; GDS: Geriatric Depression Scale; AE: Adverse Event; INI: intranasal insulin. See text for more details.

Table 1.**Inclusion and exclusion criteria**

Inclusion criteria
Men and women 50–85 years old
Ability to walk for six minutes
Diabetic group: Diagnosis and treatment for T2DM with non-insulin oral or injectable agents or diet
Control group: Fasting plasma glucose <126 mg/dL and HbA1c <6.5%
Exclusion criteria
Insulin use
Insulin allergy
Type 1 Diabetes Mellitus
History of severe hypoglycemia
Dementia
MMSE scores < 20
Liver failure or transplant
Renal failure or transplant
Serious systemic disease that would interfere with conduction of the trial
Acute medical condition that required hospitalization or surgery within the past 6 months (e.g., malignancies, myocardial infarction, stroke)

Abbreviations: T2DM: Type 2 Diabetes Mellitus; HbA1c: Hemoglobin-A1c; MMSE Mini Mental State Examination