A Single Center Feasibility Study of Intranasal Insulin in Frontotemporal Dementia
NIFT-D (Nasal Insulin in Frontotemporal dementia)

Clinical Study Protocol

US IND Number: 139885

Serial Number: 0008

Amendment 3.2 Date: August 27, 2019

Amendment 3.1 Date: May 17 2019

Amendment 3 Date: April 17, 2019

Amendment 2 Date: Dec 14 2018

Amendment 1 Date: Aug 01 2018

Original Protocol Date: July 5 2018

Sponsor
Michael H Rosenbloom
HealthPartners Center for Memory & Aging
HealthPartners Neuroscience Center
295 Phalen Blvd,
St Paul, MN 55130

This study will be conducted in compliance with the protocol, IND regulations and other applicable regulatory requirements.

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and pertinent information to the study personnel under my supervision and my local ethics committee/institutional review board (EC/IRB). I will discuss this material with them and ensure they are fully informed regarding the study medication and the conduct of the study according to this protocol, applicable law, applicable regulatory requirements including 21 CFR parts, 50, 54, 56, 312 and 812, general standards of good clinical practice and local EC/IRB requirements.

_____

Principal Investigator

_____

Date

Table of Contents

LIST OF TABLES

DEFINITIONS

Adverse event (AE)	Any undesirable patient experience that may include but is not limited to an abnormal sign, symptom, illness, abnormal laboratory value, or other medical event.
Appetite and Eating Habit Questionnaire (APEHQ)	A set of questions examining changes in eating behaviors
Columbia-Suicide Severity Rating Scale (C-SSRS)	A scale designed to quantify the severity of suicidal ideation and behavior.
Data Safety Monitoring Board (DSMB)	An independent group assigned to review safety data to monitor for incidence of trends that would warrant termination of the trial.
ExecutiveAbilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER)	A set of cognitive tests that assess working memory, inhibition, set-shifting, fluency, planning, insight, and social cognition/behavior.
Frontotemporal Dementia (FTD)	A type of dementia resulting due to a degenerative process in the frontal and temporal lobes, refers to a continuum of disorders
Intranasal (IN)	A method of drug delivery that is particularly applicable to delivering centrally acting medications into the central nervous system.
Mini Mental State Exam (MMSE)	A 30 point cognitive screening tool that assesses orientation, working memory, short term memory, visuospatial construction, and language.
Montreal Cognitive Assessment (MOCA)	A 30 point screening instrument for cognitive impairment that has a 90% sensitivity for MCI and 100% sensitivity for AD.
Serious adverse events (SAE)	Any symptom, sign, illness or experience that develops during the study and results in a life-threatening situation, hospitalization, significant disability, and other events determined by the investigator to be significant.
FTD Types **- Behavioral variant frontotemporal dementia (bv-FTD)** **- Semantic Dementia (SD)** **- Progressive non-fluent aphasia (PNFA)** **- Amyotrophic lateral sclerosis (ALS)** **- Progressive supranuclear palsy (PSP)** **- Corticobasal degeneration**	Different types of frontotemporal dementia

PROTOCOL SUMMARY

PROTOCOL TITLE	**Nasal Insulin in Frontotemporal Dementia (NIFT-D)**
SHORT TITLE	IN Insulin in FTD
STUDY PHASE	Phase II
STUDY OBJECTIVES AND PURPOSE	
Primary Objectives: • Evaluate the feasibility of using the EXAMINER battery as a cognitive outcome measure in frontotemporal dementia (FTD) • Evaluate the HealthPartners Center for Memory & Aging's recruitment capacity for FTD subjects • Assess the safety and tolerability of intranasal (IN) insulin in FTD subjects	
Exploratory Objectives: • Evaluate the effect of IN insulin on executive function and behavior in FTD • Evaluate the effect of IN insulin on eating behavior in FTD	
STUDY DESIGN	
Study Type	Feasibility
Control Type	None
Study Indication Type	Treatment
Blinding Schema	N/A
Device	Aerosol nasal Device
Study Design	Prospective, non-randomized, no placebo controlled
Planned Duration of Subject Participation	9 weeks
Planned Duration of Treatment	4 weeks
PRIMARY ENDPOINTS	
• Number of subjects completing the EXAMINER battery • Number of subjects enrolled • Total number of AEs and SAEs	

SECONDARY ENDPOINTS
• Reasons for subjects failing to complete EXAMINER battery • Number of subjects completing the study • Number of screen failures • Reasons for screen failure • Number of unique subjects with an AE/SAE
EXPLORATORY ENDPOINTS
• Pre-post change in executive function and behavior (EXAMINER Battery) • Pre-post change in Appetite and Eating Habits Questionnaire (APEHQ)
INVESTIGATIONAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION

Investigational Product	Regular insulin (Novolin-R) 20 IU/IN (0.1ml/10 units IN in each nostril) BID
SUBJECT SELECTION	
Targeted Accrual	12 subjects. We estimate a need to consent 20 subjects in order to reach this goal.

INCLUSION CRITERIA
1. Male or female subject meeting international consensus criteria for probable behavioral variant frontotemporal dementia or criteria for semantic dementia (Gorno-Tempini et al., 2011; Rascovsky et al., 2011) 2. Subject has a MMSE score ≥18. 3. Subject is > 40 and <90 years of age. 4. Female subjects are post-menopausal or have a negative pregnancy test 5. The subject must be proficient in speaking, reading and understanding English in order to comply with procedural testing of cognitive function, memory and physiology. 6. Subject has a dedicated family member /caregiver, who will be able to attend all visits and report on subject's status. 7. Subject and family member/caregiver have both provided fully informed written consent prior to participation. In the event that subject is legally unable to provide informed written consent due to deterioration in cognitive abilities, fully informed written consent must be provided by a legally authorized representative. 8. Subject must have undergone a brain CT or MRI as part of receiving FTD diagnosis
EXCLUSION CRITERIA
1. Subject has medical history and/or clinically determined evidence of other CNS disorders including, but not limited to brain tumor, active subdural hematoma, seizure disorder, multiple sclerosis, Alzheimer's disease, vascular dementia, corticobasal syndrome, progressive supranuclear palsy, Parkinson's disease, multiple system atrophy, Lewy body dementia, normal pressure hydrocephalus, Huntington's disease, or Jakob-Creutzfeldt disease presenting as dementia. 2. Subject has medical history and/or clinically determined disorders: current B12 deficiency, chronic sinusitis, untreated thyroid disease, or significant head trauma.

3. Subject has history of any of the following: moderate to severe pulmonary disease, poorly controlled congestive heart failure, significant cardiovascular and/or cerebrovascular events within previous 6 months, condition known to affect absorption, distribution, metabolism, or excretion of drugs such as any hepatic, renal or gastrointestinal disease or any other clinically relevant abnormality that inclusion would pose a safety risk to the subject as determined by investigator.
4. Subject has had previous nasal and/or oto-pharyngeal surgery and severe deviated septum and/or other anomalies.
5. Subject has a history of any psychiatric illness that would pose a safety risk to the subject as determined by investigator.
6. Subject is currently taking any medications (anticholinergics, antihistamines, benzodiazepines, barbiturates, or insulin) that are clinically contraindicated as determined by investigator.
7. Subject has undergone a recent change (<1 month) in their SSRI or anti-depressant medication.
8. Subject has current or recent drug or alcohol abuse or dependence as defined by DSM-IV TR.
9. Screening laboratory results that are medically relevant, in which inclusion would pose a safety risk to the subject as determined by investigator.
10. The subject has participated in a clinical trial investigation within 1 month of this study.
11. The subject has an insulin allergy.

1 INTRODUCTION

1.1 Background/Rationale

Frontotemporal dementia (FTD) with its multiple pathological manifestations, is a disease that results in progressive deterioration of social comportment, executive function, and language. FTD refers to a continuum of disorders that includes behavioral variant frontotemporal dementia (bv-FTD), semantic dementia (SD), progressive non-fluent aphasia (PNFA), amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and corticobasal degeneration and is responsible for 12% of the cases of young onset dementia and represents the second most common cause of dementia in this population. In addition to the various clinical syndromes, FTD is associated with various neuropathological findings that include tar DNA binding protein-43 (TDP-43), tau, and fused in sarcoma (FUS). (Harvey et al., 2003).

Despite the debilitating nature of FTD and the relatively high prevalence in the younger patient population, available pharmacological interventions are limited to symptomatic treatments such as selective serotonin reuptake inhibitors (SSRIs) and neuroleptics that are geared toward behavioral management. Drugs approved by Food and Drug Administration (FDA) for AD have been found to ineffective in FTD as in the case of memantine (Boxer et al., 2013) or detrimental to behavioral symptoms as in the case of cholinesterase inhibitors (Mendez et al., 2007). Thus, there are no therapeutic agents that have been developed that specifically treat the progressive cognitive symptoms of FTD.

bv-FTD is the most common FTD clinical syndrome, representing 50-70% of cases within the U.S. and Europe (Bang et al., 2015), and leading to progressive dysfunction of neural networks responsible for social behavior, emotional regulation, theory of mind, and decision-making (Rosenbloom et al., 2012; Seelaar et al., 2011). The five major clinical features associated with bv-FTD are characterized by 1) early behavioral disinhibition; 2) early apathy or inertia; 3) early loss of sympathy or empathy; 4) early perseverative, stereotyped, or compulsive/ritualistic behavior; and 5) hyperorality and dietary changes (Rascovsky et al., 2011). bv-FTD has a variety of underlying pathologies that include tau 36-50% of the time, TDP-43 50% of the time, and FUS 10% of the time (Bang et al., 2015).

Semantic dementia (SD) or the semantic variant of primary progressive aphasia (sv-PPA) leads to progressive, focal atrophy of the anterior temporal lobe and amygdala. The clinical presentation varies based on the lateralization of neurodegeneration: left anterior temporal atrophy, which is the most common disease manifestation, results in a fluent aphasia consisting of deficits that involves language deficits whereas the right anterior temporal atrophy leads to behavioral changes (Bang et al., 2015). Common language manifestations include impaired object knowledge, surface dyslexia, and impaired single word comprehension (Bang et al., 2015). Although sv-PPA is most commonly associated with language dysfunction, patient with right anterior temporal atrophy manifest symptoms of social disinhibition, depression and aggressive behavior (Chan et al., 2009). sv-PPA is almost exclusively associated with TDP-43 neuropathology (Bang Lancet 2015).

The non-fluent variant of primary progressive aphasia (nfv-PPA) is the third most common clinical syndrome under the FTD umbrella and results from dominant hemispheric atrophy involving the insular cortex. Patients present with telegraphic, agrammatical speech, apraxia of speech and difficulty with comprehending complex sentences; there is relative sparing of object knowledge and single word

comprehension (Gorno-Tempini et al., 2011). Associated neuropathology includes tau (36-50%)>TDP43 (50%)>FUS (10%) (Bang Lancet 2015/Neumann Brain 2009).

For the purposes of this study, we are including subjects carrying the diagnosis of bv-FTD and sv-PPA while excluding nfv-PPA subjects as behavioral symptoms are less common in this FTD subtype.

Intranasal (IN) delivery offers a non-invasive route to deliver large molecules such as insulin directly to the brain while minimizing systemic exposure. Peptides, proteins, vaccines, drug treatments and ions of various sizes are able to pass along the olfactory and trigeminal nerves and are deposited directly into the CNS without having to pass through the blood brain barrier (BBB), which may degrade or limit the amount arriving at the target (Born et al., 2002; Derad et al., 1998; Dhanda et al., 2005; Garmise et al., 2007; Kern et al., 1997; Perras et al., 1999; Thorne et al., 1995; Thorne et al., 2004). CSF insulin levels in healthy adults have been detected as early as 10 minutes following IN delivery while not measurably increasing systemic blood-glucose levels (Born et al., 2002; Kern et al., 1999). Similar observations of the safety of IN insulin have been made in memory impaired adults (Reger et al., 2006; Reger et al., 2008).

Originally thought to exist solely in the periphery, insulin has since been determined to be instrumental in the overall health and function of the CNS (Zhao and Alkon, 2001). Central insulin and insulin receptors (IRs) have been established as differing from that of the systemically occurring counter parts that specifically regulate glucose utilization. In rodents, insulin receptors and insulin-sensitive glucose transporters are selectively co-localized in brain areas responsible for memory, thus providing a platform for insulin signaling whereby selective increases in cerebral glucose utilization could modulate memory (Craft and Watson, 2004; Watson and Craft, 2003). Consistent with evidence of insulin functioning as a neuromodulator for memory-related function is the high-density of IRs in the hippocampus and cerebral cortex, brain regions integral to the formation, retention and recall of information (Singh et al., 1997; Zhao and Alkon, 2001). Systems with impaired insulin signaling pathways have demonstrated inhibition of acetylcholine biosynthesis and subsequently have incurred debilitating effects on neuronal plasticity (Rivera et al., 2005; Stockhorst et al., 2004).

Increased insulin resistance and glucose intolerance has been observed in a multitude of neurodegenerative processes including Alzheimer's disease (Craft and Watson, 2004), Parkinson's disease (Sandyk, 1993), and Huntington's disease (Petersén and Björkqvist, 2006). Likewise, multiple investigations suggest a similar disturbance in frontotemporal dementia (FTD). Beyond the potential impact on cognitive and behavioral symptoms, IN insulin's role in FTD appears particularly relevant upon consideration of the high frequency of abnormal feeding behaviors and metabolic syndrome in this population. Approximately 60% of bv-FTD patients demonstrate hyperorality, binge-eating, and increased carbohydrate consumption upon clinical presentation (Piguet et al., 2009). Patients with bv-FTD consume more calories and have a greater predilection for sucrose-containing food products compared to AD (Ahmed et al., 2016a). This clinical characteristic is predominant enough such that it is one of the five major clinical features associated with bv-FTD and has been included in the international consensus criteria. In addition, changes in food consumption have also been observed in semantic dementia (SD). Brain regions linked to these eating disturbances have been identified in the frontoinsular cortex and anteromedial temporal brain areas (Whitwell et al., 2007; Woolley et al., 2007). Both bv-FTD and SD patients manifest systemic metabolic abnormalities that include increased triglyceride levels, insulin resistance, and reduced HDL levels relative to controls, suggesting the presence of a metabolic syndrome (Ahmed et al., 2014b). In addition, both conditions have elevated

body mass indices (BMI) compared to controls and bv-FTD patients have a higher prevalence of diabetes (Ahmed et al., 2016b). However, whether the metabolic syndrome is a contributing factor or the end product of a neurodegenerative process remains to be determined.

We proposed a pilot study of IN insulin in FTD, more specific bv-FTD and SD. The majority of clinical trials of dementia employ outcome measures that focus on memory and have greater relevance to Alzheimer's disease. For instance, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) is a battery that is heavily-weighted toward cognitive tasks affected in Alzheimer's disease, but would be unsuitable to measure change in FTD. For this reason, we will be utilizing the EXAMINER cognitive battery (https://memory.ucsf.edu/examiner) which was developed at the University of California, San Francisco to reliably and validly assess domains of executive function—the primary cognitive modality impacted in FTD. In addition, the battery includes outcomes with respect to social cognition. EXAMINER has the following attributes: modular (separate modules testing various elements of executive function), modifiable (any standard battery can be adapted to a range of experimental and clinical situations), efficient (relatively short administration time), applicable to a broad range of individuals from different age and ethnic groups, and reliable.

We aim to evaluate the feasibility of the EXAMINER cognitive battery as a cognitive outcome measure in FTD, the ability of our Center's ability to sufficiently recruit subjects with FTD, and the safety of IN regular insulin administered 20 IU BID in bv-FTD and SD over a 4 week period. Prior studies performed in the AD population have demonstrated favorable effects of this regimen in the MCI/AD population (Craft et al., 2012).

In addition, the clinical trial will investigate exploratory outcomes related to the effect of IN insulin on executive performance as measured by the EXAMINER battery and feeding behavior as measured by Change in Appetite and Eating Habits Questionnaire (APEHQ).

1.2 Supporting Data

Preclinical studies have suggested that insulin signaling deficits play a major role in the development of neurodegenerative diseases such as AD. Early in the course of AD reduced glucose utilization and deficient energy metabolism develop, thus indicating a role for IN insulin in the progression of this neurodegenerative disease (Steen et al., 2005). Although brain deposition of beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) are both critical pathological signatures of AD, they are also modulated by CNS insulin activity. As AD progresses, the presence of soluble Aβ aggregates further induces tau hyperphosphorylation as well as decreases the number of synaptic insulin receptors (IRs) (Craft and Watson, 2004). The down-regulation of dendritic surface IRs from accumulating Aβ compromises synaptic function in brain regions associated with memory and cognitive function, leading to the disruption in the insulin-signaling pathway that is characteristic of AD (Zhao et al., 2008). Insulin further inhibits neurofibrillary tangle production by maintaining a phosphorylation equilibrium between kinase and phosphatase activity (Craft, 2006; Hong and Lee, 1997; Planel et al., 2007; Wang et al., 2007). Such evidence of signaling deficits in AD have resulted in the theory of this condition representing a "type 3 diabetes" of the brain (Steen et al., 2005).

Clinical investigations of intranasal insulin in AD have demonstrated therapeutic effects impacting memory, attention and cognition without significantly altering serum insulin or glucose levels. A clinical trial consisting of 26 memory impaired subjects (13 with AD and 13 with mild cognitive impairment) and

35 normal controls showed that a single dose IN insulin 20 IU or 40 IU resulted in improvements on two declarative memory tasks compared to placebo within 15 minutes of drug administration (Reger et al., 2006). IN insulin administered at 20 IU resulted in greater story recall whereas doses at 40 IU more favorably improved word list recall. There was no impact on IN insulin on serum glucose or insulin levels. Another study of 24 early AD/mild cognitive impairment subjects showed that 20 IU BID of intranasal insulin resulted in sustained benefit in over a 21 day period (Reger et al., 2008). Furthermore, IN insulin induced favorable changes in the serum Aβ 40/42 ratio while having no impact on systemic glucose or insulin levels. Most recently, Craft and colleagues have demonstrated improved delayed memory and preserved caregiver-rated functional ability as represented by the ADAS-Cog and ADCS-ADL, respectively in MCI/AD patients treated with regular insulin 10 and 20 IU bid during a four month treatment trial (Craft et al., 2012). These changes in memory and function were associated with favorable changes in CSF tau and tau-Ab42 ratio. Additionally, IN insulin minimized progression in terms of loss of cerebral hypometabolism as measured by FDG-PET.

There have been no clinical investigations to our knowledge of IN insulin in FTD. Relative to other neurodegenerative processes, FTD is a more complex disorder to treat based on the multitude of underlying neuropathologies that include TDP-43, tau, and FUS proteins. However, there are multiple factors suggesting a role for insulin in modifying this disease process. Tau phosphorylation through the activity of the GSK-3B enzyme is a critical step in the formation of tau-based inclusions. Insulin has been shown to inhibit the enzyme GSK-3B, resulting in decreased tau phosphorylation and aggregation. Up to 50% of FTD pathology is associated with CNS tau deposition, and so this mechanism of action may benefit a substantial portion of individuals carrying the diagnosis (Baborie et al., 2011; Josephs et al., 2011; Sieben et al., 2012). In addition, evidence has suggested that intercellular spread of tau aggregates through a conformational change that resembles a prion-like mechanism may be responsible for the propagation of neurodegeneration in affected individuals (Holmes and Diamond, 2014). Targeted inhibitors of GSK-3B have already been tested in clinical trials for progressive supranuclear palsy, a neurodegenerative tauopathy that falls within the spectrum of FTD disorders (Tolosa et al., 2014). Finally, patients with FTD demonstrate regional FDG-PET involving the frontotemporal lobes, thus suggesting the possibility of abnormal regional glucose metabolism in this disorder (Foster et al., 2007).

2 Summary of Device Description

2.1 Intranasal device

The delivery of drugs to the CNS remains a development challenge mainly due to the impenetrable nature of the BBB. Device innovative approach enables broad, consistent drug delivery (either liquids or powders) to the upper area of the nasal cavity, which improves the absorption of the active ingredients when compared to commercial nasal delivery devices. Currently available nasal devices such as droppers, sprays, or pumps that deliver aerosol mainly to the lower and mid turbinate of the nasal cavity and only minor amounts, about 5% to the upper turbinate of the nasal cavity (Djupesland and Skretting, 2012). Device company has conducted animal studies using an aerosol nasal device with the same technology that is designed for humans. To address the different nasal cavity size and structure, adaptations were used for the device to fit each animal model.

The Aerosol nasal device is an aerosol nasal delivery platform that uses pressurized delivery through the discharge of compressed air, resulting in an aerosol that delivers the drug in a narrow plume geometry, which targets the olfactory epithelium in the upper nasal cavity. From the olfactory epithelium, therapeutics rapidly reach the central nervous system, traveling extracellularly along the olfactory nerves. The device is not currently commercially available, but numerous studies have demonstrated its ability to intranasally deliver radiolabeled and therapeutic compounds to the brain.

3 Objectives

3.1 Primary Objective

- Evaluate the feasibility of using the EXAMINER battery as a cognitive outcome measure in frontotemporal dementia (FTD)
- Evaluate the HealthPartners Center for Memory & Aging's recruitment capacity for FTD subjects Assess the safety and tolerability of intranasal (IN) insulin in FTD subjects

3.2 Secondary/Exploratory Objectives

- Evaluate the effect of IN insulin on executive function and behavior in FTD
- Evaluate the effect of IN insulin on eating behavior in FTD

4 Endpoint(s)

4.1 Primary Endpoints

- Number of subjects completing the EXAMINER battery
- Number of subjects enrolled
- Total number of AEs and SAEs

4.2 Secondary Endpoints

- Reasons for subjects failing to complete EXAMINER battery
- Number of subjects completing the study
- Number of screen failures
- Reasons for screen failure
- Number of unique subjects with an AE/SAE

4.3 Exploratory Endpoints

- Pre-post change in executive function and behavior (EXAMINER Battery)
- Pre-post change in Appetite and Eating Habits Questionnaire (APEHQ)

4.4 Safety

- Incidence and severity of serious adverse events (SAEs) and adverse events (AEs)
- Frequency of change in clinically-significant vital signs, physical exam or neurological exam
- Plasma glucose level <70mg/dl

5 Study Design

This study is a single center trial of intranasal (IN) regular insulin in subjects with probable behavioral variant FTD (bv-FTD) and semantic variant PPA (sv-PPA) and is designed to assess –

1) Evaluate the feasibility of using the EXAMINER battery as a cognitive outcome measure in frontotemporal dementia (FTD),
2) Evaluate the HealthPartners Center for Memory & Aging's recruitment capacity for FTD subjects and
3) Assess the safety and tolerability of intranasal (IN) insulin in FTD subjects.

After written informed consent has been obtained from the subject and family member/caregiver, subjects will be screened to assess study eligibility based on study inclusion/exclusion criteria. Subjects who are eligible at the end of the screening visit (Visit 1) will be scheduled for a baseline to take place 2 weeks later (Visit 2). During the baseline visit, subjects will be administered the EXAMINER battery and APEHQ questionnaire. A final safety/assessment visit will take place four weeks after visit 2 (Visit 3) at which time the EXAMINER battery and APEHQ questionnaire will be re-administered. There will be two phone visits (one between visit 2 and 3 and another after visit 3) to address study drug compliance and AEs/SAEs.

5.1 Drug Administration Training

All subjects and study partners will receive extensive training at each visit regarding home administration of IN insulin using the aerosol nasal device during visits 1 and 2 (screening and baseline, respectively). Subjects will be required to administer the dose twice daily, once in the morning and again in the evening (at least 8 hours between doses). Subjects will have the opportunity to immediately do a retrial administration if they are unsuccessful in releasing the study drug intranasally. If the aerosol nasal device is discharged prior to insertion into the nose, then a retrial admission would be indicated. However, if the device is discharged following nasal insertion, then a retrial would not be permitted. The steps to ensure that subjects maintain compliance with the study protocol over 4 weeks include administering the following:

- In-clinic training sessions: screening and baseline visits
- Phone call to assess drug compliance from study coordinator 2 weeks after baseline visit.

In addition to drug administration training, subjects will be given a daily Drug Diary to record the time and date of each self-administered dose, drug vial number and any comments for study staff. Instructions and training for the Drug Diary will be given to all subjects and study partners at the same times as the drug administration training.

5.2 Drug Administration with Aerosol Nasal Device

Each dosing administration will require the following items: a) 2 Devices each with a nose piece cover; b) Device holder; c) 10 ml vial of Regular Insulin (Novolin R); d) 2 Insulin syringes; e) alcohol wipe; f) needle clipper and/or sharps container.

During the baseline/initial treatment visit the subject/study partner will administer the study drug in front of study personnel to ensure adherence to study protocol for drug administration. To ensure safety and medication compliance, subjects will be followed-up with a routine phone call 2 weeks after

baseline (safety and drug compliance) and final treatment visit (safety). Non-insulin dependent diabetic subjects will monitor their fingerstick glucose as part of routine schedule as determined by their primary clinician/endocrinologist.

Devices will be shipped to the clinical study site. One device with a nose piece cover will be supplied for each dose to be administered in the study. A kit containing the necessary items will be distributed to each subject and replaced as necessary. This will include several extra devices in case there are issues with any devices. Each device is to be loaded with a 10 unit dose of regular insulin to be used immediately with up to a maximum of 10 minutes prior to IN administration. The Nose Piece and Secondary Drug Container (temporary) are the only components of the device that will come into contact with regular insulin and subject's nasal cavity.

5.3 Device Dose Loading and Administration

1. **The care partner will prepare device.**

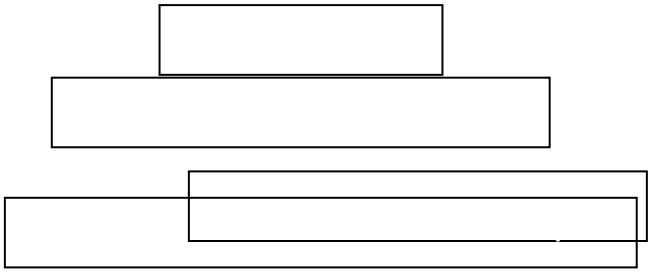
    a. Remove the syringe, device and study drug. Open the device covers and place devices in device holder (Figure 5). Carefully remove the cap from the syringe needle.
    The care partner will switch to a new study drug vial every two weeks during the dosing period. Study drug vials will be prepared by staff before subject and care partner receive them. Subjects will receive two vials of medication at the first dosing visit.

2. **The care partner will load the drug formulation into the devices.**

    a. Remove the cap from the top of the vial.

    b. Wipe the top of the vial with an alcohol wipe.

    c. Load the 0.1 ml desired regular insulin dose volume from the vial using the Insulin syringe.
        i. Immediately (within 10 minutes) before taking dose, load the devices with study drug.
        ii. Pull Syringe plunger to 0.1 ml
        iii. Insert syringe needle into the vial top, and push air into the vial
        iv. Turn the medication vial upside-down and slowly pull the syringe plunger down, withdrawing the study drug until 0.3ml line is visible just above the plunger. Tap the syringe to move any air bubbles to the top



v. Slowly push the plunger up to the 0.1ml line to push any air bubbles back into the vial. There should be a fluid level at the 0.1 ml line.
vi. Turn the medication vial upright and gently pull the syringe out without moving the plunger.

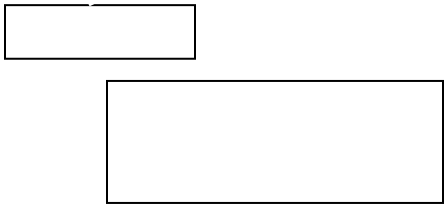
d. Insert the syringe with the needle carefully into the top of the device.

e. Slowly depress the syringe plunger, ensuring that no dose leaks. After the plunger is fully depressed, remove the syringe with the needle carefully from the device and leave the device in the device holder.
f. Dispose of the syringe and the needle by using a needle clipper and or in a sharps container.
g. Repeat these steps, using another syringe for the second device.

3. Subject will blow their nose prior to administering the first dose.
4. Subject will turn the device upside down and flick the nose piece to allow the drug to concentrate at its edge as shown in the figure. This helps the subject to see if the drug is loaded prior to administration.
5. The research staff will provide guidance to the subject on placement for nasal administration for the first dosing.
   a. Place the nose piece of the device comfortably in the nose as shown in the figure below.
   b. After the initial placement, the examiner will make slight adjustments to orient the nose piece in the proper direction.

6. Press the activation button to administer the drug in the nasal cavity.

7. Steps 3-5 will be repeated for the other nostril using the second prepared device.



5.4 Outcome Measures

Neuropsychological and behavioral batteries will be performed at baseline and visit 3 (see section 7.4 for additional details).

5.5 Study Duration

Study participation will last approximately 9 weeks, consisting of a screening visit, baseline visit, follow-up assessment visit and two phone call visits. Subjects will receive treatment for a period of 4 weeks. Subjects who discontinue treatment will continue follow-up measures as possible.

6 Study Population

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

1. Male or female subjects meeting international consensus criteria for probable behavioral variant frontotemporal dementia or criteria for semantic dementia (Gorno-Tempini et al., 2011; Rascovsky et al., 2011)
2. Subject has a MMSE score ≥18.
3. Subject is > 40 and <90 years of age.
4. Female subjects are post-menopausal or have a negative pregnancy test
5. The subject must be proficient in speaking, reading and understanding English in order to comply with procedural testing of cognitive function, memory and physiology.
6. Subject has a dedicated family member /caregiver, who will be able to attend all visits and report on subject's status.
7. Subject and family member/caregiver have both provided fully informed written consent prior to participation. In the event that subject is legally unable to provide informed written consent due to deterioration in cognitive abilities, fully informed written consent must be provided by a legally authorized representative.
8. Subject must have undergone a brain CT or MRI as part of receiving their FTD diagnosis

6.1.2 Exclusion Criteria

A subject will not be included for consideration in this study if any of the following criteria are met:

1. Subject has medical history and/or clinically determined evidence of other CNS disorders including, but not limited to brain tumor, active subdural hematoma, seizure disorder, multiple sclerosis, Alzheimer's disease, vascular dementia, corticobasal syndrome, progressive supranuclear palsy, Parkinson's disease, multiple system atrophy, Lewy body dementia, normal pressure hydrocephalus, Huntington's disease, or Jakob-Creutzfeldt disease presenting as dementia.
2. Subject has medical history and/or clinically determined disorders: current B12 deficiency, chronic sinusitis, untreated thyroid disease, or significant head trauma.
3. Subject has history of any of the following: moderate to severe pulmonary disease, poorly controlled congestive heart failure, significant cardiovascular and/or cerebrovascular events within previous 6 months, condition known to affect absorption, distribution, metabolism, or excretion of drugs such as any hepatic, renal or gastrointestinal disease or any other clinically relevant abnormality that inclusion would pose a safety risk to the subject as determined by investigator.
4. Subject has had previous nasal and/or oto-pharyngeal surgery and severe deviated septum and/or other anomalies.
5. Subject has history of any psychiatric illness that would pose a safety risk to the subject as determined by investigator.
6. Subject is currently taking any medications (anticholinergics, antihistamines, benzodiazepines, barbiturates, or insulin) that are clinically contraindicated as determined by investigator.
7. Subject has undergone a recent change (<1 month) in their SSRI or anti-depressant medication.
8. Subject has current or recent drug or alcohol abuse or dependence as defined by DSM-IV TR.
9. Screening laboratory results that are medically relevant, in which inclusion would pose a safety risk to the subject as determined by investigator.

10. The subject has participated in a clinical trial investigation within 1 month of this study.
11. The subject has an insulin allergy.

7 Study Assessments and Procedures

A summary of study events and procedures is outlined in the Study Visit Table. Demographic, Screening, and Baseline Assessments are described in Sections 7.1.1-7.1.2, the Treatment Phase is outlined in Sections 7.1.2-7.1.4, and the safety monitoring are detailed in Section 7.1.5; details of neuropsychological assessments are outlined in Section 7.4. Note that all visits are fasting unless otherwise noted.

7.1 Demographic and Baseline Assessments

7.1.1 Visit 1: Screening (Week-2)

The following procedures will be performed at this visit:

- Obtain written informed consent from study partner and subject (or subject's legally authorized representative) prior to any study related procedures.
- Review Inclusion/Exclusion Criteria.
- Review medical history, as it pertains to inclusion/exclusion criteria, such as research diagnosis, disease severity, and course of FTD
- Obtain subject's demographic information (date of birth, gender, race, education, etc.).
- Obtain details of medications taken over the course of the last 30 days.
- Complete physical exam, including neurological exam. Collect vital signs, height and weight prior to ECG and blood draw.
- Administer MMSE
- Obtain laboratory studies
- Perform a standard 12-lead ECG.
- Serum pregnancy test in women of child bearing potential
- Study Drug administration training; Hypoglycemia rescue training
- Visit 2 will be scheduled within 2 weeks (± 5 days).

7.1.2 Visit 2: Baseline/Initial Treatment Visit (Week 0)

The following procedures will be performed at this visit:

- Review Inclusion/Exclusion Criteria.
- Collect vital signs and weight.
- Collect concomitant medication information and record AEs/SAEs.
- Neuropsychological testing with EXAMINER
- Administer APEHQ
- Administer C-SSRS
- Study Drug administration training (following testing with EXAMINER).
- Hypoglycemia rescue training.
- First dose of intranasal insulin administered
- Finger glucose stick at baseline prior to first dose, and at 15 and 30 min after first dose
- Phone visit will be scheduled in 2 weeks (± 3 days).
- Visit 3 will be scheduled in 4 weeks (± 5 days).

7.1.3 Phone Visit 1: Safety Check (Week 2)

- Study staff phone call to address IN insulin compliance and AEs/SAEs
- Reminder to take the last dose the night before visit 3.

7.1.4 Visit 3: Final Treatment and Safety Visit (Week 4)

The following procedures will be performed at this visit:

- Collect vital signs and weight.
- Collect concomitant medication information and record AEs/SAEs.
- Review/collect AE/SAE information
- Physical and neurological examination
- Neuropsychological testing with EXAMINER
- Administer APEHQ
- Administer C-SSRS
- Obtain laboratory studies
- Phone visit will be scheduled in 2 weeks (± 3 days).

7.1.5 Phone Visit 2: Safety Check (Week 6)

- Study staff phone call to address AEs/SAEs

7.2 Early Withdrawal

If subject withdraws from the study after the screening visit, but before visit 2, no further evaluations are necessary. If subject withdraws from the study after visit 2, all safety assessments will be performed (see section 7.3).

7.3 Safety

For all safety assessments described below, any clinically significant change will be recorded as an AE or SAE.

7.3.1 Physical Examination

Complete physical examination will be performed at visits, 1 and 3, or if the subject withdraws or is withdrawn from the study early. Any abnormalities noted at Visit 1, will be documented as part of the subject's medical history.

7.3.2 Neurological Examination

Neurological examination will be performed at visits 1, 3 or if the subject withdraws early. Any abnormalities noted at Visit 1, will be documented as part of the subject's medical history.

7.3.3 Vital Signs

Vital signs will be recorded at all visits. For within subject consistency, brachial artery pressure will be obtained in the routine fashion.

Blood pressure and heart rate to be measured after subject has been sitting quietly for a minimum of 5 minutes. Diastolic blood pressure will be measured at the disappearance of Korotkoff sounds. Vitals sign will be monitored by clinical staff during each visit of the study.

A blood glucose < 70 mg/dL will be considered clinically significant. Subjects will be given training regarding hypoglycemic rescue therapy and contacting 911 in severe cases. Any episodes will be reported to the study coordinator and research team. The likelihood of peripheral hypoglycemia is relatively low based on numerous clinical trials performed in the AD and healthy aging population showing no effects of IN insulin on peripheral glucose.

Vital signs will be taken prior to ECG and blood draw.

7.3.4 Weight

Body weight will be measured at all visits.

7.3.5 ECG

A standard 12-lead ECG will be performed on subjects at visit 1.

7.3.6 Laboratory Samples

All subjects will be required to fast for a minimum of 12 hours prior to collection of blood sampling.

See Table 1 for a specific list of laboratory assessments.

Table 1: Schedule of Assessments

Assessment/ Procedure	**Visit 1: Screen**	**Visit 2: Baseline/Initial Treatment**	**Phone Visit 1: Safety Check**	**Visit 3: Final Treatment / Safety**	**Phone Visit 2: Safety Check**	**Early Withdrawal**
			☎		☎	
Schedule - Week and Windows	**- 2**	0	2	4	6	
		± 5 days	**± 3 days**	**± 5 days**	**± 3 days**	
Informed consent	**X**					
Review of inclusion/exclusion criteria	**X**	**X**				
Medical History, demographic	**X**					
Physical/neurological exam	**X**			**X**		X
Vital signs	**X**	**X**		X		X
Height	**X**					
Weight	**X**	**X**		**X**		**X**
12-lead ECG	**X**					
Basic Metabolic Panel (Na, K, CO2, CL, BUN, Creatinine, Glucose and Ca)	**X**			**X**		**X**
Insulin Level	**X**			**X**		
HbA1c	**X**					
Thyroid Stimulating Hormone (TSH)	**X**					
Vitamin B12	**X**					
Pregnancy Test (in females)	**X**					
EXAMINER BATTERY		**X**		**X**		
MMSE	**X**					
APEHQ		**X**		**X**		
C-SSRS		**X**		**X**		**X**
Study Drug administration training	**X**	**X**				
Hypoglycemia rescue training	**X**	**X**				
Glucose finger sticks (baseline before 1st dose; 15 & 30 minutes after 1st dose)		**X**				
Concomitant mediations		**X**		**X**		
IN INSULIN compliance			**X**			
Adverse events		**X**	**X**	**X**	**X**	**X**

7.4 Neuropsychological Assessment

See Table 1 for a specific list of neuropsychological assessments

7.4.1 EXAMINER BATTERY

The EXAMINER battery was developed at the University of California, San Francisco Memory and Aging Center as a means of validly assessing domains of executive function in an assortment of ages and disorders to capture real-life social and executive deficits in subjects with frontal lobe disorders (http://www.memory.ucsf.edu). The battery consists of subtests in a variety of domains that include working memory, inhibition, set-shifting, fluency, planning, insight, and social cognition/behavior.

7.4.1.1 Working Memory Subtests:

7.4.1.1.1 Dot Counting:

The dot counting task measures verbal working memory. The examinee is asked to look at a screen with a mixed array of green circles, blue circles and blue squares. The examinee is asked to count all of the blue circles on the screen one at a time, out loud and remember the final total. Once the examinee finishes counting the blue circles on one screen, the examiner switches the display to a different mixed array of green circles, blue circles and blue squares. The examinee is instructed to count the blue circles in the new display. The number of different displays presented to the examinee in each trial increases from two to seven over six experimental trials. After counting the blue circles on all of the displays presented within a trial, the examinee is asked to recall the total number of blue circles that were counted in each of the different displays in the order in which they were presented. Partial credit is given based on how many totals the examinee can recall correctly from each trial.

7.4.1.1.2 N-Back

The n-back paradigm is a widely used measure of working memory that requires flexible updating capabilities. EXAMINER includes a spatial 1-back and 2-back task to assess spatial working memory. The 1-back requires maintaining and updating 1 location at a time, whereas the more difficult 2-back requires maintaining and updating 2 locations.

7.4.1.2 Inhibition

7.4.1.2.1 Flanker

A row of five arrows is presented in the center of the screen. The examinee is required to indicate whether the centrally presented arrow is pointing either to the left or right by pressing the left or right arrow key. The examinee is presented with two different conditions during the task, incongruent and congruent. In the congruent trials, the non-target arrows point in the same direction as the target arrow and in the incongruent trials they point in the opposite direction. Examinees should respond as quickly and accurately as possible.

7.4.1.2.2 Continuous Performance Task

The continuous performance task is a classic response inhibition task, which requires subjects to respond to a certain type of stimulus and withhold a response to another.

7.4.1.2.3 Anti-saccades

The subjects look at a fixation point in the center of a computer screen and move their eyes upon presentation of a laterally presented stimulus. In the first block (pro-saccade), subjects are instructed to move their eyes in the direction of the presented stimulus. In the second and third blocks (anti-saccade), subjects are instructed to move their eyes in the opposite direction of the presented stimulus.

7.4.1.2.4 Dysexecutive Errors

An underlying assumption in developing the EXAMINER battery is that executive related deficits can manifest as impulsive errors, failure to shift set, perseverative behavior, and stimulus-boundedness, even when achievement scores on tests are unremarkable. Accordingly, we generated a composite error score using false responses and rule violations on a variety of EXAMINER tasks, including: CPT, verbal fluency tasks, Flanker, and Set Shifting.

7.4.1.3 Set-Shifting

Subjects are required to match a stimulus on the top of the screen to one of two stimuli in the lower corners of the screen. In task-homogeneous blocks, subjects perform either Task A (e.g., classifying shapes) or Task B (e.g., classifying colors). In task-heterogeneous blocks, subjects alternate between the two tasks pseudo-randomly. The combination of task-homogeneous and task-heterogeneous blocks allows measurement of general switch costs (latency differences between heterogeneous and homogeneous blocks) and specific switch costs (differences between switch and non-switch trials within the heterogeneous block).

7.4.1.4 Fluency

7.4.1.4.1 Phonemic Fluency

For the phonemic fluency task, examinees are instructed to name as many words as they can that begin with a particular letter of the alphabet as quickly as they can. Sixty seconds are allowed for each letter.

7.4.1.4.2 Categorical Fluency

For the category fluency task, examinees are asked to generate as many items that they can think of that belong to a particular category as quickly as possible. Sixty seconds are allowed for each category.

7.4.1.5 Planning

7.4.1.5.1 Unstructured Task

This task was modeled after the 6-elements test (Shallice and Burgess, 1991). Subjects are presented with three booklets, each containing five pages of simple puzzles (4 per page).The puzzles were designed to be cognitively simple (e.g., connect the dots; trace the design) but average completion times range from 4 to 60 seconds. Each puzzle has a designated point value, and subjects are given 6 minutes to earn as many points as possible. Irrespective of actual point value, puzzles can have a high cost-benefit ratio (i.e., the time required to complete the puzzle makes it less desirable) or a low cost-benefit ratio (i.e., the time required to complete the puzzle makes it more desirable). In addition, the proportion of low cost-benefit items decreases as subjects proceed through a booklet. Subjects need to plan ahead, avoid items that are strategically poor choices, and be cognizant of when a particular booklet offers diminishing returns.

7.4.1.6 Insight

Examinees are asked to rate themselves on their performance immediately after completing the well-normed verbal fluency tasks. They are instructed to assess their own performance relative to a hypothetical sample of 100 people of a similar age and level of education.

7.4.1.7 Social Cognition and Behavior

7.4.1.7.1 Social Norms Questionnaire

This task measures subjects' crystallized knowledge of social norms in a linguistically and cognitively simple manner. This yes-no questionnaire is designed to determine the degree to which subjects actually understand and can accurately identify implicit but widely accepted social boundaries in the dominant U.S. culture. The Social Norms Questionnaire includes both socially inappropriate behaviors (e.g., "Cut in line if you are in a hurry," "Pick your nose in public,") and generally acceptable behaviors (e.g., "Tell a coworker your age"). The subject must decide whether the behavior is socially appropriate or not if it were hypothetically enacted with an acquaintance or coworker.

7.4.1.7.2 Behavioral Rating Scale

This rating scale is completed by the examiner after completion of the testing. Examiners restrict their ratings to behaviors that they have observed directly, but include all observed behaviors, regardless of the context. Thus, although behaviors during the actual assessment will likely provide the bulk of data, examiners should also note behaviors exhibited in all other situations, such as the waiting room and walking to and from the exam room. There are nine behavioral domains to rate, including agitation, stimulus-boundedness, perseverations, decreased initiation, motor stereotypies, distractibility, degree of social/emotional engagement, impulsivity, and social appropriateness.

7.4.2 Appetite and Eating Habit Questionnaire (APEHQ)

The APEHQ consists of 34 questions that examine changes in eating behaviors in the following domains: swallowing, appetite, eating habits (stereotypic eating behavior and table manners), food preference (including sweet preference and other food fads), and other oral behaviors (eg, food cramming, increased smoking). Caregivers are asked to rate the frequency (0 = never, 1 = less than weekly, 2 = about once a week, 3 = several times a week, 4 = daily or continuously) and severity (0 = N/A [not applicable], 1 = mild, 2 = moderate, and 3 = marked) for each behavior. A composite score of frequency × severity is calculated for each question, and an overall score derived for each domain (Ahmed et al., 2014a).

7.4.3 Columbia-Suicide Severity Scale 0 (C-SSRS)

The Columbia–Suicide Severity Rating Scale (C-SSRS) was designed to quantify the severity of suicidal ideation and behavior (Posner K, 2011). In this study, suicidal ideation and behavior will be prospectively assessed using the C-SSRS. The C-SSRS will be administered by trained raters at specified time points, as indicated in table 1 as well as when clinically indicated. Any subjects demonstrating evidence of suicidality will prompt immediate consultation with the site's on-call psychiatrist for assistance with decision-making and potential referral to behavioral health services.

8 Investigational Product(s)

8.1 Description of Investigational Product

The Center for Memory & Aging will utilize the following investigational products:

- Intranasal delivery route
- Regular insulin [(Novolin-R); see section15.3]
- Aerosol nasal device(Sections 2, 5.2, 5.3, 15.2 and Investigator's brochure- 15.1)

8.2 Handling and Storage

The study drug (insulin) will be given to subject/care partner after training for administration at visit 2.

Subjects will be instructed to keep study drug at room temperature according to label recommendations.

The study drug will be kept at study site per label recommendations and institutional Standard Operational Policy. To ensure that a stable temperature and/or conditions are maintained, site staff will verify and document refrigerator/room temperature at a minimum of three times per week or monitored continuously if automated systems such as temp trak are used. A log will be securely stored

at the HealthPartners Center for Memory & Aging. Study staff will be responsible for safeguarding and maintaining the master log.

8.3 Packaging and Labeling

All study drug will be labeled according to the following specifications:

- Protocol identifier/IRB study number
- Quantity statement
- Subject ID #
- "For Clinical Trial Use Only"
- Study contact # 651-495-6262

8.4 Occupational Safety

No known significant safety risks exist to site personnel in direct or indirect contact with the study drug.

9 Concomitant Medications and Non-Drug Therapies

9.1 Permitted Medications

Any medication not listed in list of Prohibited Medications (Table 2) will be permitted during this study. A record will be kept by site staff detailing doses and indication of any concomitant medications used by subjects.

9.2 Prohibited Medications

Subjects taking prohibited medications at time of screening will not be allowed to participate in study, unless such treatment is discontinued at least 30 days prior to screening. These medications include anticholinergics, and centrally acting antihistamines (e.g. Benadryl), opiates, benzodiazepines, barbiturates, muscle relaxants, and insulin. Randomized subjects taking a prohibited medication (episodic or PRN) will be considered for study participation on an individual basis.

Table 2: Prohibited Medications

Anticholinergics
Antihistamines (centrally-acting)
Barbiturates
Benzodiazepines
Insulin
Muscle relaxants
Opioids

10 Subject Completion and Withdrawal

10.1 Subject Completion

Subjects completing all 5 study visits (including the 2 phone visits) will be considered to have completed study.

10.2 Subject Withdrawal

Subject may withdraw from study at any time for any reason without penalty or be terminated from the study by the clinical investigator (see provisions for termination by study team.) Investigational team will document the reason(s) for withdrawal. In the event a subject chooses to withdraw from study before Visit 3, the safety procedures described in Section 7.3 will be performed ideally within 3 days following subject's decision to withdraw. For all subjects who withdraw, all final safety assessments will be collected regardless of time elapsed since previous visit. In addition to the termination visit, subjects who withdraw early will be contacted within 7 days by study staff via telephone to assess development of new and/or ongoing AEs and concomitant medications. Efforts will be made to recruit subjects to replace any withdrawals at any point so as to maintain an n=12.

Subject's participation may be terminated at the discretion of the investigator. Individuals may be withdrawn for the following reasons:

- Clinically significant adverse events
- Lost to follow-up
- Protocol violations
- Inability to tolerate study medication
- Other

11 Adverse Events (AE) and Serious Adverse Events (SAE)

11.1 Definition of AE

An adverse event is any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with clinical signs or symptoms
- Leads to treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

11.2 Definition of SAE

Adverse events are classified as either serious or non-serious. A serious adverse event is any event that results in:

- Death
- Life-threatening situation
- Hospitalization or prolongation of hospitalization
- Disability or incapacitation

- Other events determined by investigator to be medically significant in which subject's well-being is jeopardized (e.g. events that have high likelihood of escalating to the point of meeting criteria outlined above)

11.2.1 Clinical Laboratory Abnormalities & Other Abnormal Assessments as AEs & SAEs

Any new abnormal, vital, examination, or laboratory finding judged clinically significant by the investigator will be documented as an AE or SAE, if meeting the definitions for such. Abnormal lab findings or other abnormal assessments associated with the disease under study will not be considered AEs or SAEs unless more severe than expected, as judged by the investigator.

11.2.2 Time Period and Frequency of Detecting AEs and SAEs

Upon consenting, a subject is considered to be a subject in the study, and until that person either withdraws or completes study, AEs and SAEs will be recorded. The investigational team will promptly report any AE/SAE as required per federal guidelines.

11.2.3 Device Failures and Malfunctions

Device Quality Control. All failures, performance issues and malfunctions of the device as reported by the participants will be reported to Device company.

12 Data Analysis and Statistical Considerations

12.1 Analysis Overview

The study population will be summarized descriptively by demographics and baseline clinical values. Clinical values will include scores from all components of the EXAMINER battery as well as other neuropsychological assessment scores, vital signs, and laboratory values. We will examine the distribution of our exploratory endpoints (the EXAMINER battery and APEHQ scores) using graphs and measures of normality to ensure we have planned the appropriate analyses.

Main analyses of these scores will only include subjects with non-missing data. Reason for missing data will be reported as often as possible to better inform future studies. Sensitivity analyses will be conducted to compare baseline values of tests between subjects who were able to complete the study and those who withdrew early. Neither methods of imputation nor adjustment for multiple comparisons will be utilized as they were deemed too conservative for this feasibility study. All statistical analyses will be conducted in SAS Version 9.4 using a 0.05 level of significance unless otherwise stated.

12.2 Statistical Analysis of Primary Outcomes

To evaluate the feasibility of using the EXAMINER battery as a cognitive outcome measure in the FTD population, we will report the number and percentage of our sample who were able to complete the battery. We will also document any reasons for incomplete data. We will then describe any factors that affect implementation ease or difficulty including battery components that were more challenging for subjects with advanced FTD. Finally, we will discuss the speed and efficiency of administering the tool.

The Center for Memory & Aging's recruitment capacity will be assessed by reporting the number and percentage of subjects who were: 1. contacted for participation, 2. screened, 3. screened positive, 4. able to complete the study. We will also report the average number of visits attended by our sample and any reason for screen failure or early withdrawal.

The number of unique subjects who experienced an adverse event or serious adverse event as well as the total number of each will be reported. A brief written description of these events will be provided. Suicidality, as assessed by the C-SSRS, will be included as an adverse event.

12.3 Statistical Analysis of Exploratory Outcomes

Four summarizing scores are calculated and output using the EXAMINER battery: 1. Executive Composite Score, 2. Fluency Factor Score, 3. Cognitive Control Factor Score, and 4. Working Memory Factor Score. Five domains are assessed by the APEHQ: 1. swallowing, 2. appetite, 3. eating habits, 4. food preferences, and 5. other oral behaviors. For each of these scores, we will report the mean and standard deviation from both time points as well as calculate the pre-post change among subjects who completed the two assessments. We will utilize these values to better inform future studies about possible effect sizes and do not anticipate seeing a significant change. Therefore, no inferential statistics will be performed; we will simply describe any trends we might see.

To account for missing data, UCSF is developing a formula for a global executive score called an Item Response Theory (IRT) derived score, which our researchers will also calculate. Currently, this score formula is not yet finalized by UCSF, however, it will not require any additional information or testing by patients; we plan to include this calculation in our final analyses.

Insulin levels and basic metabolic panel values (Na, K, CO2, Cl, BUN, Creatinine, Glucose and Ca) will be summarized at each time point using means and standard deviations. Changes will be discussed descriptively.

As a sensitivity analysis, we will also descriptively compare baseline EXAMINER scores, APEHQ scores, and laboratory values between subjects who completed the study and those who withdrew early or were unable to complete the final battery.

12.4 Statement of Precision

The main purposes of this study are to assess the feasibility of using the EXAMINER battery as a cognitive outcome assessment tool and evaluate the Center for Memory & Aging's ability to recruit within the FTD population. We will consider it to be feasible if at least 80% of our sample is able to complete the battery and we are able to recruit 12 subject within our enrollment period. With a sample size of 12, we will be able to estimate an EXAMINER battery completion rate of 80% to within a 95% confidence interval of ±22.6%. We do not except to see significant changes in the exploratory outcomes (EXAMINER, APEHQ, and laboratory values) and, therefore, have not included a power calculation for these outcomes.

13 Study Conduct Considerations

13.1 Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with GCP. Subject privacy requirements will also be observed as well as the fundamental concepts of the Declaration of Helsinki (e.g. IRB approval of the study,

obtaining informed consent from all subjects, and meeting reporting requirements). The clinical trial will be registered on the clinicaltrials.gov website.

13.2 Data Safety Monitoring Board

The DSMB will be an independent group who are not participating in the trial and have no direct affiliation with HealthPartners Center for Memory & Aging. They will serve as an advisory panel to HealthPartners Center for Memory & Aging. The DSMB will be comprised of a neurologist, statistician, and intranasal insulin researcher. An un-blinded study liaison will participate in open sessions of the DSMB and serve as a liaison to the study team. A DSMB Charter will be established prior to initiation of the study. The DSMB responsibilities include but are not limited to the following:

- Stopping the study if the rate of SAE's raises safety concerns. The details will be specified in the DSMB charter.

The DSMB will convene following the study completion of 6 subjects or earlier in the case of SAEs. During the course of the trial, the DSMB will review accumulating safety data to monitor for incidence of trends that would warrant termination of the trial. The frequency of the DSMB meetings, responsibilities, membership, and procedures will be documented in the DSMB charter.

13.3 Quality Assurance

In the event of a regulatory agency audit or inspection, site will allow the auditor/inspector access to all records documented and facilities utilized in conducting the study. Site will also make accommodations (e.g. time, schedule) to discuss findings, concerns, and questions with auditor/inspector.

13.4 Study Closure

Upon completion of all subject visits, data entry and analysis, investigator will inform local IRB of study closure.

13.5 Records Retention

All site records will be maintained and stored in a safe and secure location for a minimum of 15 years post study completion.

13.6 Provision of Study Results and Information to Investigators

Study results will be made available by the study statistician once analysis is complete.

13.7 Data Management

Data collection/reporting tools will be developed internally (i.e. CRFs and source documents). Data collected and stored electronically will remain confidential and secure (e.g. secured server, encrypted data, password protected file)

13.8 Device Accountability

A Device Tracking Log will be maintained at the investigational site. Aerosol nasals will be recorded on the log upon delivery to the investigational site and will be stored in a secured area. The Device Tracking Log will be updated as each device is delivered, dispensed, returned and the reason for the return. Serial numbers, expiration date and model number of devices delivered to the site will also be recorded.

14 References

Ahmed, R.M., et al., 2014a. Quantifying the eating abnormalities in frontotemporal dementia. JAMA neurology. 71**,** 1540-1546.

Ahmed, R.M., et al., 2014b. Systemic metabolism in frontotemporal dementia. Neurology. 83**,** 1812-1818.

Ahmed, R.M., et al., 2016a. Assessment of eating behavior disturbance and associated neural networks in frontotemporal dementia. JAMA neurology. 73**,** 282-290.

Ahmed, R.M., et al., 2016b. Amyotrophic lateral sclerosis and frontotemporal dementia: distinct and overlapping changes in eating behaviour and metabolism. The Lancet Neurology. 15**,** 332-342.

Baborie, A., et al., 2011. Pathological correlates of frontotemporal lobar degeneration in the elderly. Acta neuropathologica. 121**,** 365-371.

Bang, J., Spina, S., Miller, B.L., 2015. Frontotemporal dementia. Lancet. 386**,** 1672-82.

BD. BD Insulin Syringes with Ultra-Fine Needle. Vol., ed.^eds.

Born, J., et al., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci. 5**,** 514-6.

Boxer, A.L., et al., 2013. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 12**,** 149-156.

Chan, D., et al., 2009. The clinical profile of right temporal lobe atrophy. Brain. 132**,** 1287-1298.

Craft, S., Watson, G.S., 2004. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 3**,** 169-78.

Craft, S., 2006. Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. Alzheimer Dis Assoc Disord. 20**,** 298-301.

Craft, S., et al., 2012. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Archives of Neurology. 69**,** 29-38.

Derad, I., et al., 1998. Intranasal angiotensin II directly influences central nervous regulation of blood pressure. Am J Hypertens. 11**,** 971-7.

Dhanda, D.S., et al., 2005. Approaches for Drug Deposition in the Human Olfactory Epithelium. Drug Delivery. 5**,** 64-72.

Djupesland, P.G., Skretting, A., 2012. Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. Journal of aerosol medicine and pulmonary drug delivery. 25**,** 280-289.

Foster, N.L., et al., 2007. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain. 130**,** 2616-2635.

Garmise, R.J., Staats, H.F., Hickey, A.J., 2007. Novel dry powder preparations of whole inactivated influenza virus for nasal vaccination. AAPS PharmSciTech. 8**,** E81.

GLUCOPRO. GLUCOPRO Insulin Syringe. Vol., ed.^eds.

Gorno-Tempini, M.L., et al., 2011. Classification of primary progressive aphasia and its variants. Neurology. 76**,** 1006-1014.

Grajower, M.M., et al., 2003. How long should insulin be used once a vial is started? Diabetes Care. 26**,** 2665-2669.

Guo, C., et al., 2009. Evaluation of Impaction Force of Nasal Sprays and Metered-Dose Inhalers Using the Texture Analyser☆. Journal of pharmaceutical sciences. 98**,** 2799-2806.

Harvey, R., Skelton-Robinson, M., Rossor, M., 2003. The prevalence and causes of dementia in people under the age of 65 years. Journal of Neurology, Neurosurgery & Psychiatry. 74**,** 1206-1209.

Holmes, B.B., Diamond, M.I., 2014. Prion-like properties of Tau protein: the importance of extracellular Tau as a therapeutic target. Journal of Biological Chemistry. 289**,** 19855-19861.

Hong, M., Lee, V.M., 1997. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. J Biol Chem. 272**,** 19547-53.

Josephs, K.A., et al., 2011. Neuropathological background of phenotypical variability in frontotemporal dementia. Acta neuropathologica. 122**,** 137-153.

Kern, W., et al., 1997. Evidence for central nervous effects of corticotropin-releasing hormone on gastric acid secretion in humans. Neuroendocrinology. 65**,** 291-8.

Kern, W., et al., 1999. Central nervous system effects of intranasally administered insulin during euglycemia in men. Diabetes. 48**,** 557-63.

Mendez, M.F., et al., 2007. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry. 15**,** 84-7.

MONOJECT. MONOJECT SoftPack .5 cc/ml Insulin Syringe. Vol., ed.^eds.

Perras, B., et al., 1999. Sleep and endocrine changes after intranasal administration of growth hormone-releasing hormone in young and aged humans. Psychoneuroendocrinology. 24**,** 743-57.

Petersén, Å., Björkqvist, M., 2006. Hypothalamic–endocrine aspects in Huntington's disease. European Journal of Neuroscience. 24**,** 961-967.

Piguet, O., et al., 2009. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. Neurology. 72**,** 732-737.

Planel, E., et al., 2007. Insulin dysfunction induces in vivo tau hyperphosphorylation through distinct mechanisms. J Neurosci. 27**,** 13635-48.

Posner K, B.G., Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ, 2011. The Columbia-Suicide Rating Scale: Initial Validity and Internal Consistency Findings from Three Mulitsite Studies with Adolescents and Adults. Am J Psychiatry. 168**,** 1266-1277.

Rascovsky, K., et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 134**,** 2456-77.

Reger, M.A., et al., 2006. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging. 27**,** 451-8.

Reger, M.A., et al., 2008. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology. 70**,** 440-8.

Rivera, E.J., et al., 2005. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 8**,** 247-68.

Rosenbloom, M.H., Schmahmann, J.D., Price, B.H., 2012. The functional neuroanatomy of decision-making. The Journal of neuropsychiatry and clinical neurosciences. 24**,** 266-277.

Sandyk, R., 1993. The relationship between diabetes mellitus and Parkinson's disease. International Journal of Neuroscience. 69**,** 125-130.

Sastri, V.R., 2013. Plastics in medical devices: properties, requirements, and applications, Vol., William Andrew.

Seelaar, H., et al., 2011. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. Journal of Neurology, Neurosurgery & Psychiatry. 82**,** 476-486.

Shallice, T., Burgess, P.W., 1991. Deficits in strategy application following frontal lobe damage in man. Brain. 114**,** 727-741.

Sieben, A., et al., 2012. The genetics and neuropathology of frontotemporal lobar degeneration. Acta neuropathologica. 124**,** 353-372.

Singh, B.S., et al., 1997. Insulin gene expression in immortalized rat hippocampal and pheochromocytoma-12 cell lines. Regul Pept. 69**,** 7-14.

Steen, E., et al., 2005. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis. 7**,** 63-80.

Stockhorst, U., et al., 2004. Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans. Physiol Behav. 83**,** 47-54.

Thorne, R.G., et al., 1995. Quantitative analysis of the olfactory pathway for drug delivery to the brain. Brain Res. 692**,** 278-82.

Thorne, R.G., et al., 2004. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience. 127**,** 481-96.

Tolosa, E., et al., 2014. A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Movement Disorders. 29**,** 470-478.

Wang, J.Z., Grundke-Iqbal, I., Iqbal, K., 2007. Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration. Eur J Neurosci. 25**,** 59-68.

Watson, G.S., Craft, S., 2003. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs. 17**,** 27-45.

Whitwell, J.L., et al., 2007. VBM signatures of abnormal eating behaviours in frontotemporal lobar degeneration. Neuroimage. 35**,** 207-213.

Woolley, J., et al., 2007. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. Neurology. 69**,** 1424-1433.

Zhao, W.Q., Alkon, D.L., 2001. Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol. 177**,** 125-34.

Zhao, W.Q., et al., 2008. Amyloid beta oligomers induce impairment of neuronal insulin receptors. Faseb J. 22**,** 246-60.