Single Center Safety and Tolerability Trial of Intranasal Insulin in Parkinson's disease

Clinical Study Protocol

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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.

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Principal Investigator

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Date

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PROTOCOL SUMMARY

PROTOCOL TITLE	Single Center Safety and Tolerability Trial of Intranasal Insulin in Parkinson's disease
SHORT TITLE	IN Insulin for PD
STUDY PHASE	Phase II
STUDY OBJECTIVES AND PURPOSE	
Primary Objectives: • To determine the safety and tolerability of three different doses of intranasal insulin in patients with Parkinson's disease (PD)	
Secondary Objectives: • To evaluate efficacy of intranasal insulin on cognitive functioning in PD • To evaluate efficacy of intranasal insulin on motor function in PD • To evaluate efficacy of intranasal insulin on mood and apathy in PD • To identify which outcome measures are most sensitive to effects of intranasal insulin in PD	
STUDY DESIGN	
Study Type	Dose-finding
Control Type	None
Study Indication Type	Dose-finding, safety
Blinding Schema	Double blinded
Device	SipNose nasal device
Study Design	randomized, parallel-group, double blind, placebo-controlled
Planned Duration of Subject Participation	8 weeks (Treatment duration: 3 weeks)
PRIMARY ENDPOINTS	
• Composite safety event of either: a reduction of fasting glucose to <70 mg/dL or an unintended reduction of weight >5% • Pre-post change in safety measures (fasting glucose and weight) • Number of AEs and SAEs	
SECONDARY ENDPOINTS	
• Pre-post change in cognitive function measures	

• Pre-post change in motor function measures • Pre-post change in mood and apathy measures	
INVESTIGATIONAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION	
Investigational Product	Regular insulin (Novolin-R) in 3 different doses and placebo Dose 1, group with 7 participants: 20 IU/IN (10 units IN in one nostril twice daily x 21 days, volume 100 µl) Dose 2, group with 7 participants : 40 IU/IN (10 units IN in each nostril twice daily x 21 days, volume 100 µl) Dose 3, group with 9 participants: 80 IU/IN (20 units IN in each nostril twice daily x 21 days, volume 200 µl) Dose 4, group with 7 participants: placebo (each nostril, twice daily)
SUBJECT SELECTION	
Targeted Accrual	30 subjects. We estimate a need to consent 50 participants in order to reach this goal.
INCLUSION CRITERIA	

1. Subject has Idiopathic PD defined by the cardinal sign, bradykinesia, plus the presence of at least 1 of the following: resting tremor or rigidity and without any other known or suspected cause of Parkinsonism (according to MDS clinical diagnostic criteria for Parkinson's disease-Postuma et al, Movement Disorders 2015), confirmed by a fellowship trained movements disorder specialist
2. Subject is Hoehn & Yahr stage less than or equal to 3
3. Subject has a MOCA score ≥16.
4. Subject is > 40 and <90 years of age.
5. Female subjects are post-menopausal or have a negative pregnancy test
6. The subject must be proficient in speaking, reading and understanding English in order to comply with procedural testing of cognitive function, memory and physiology.
7. Subject has provided 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 is on a stable dose (at least 1 month prior to baseline visit) of antiparkinsonian agents and is willing to remain on this dose for the duration of the study. If the subject is on a cholinesterase inhibitor, a stable dose without changes for 1 month is also required.
9. Subject has undergone a brain CT or MRI prior to the study as part of their previous diagnostic workup for PD to rule out underlying structural lesions, as determined clinically significant by the investigator

EXCLUSION CRITERIA

1. Subject has atypical Parkinson's syndrome(s) due to drugs (e.g., metoclopramide, neuroleptics), metabolic neurogenetic disorders (e.g., Wilson's Disease), encephalitis, cerebrovascular disease, or degenerative disease (e.g., Progressive Supranuclear Palsy, Multiple System Atrophy, Corticobasal Degeneration, Lewy Body dementia)
2. Subject has medical history and/or clinically determined disorders: 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 sedative medications that are clinically contraindicated as determined by investigator.
7. Subject has undergone a recent change (<1 month) in their anti-parkinsonian medication, cholinesterase inhibitor 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. Subject has participated in a clinical trial investigation within 3 months of this study.
11. Subject has an insulin allergy.
12. Subject has Insulin-dependent diabetes

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.
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.
Hoehn and Yahr scale	Commonly used scale for describing progression of Parkinson's symptoms, ranging from 1 (unilateral symptoms only) to 5 (wheelchair bound or bedridden)
Intranasal (IN)	A method of drug delivery that is particularly applicable to delivering centrally acting medications into the central nervous system.
Montreal Cognitive Assessment **(MoCA**)	Brief 30-point cognitive screening measure that has been validated for use among individuals with Parkinson's disease.
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.
United Parkinson's Disease Rating Scale (UPDRS)	Is the most widely used clinical rating scale for Parkinson's disease. Part III of the rating scale evaluates motor symptoms in Parkinson's disease (PD)

1 INTRODUCTION

1.1 Background/Rationale

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's dementia and was originally described as a motor disease (Parkinson, 1817). The diagnosis of PD is still based on the core motor features of bradykinesia, resting tremor, and rigidity (Postuma et al., 2015), primarily as a result of degeneration of nigrostriatal dopaminergic neurons. In addition to the classic motor symptoms, however, PD is increasingly recognized as a multisystem disorder. A variety of non-motor symptoms, including cognitive deficits and dementia, are commonly observed in patients with PD (Aarsland et al., 2017).

1.1.1 PD and Cognition

Strong evidence indicates that in comparison with age-matched groups without PD, people with PD exhibit more rapid decline in a number of cognitive domains — in particular, executive, attentional and visuospatial domains, but also memory. The full spectrum of cognitive abilities can be observed in PD, from normal cognition, through early mild subjective and objective decline (mild cognitive impairment (MCI)), to mild, moderate and even severe PD dementia (PDD).

Cognitive impairment might occur very early in the course of PD, sometimes even before the onset of motor symptoms. Among PD patients without dementia, approximately 25–30% have MCI, which is evident at the time of diagnosis in 10–20% of patients (Svenningsson et al., 2012). Presence of MCI is associated with a shorter time to progression to a dementia diagnosis, although considerable variability is observed, with some patients remaining stable and a few even reverting to normal cognition (Pedersen et al., 2013).

PD dementia is particularly prevalent in the advanced stages, resulting in high morbidity and mortality. Several long-term longitudinal studies have indicated that the majority of patients with PD will develop dementia if they survive for more than 20 years after diagnosis (Hely et al., 2008). On the basis of numerous studies, it has been documented that dementia in PD has important adverse implications for functioning, quality of life, caregiver burden, and health-related costs (Aarsland et al., 2017).

1.1.2 PD and Insulin

Historically insulin was thought solely to be a peripherally acting hormone responsible for glucose homeostasis and energy metabolism. However, accumulating evidence indicates insulin can cross the blood-brain-barrier and influence a multitude of processes in the brain including regulating neuronal survival and growth, dopaminergic transmission, maintenance of synapses and pathways involved in cognition (Athauda and Foltynie, 2016).

Multiple research studies have identified links between PD and type 2 diabetes mellitus (T2DM), particularly highlighting associations between Parkinson's disease pathogenesis and the mechanisms underlying the development of insulin resistance. A recent large cohort study by De Pablo-Fernandez et al. (De Pablo-Fernandez et al., 2018), reported an increased rate of subsequent PD in T2DM, suggesting a shared genetic predisposition and/or disrupted shared pathogenic pathways.

Both insulin and glucagon-like peptide 1 agonists (GLP-1) have previously been found to have neuroprotective effects in animal models of synucleinopathies, including PD and multiple system atrophy (Bassil et al., 2017), possibly due to effects on neuronal survival and growth, maintenance of

synapses, and dopaminergic transmission. Insulin deficiency or resistance has been implicated in the pathogenesis of several neurodegenerative diseases (Jankovic, 2017).

A review article by Aviles-Olmos et al. (2013) highlights varying associations between diabetes or abnormal glucose tolerance and sporadic forms of Parkinson's disease from both cross-sectional and cohort studies. Survey data reveal that diabetes is established in 8–30% of patients with PD, consistently in excess of the prevalence found in non-Parkinson's disease individuals (Chalmanov and Vurbanova, 1987; Pressley et al., 2003). Another investigation found no link between the two diseases: A meta-analysis of 14 studies comprising a total of 21,395 patients with PD and 84,579 individuals without PD found a negative association between T2DM and PD (Lu et al., 2014).

A case control study showed that patients with PD dementia had a higher prevalence of abnormal glucose metabolism, mainly insulin resistance, than non-demented patients with PD (Bosco et al., 2012). Another study found that patients with PD and comorbid DM exhibited increased impairment in attentional function and executive function deficits than PD patients without DM (Ashraghi et al., 2016).

Several discoveries have highlighted common cellular pathways that potentially relate neurodegenerative processes with abnormal mitochondrial function and abnormal glucose metabolism. This includes converging evidence identifying that peroxisome proliferator activated receptor gamma coactivator 1-α (PGC1α), a key regulator of enzymes involved in mitochondrial respiration and insulin resistance, is potentially pivotal in the pathogenesis of neurodegeneration in Parkinson's disease (Ashraghi et al., 2016; Sandyk, 1993). Other studies suggested that the insulin- or IGF-1-activated PI3K/Akt/GSK3β signaling pathway may be involved in PDD pathogenesis (Yang et al., 2018).

Besides in PD, increased insulin resistance and glucose intolerance has been observed in a multitude of neurodegenerative processes including Alzheimer’s disease (Craft, 2006), and Huntington’s disease (Saleh et al., 2010).

1.1.3 Previous clinical trials investigating diabetic medications in PD

On the basis of the links between PD and type 2 diabetes mellitus, some of the existing licensed treatments for type 2 diabetes mellitus were thought to potentially have beneficial effects on related pathways of mitochondrial function in PD.

Pioglitazone is a licensed treatment for patients with type 2 diabetes mellitus. It acts to reduce insulin resistance and belongs to the class of thiazolidinediones. It was studied in the NET-PD trial, but failed to show an effect on disease modification in early PD (Investigators, 2015).

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist, already used for the treatment of T2DM. In a single-center, randomized, double-blind, placebo-controlled trial, patients with moderate PD received subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. This showed positive effects on off-medication motor scores in Parkinson’s disease, but it is still unclear if exenatide affects the underlying disease pathophysiology. The conclusion was made that the findings warrant further investigation of exenatide as a potential disease-modifying therapy in patients with PD (Athauda et al., 2017).

Besides exenatide and pioglitazone, other drugs that increase insulin sensitivity, including metformin, pioglitazone and MSDC-0160, have been or are currently being investigated as potential disease-

modifying therapies in patients with PD. MSDC-0160 was shown to inhibit the activities of the mitochondrial pyruvate carrier (MPC) complex and act as an insulin sensitizer without activating peroxisome proliferator–activated receptor-γ (PPARγ) (Ghosh et al., 2016). The MPC complex is the target of thiazoledinediones. These insulin sensitizers have been suggested to reduce the risk of developing PD and have been shown to be neuroprotective in both in vitro and in vivo models. The use of these agents in patients with T2DM has declined, however, owing to an increased risk of a variety of adverse effects, including fluid retention, weight gain, bladder cancer and other cancers. MSDC-0160, which promises to have fewer adverse effects than the thiazolidinediones, was found to be neuroprotective in various mouse models of PD (Jankovic, 2017).

1.1.4 Intranasal Insulin

Central insulin and central insulin receptors have been established as differing from that of the systemically occurring counter parts that specifically regulate glucose utilization (Zhao and Alkon, 2001). 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).

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., 2008b).

Clinical investigations of intranasal insulin in Alzheimer's dementia (AD) have demonstrated therapeutic effects impacting memory, attention and cognition without significantly altering serum insulin or glucose levels (Reger et al., 2008). Based on a study by Born et al (2002), a single dose of 40 IU insulin is expected to induce temporary increases in cerebrospinal fluid concentrations of insulin distinctly above the normal level in healthy individuals. Craft and colleagues have demonstrated improved delayed memory and preserved caregiver-rated functional ability as represented by the Alzheimer Disease's Assessment Scale-cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL) scale, respectively in AD and Mild Cognitive Impairment (MCI). In this study, patients were treated with regular insulin 10 and 20 IU twice daily during a four month treatment trial (Craft et al., 2012). In a study by Benedict at al. (2007) with 36 healthy men, word list recall was improved after 8 weeks of treatment with intranasal insulin, using doses of 160 IU per day.

Previous animal studies have demonstrated that intranasal insulin treatment can normalize the production and functionality of dopamine and improves motor impairment in 6-OHDA-induced rate PD models (Pang 2016). Although there are no clinical intranasal insulin studies in PD, there have been previous attempts of using other forms of intranasal treatments in PD. This includes a recent study using intranasal Glutathione in PD (Mischley et al., 2017) and intranasal apomorphine (Dewey et al., 1998; van Laar et al., 1992). All intranasal treatments were well tolerated in this population.

In this study, we aim to investigate which intranasal insulin dose out of three doses and placebo, administered at three different doses or placebo over a 21-day period, is the optimum dosage based on safety and tolerability in Parkinson's disease. A similar design was used in a trial investigating intranasal oxytocin in frontotemporal dementia (Finger et al., 2014). Dosing for the first two groups of this study is based on previously conducted intranasal insulin studies in AD and MCI (Craft et al., 2012; Craft et al., 2017), using daily doses on 20 and 40 IU of intranasal insulin. Higher dose have been found to be safe in healthy adults (Benedict et al., 2007a). Prior studies performed have demonstrated favorable effects of this regimen in the MCI/AD population without peripheral hypoglyemia (Craft et al., 2012).

Furthermore, this clinical trial will investigate exploratory outcomes related to the effect of IN insulin on cognition, mood, apathy and motor performance measured by the MDS- UPDRS (United Parkinson's Disease Rating Scale, (Goetz et al., 2008)). To our knowledge, there are no published clinical trials investigating the use of IN insulin in PD.

1.1.5 Safety of Intranasal Insulin

Novolin R has been approved for subcutaneous or intravenous use since 1991. The most common side effect noted with these two routes is hypoglycemia (Regular Insulin, Drug Monograph). A recent review of safety of Intranasal human insulin trials revealed no safety concerns, with no serious adverse events or symptomatic hypoglycemia in a total of 1092 individuals studied (Schmid et al., 2018). Tables 1 (acute) and 2 (chronic) of this review provide a summary of the human studies with intranasal Insulin. The majority of the studies used regular Insulin (Novolin R or Actrapid, Humulin R, Insuman Rapid, H-insulin 100) with similar excipients and none are believed to be in a range that causes harm (Hamidovic, 2015).

Study of pharmacokinetics of intranasal insulin in mice showed only 3% of intranasal insulin entered the circulation and no peripheral metabolic effects were detected up to a day after intranasal administration (Salameh et al., 2015). Treatment with 40 IU insulin in humans found no significant changes in circulating insulin levels, suggesting that intranasal insulin does not pass into the circulation (Born et al., 2002; Kern et al., 1999). Though some studies with higher doses (160IU [2X the proposed dose in this protocol]) have shown small detectable increase in insulin levels, no significant change in blood glucose levels were noted (Kullmann et al., 2018). Notably, intranasally administered insulin improves memory in healthy adults and Alzheimer's patients without altering blood levels of insulin or glucose (Benedict et al., 2004; Benedict et al., 2007b; Craft et al., 2012; Craft et al., 2017; Reger et al., 2008a; Reger et al., 2008b; Schioth et al., 2011; Schioth et al., 2012)

The most common side effect with intranasal insulin administration noted is transient local or nasal irritation. Please refer to Table 3 of the Schmid et al., 2018 review for a summary of the local or nasal effects of Intranasal Insulin in humans. In 2012, Craft et al reported, that number of adverse events was higher for the 20 IU and 40 IU when compared to the placebo group; however, there were no SAE's and mostly minor AEs such as rhinitis were reported (Table 4, (Craft et al., 2012)). Similar minor AEs were reported in the 2017 by Craft et al using intranasal insulin (Supplementary table 2, (Craft et al., 2017)). All the documents are attached. Overall, intranasal insulin at the proposed dose in this protocol, is expected to be safe with limited side effect profile. We plan to monitor the subjects for hypoglycemia and Insulin levels.

2 Summary of Device Description

2.1 Intranasal SipNose Device Overview

REDACTED

Table 1: REDACTED

2.1.1 Intranasal SipNose Device

REDACTED

2.1.2 SipNose Utility, Reliability, and Safety

REDACTED

2.1.2.1 Utility

REDACTED

2.1.2.2 Reliability

REDACTED

2.1.2.3 Safety

REDACTED

2.1.2.4 Device-Drug Contact and Safety

REDACTED

3 Objectives

3.1 Primary Objective

- To determine the safety and tolerability of three different doses of intranasal insulin in patients with Parkinson's disease (PD)

3.2 Secondary Objectives

- To evaluate efficacy of intranasal insulin on cognitive functioning in PD
- To evaluate efficacy of intranasal insulin on motor function in PD
- To evaluate efficacy of intranasal insulin on mood and apathy in PD
  To identify which outcome measures are most sensitive to effects of intranasal insulin in PD

4 Endpoint(s)

4.1 Primary Endpoints

- Composite safety event of either: a reduction of fasting glucose to <70 mg/dL or an unintended reduction of weight >5%
- Pre-post change in safety measures (fasting glucose and weight)
- Number of AEs and SAEs

4.2 Secondary Endpoints

- Pre-post change in cognitive function
- Pre-post change in motor function

- Pre-post change in mood and apathy

4.3 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
- Change in weight

5 Study Design

This study is a single center trial to determine dose finding, safety and tolerability of 3 doses of intranasal (IN) regular insulin (Table #2) and placebo in patients with Parkinson's disease.

Table 2: Intranasal Drug Dosing

Group	Drug	Dose	Volume	N=
Dose group 1	Insulin	20 IU/IN (10 IU, one nostril, twice daily)	100µl	7
Dose Group 2	Insulin	40 IU/IN (10 IU, each nostril, twice daily)	100µl	7
Dose Group 3	Insulin	80 IU/IN (20 IU, each nostril, twice daily)	200µl	9
Dose Group 4	Placebo	0.9% Saline (each nostril, twice daily)	200µl	7

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 and randomization visit (Visit 2). During the baseline visit, subjects will be administered a cognitive battery. Subjects will also undergo a neurological examination, including the UPDRS (United Parkinson's Disease Rating Scale- MDS) to be performed in the "ON-STATE" (after taking Anti-Parkinson's medications according to the subject's regular medication schedule). A final safety/assessment visit will take place 3 weeks after visit 2 at which time the tests will be re-administered.

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 SipNose 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 SipNose 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 3 weeks include administering the following during the study:

- In-clinic training session during screening and baseline visits
- Phone calls to assess compliance from study coordinator at weeks 1 and 2 (approximately 1 and 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 SipNose

REDACTED

5.3 Device Dose Loading and Administration

REDACTED

5.4 Study Duration

Study participation will last approximately 8 weeks, consisting of a screening visit, baseline visit, a follow-up assessment visit and three phone visits. Patients who discontinue treatment will continue follow-up measures as possible and will be analyzed as randomized per the intent to treat principal.

6 Study Population

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

1. Subject who has Idiopathic PD defined by the cardinal sign, bradykinesia, plus the presence of at least 1 of the following: resting tremor or rigidity and without any other known or suspected cause of Parkinsonism (according to MDS clinical diagnostic criteria for Parkinson's disease- Postuma et al, Movement Disorders 2015), confirmed by a fellowship trained movements disorder specialist
2. Subject who is Hoehn & Yahr stage less than or equal to 3
3. Subject has a MOCA score ≥16.
4. Subject is >40 and <90 years of age.
5. Female subjects who are post-menopausal or have a negative pregnancy test
6. The subject must be proficient in speaking, reading and understanding English in order to comply with procedural testing of cognitive function, memory and physiology.
7. Subject has provided 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 is on a stable dose (at least 1 month prior to baseline visit) of antiparkinsonian agents and is willing to remain on this dose for the duration of the study. If the subject is on a cholinesterase inhibitor, a stable dose without changes for 1 month is also required.
9. Subject must have undergone a brain CT or MRI prior to the study as part of their previous diagnostic workup for PD to rule out underlying structural lesions, as determined clinically significant by the investigator

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 who has atypical Parkinson's syndrome(s) due to drugs (e.g., metoclopramide, neuroleptics), metabolic neurogenetic disorders (e.g., Wilson's Disease), encephalitis, cerebrovascular disease, or degenerative disease (e.g., progressive Supranuclear Palsy, Multiple system atrophy, corticobasal degeneration, Lewy Body dementia)
2. Subject has medical history and/or clinically determined disorders: 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 sedative medications that are clinically contraindicated as determined by investigator.
7. Subject has undergone a recent change (<1 month) in their anti-parkinsonian medication, cholinesterase inhibitor 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 3 months of this study.
11. The subject has an insulin allergy.
12. The subject has Insulin-dependent diabetes

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 7.1.2-7.1.5, and the Safety monitoring are detailed in Section 7.3; details of neuropsychological assessments are outlined in Section 7.5.

The diagnosis of Parkinson's disease will be confirmed by exam or chart review by a movement disorders neurologist prior to study enrollment. A recent office visit (within 3 months) may be used to replace a portion of the screening visit if information needed for determining eligibility is present within the electronic medical record. Upon confirmation of eligibility, subject returns for assessments and procedures as described below.

7.1 Demographic and Baseline Assessments

7.1.1 Visit 1: Screening

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.
- Administer MoCA

- Review Inclusion/Exclusion Criteria.
- Review medical history, as it pertains to inclusion/exclusion criteria, such as research diagnosis, disease severity, and course of PD
- 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 with UPDRS part III. Collect vital signs, height and weight prior to ECG and blood draw.
- Obtain laboratory studies
- Perform a standard 12-lead ECG.
- Study Drug administration training, including Study Drug Diary 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)-fasting

The following procedures will be performed at this visit:

- Review Inclusion/Exclusion Criteria.
- Collect vital signs, orthostatic vital signs and weight.
- Collect concomitant medication information and record AEs/SAEs.
- Neuropsychological testing, including scales for mood, apathy and suicidality assessment (7.5)
- Perform UPDRS III
- Obtain laboratory studies, blood draw and glucose finger sticks
- Study Drug administration training (following cognitive testing).
- Hypoglycemia rescue training.
- Randomization of subject
- Administer first intranasal dose in clinic and provide study kit
- Visit 3 will be scheduled in 21 days (± 5 days).

7.1.3 Phone Visit 1: Safety Check (week 1)

- Study staff phone call to address AEs/SAEs 1 week (± 5 days) after visit 2

7.1.4 Phone Visit 2: Safety Check (week 2)

- Study staff phone call to address AEs/SAEs 2 weeks (± 5 days) after visit 2

7.1.5 Visit 3: Final Treatment and Safety Visit (week 3)-fasting

The following procedures will be performed at this visit:

- Collect vital signs, orthostatic vital signs and weight.
- Collect concomitant medication information and record AEs/SAEs.
- Collect administration supplies, study diary, and remaining study drug
- Physical and neurological examination
- Neuropsychological testing, including scales for mood, apathy and suicidality assessment (7.5)
- Administer MoCA
- Perform UPDRS III

- Obtain laboratory studies

See **Table 3** for specific list of laboratory assessments

7.1.6 Phone Visit 3: Safety Check (week 4)

- Study staff phone call 1 week (± 5 days) after visit 3 to follow up and address AEs/SAEs

7.2 Early Withdrawal

If subject withdraws from the study after the screening visit, but before initial study drug administration, no further evaluations are necessary. If subject withdraws from the study after initial study drug administration, 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. 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. Orthostatic vital signs will be measured after patients have remained in the supine position for 5 minutes, and again after 2 minutes standing. We will collect three sets of orthostatic vital signs at baseline, at least 10 minutes apart, and use the average of these 3 measurements for comparison to a single measurement of post-treatment orthostatic vital signs (Visit 3).

A blood glucose < 70 mg/dL will be considered clinically significant. Patients 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

At the screening visit, the laboratory samples will be drawn independent of fasting or non-fasting status. At the baseline and final visit, all subjects will be required to fast for a minimum of 12 hours prior to collection of blood sampling on designated fasting visits.

At the baseline visit, the subject will receive the first intranasal dose in clinic. Once before the administration of the first dose (baseline) and twice after the administration of the first dose (approximately 15 minutes and 30 minutes after first dose), glucose finger sticks will be performed to measure blood sugar levels for patient safety.

See **Table 3** for specific list of laboratory assessments

7.4 PD Motor Assessment

The **United Parkinson's Disease Rating Scale (UPDRS)** is the most widely used clinical rating scale for Parkinson's disease. In this study, we only use part III of the rating scale, which is a clinician-scored monitored motor evaluation, allowing ratings from 0 (no symptoms) to 4 (severe symptoms) for each Parkinson's motor symptom. The Movement Disorders Society (MDS) commissioned a revision of the scale, resulting in a new version, termed the MDS sponsored UPDRS revision (MDS-UPDRS) (Goetz et al, 2008). In this study, the MDS-UDPRS version will be used.

7.5 Neuropsychological Assessment

The neuropsychological battery consists of subtests in a variety of domains that include working memory, visuospatial skills, processing speed, inhibition, set-shifting, verbal fluency, learning, memory, and mood.

7.5.1 Global Cognition:

7.5.1.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening measure that has been validated for use among individuals with Parkinson's disease. The total score for this test is 30 points, but one point will be added for individuals with ≤ 12 years of education, up to a maximum of 30 points. The cutoff point for normal cognition is 26/30 in the general population (Nasreddine et al., 2005) and in individuals with Parkinson's Disease (Hoops et al., 2009).

7.5.2 Working Memory:

7.5.2.1 WAIS-IV Digit Span:

The Digit Span task includes three different components: Digits Forward, Digits Backward, and Digit Sequencing (Wechsler, 2008). During Digits Forward, the participant is read a series of numbers and is asked to recall the numbers in the same order. Digits Backward requires the participant to recall the numbers in reverse order. Digit Sequencing requires the participant to recall the numbers in ascending order. During the first trial of each component, only 2 digits are read to the participant and the number of digits become gradually longer in length as the test continues.

7.5.3 Processing Speed and Set-Shifting

7.5.3.1 Trailmaking Test Part A and B

Trailmaking test is often used in research and clinical practice to assess processing speed, visual scanning, and mental flexibility (Heaton et al., 2004). Part A requires participants to connect a series of

dots in order from 1 to 25 as quickly as possible while maintaining accuracy. Part B requires participants to connect a series of dots with numbers and letters in ascending order by starting with a number and then connecting a line to the next letter, and back to the next number as quickly as possible. The task is timed and the number of errors are recorded.

7.5.4 Visuospatial Ability

7.5.4.1 Judgement of Line Orientation

Judgement of Line Orientation is a test of visual perception where participants are asked to estimate the angle between two line segments (Benton et al., 1978). There are 30 items and the participant earns one point for each response where they correctly identify both line segments for each item.

7.5.5 Learning and Memory

7.5.5.1 Logical Memory

Logical Memory is an auditory story-recall subtest from the Wechsler Memory Scale – Fourth Edition (Wechsler, 2009). Participants are read two short stories and are immediately asked to recall as much detail as they can remember. Following a 20-30 minute delay, they are asked again to recall details from the stories. Finally a forced-choice Yes/No recognition task will also be administered.

7.5.5.2 Hopkins Verbal Learning Test- Revised

The Hopkins Verbal Learning Test- Revised is a list-learning task which includes a list of 12 words (Brandt, 1991). There are 3 semantic categories within each list, meaning 4 of the words are semantically related. Standard test administration includes 3 learning trials where the entire list of 12 words is verbally presented to the participant and they are asked to repeat as many words as they can recall after each presentation. The test also includes a 20-25 minute delay where participants are then asked to recall the words previously learned. This is followed by a 24-word yes/no recognition task, which includes the 12 target words from the original list and 12 foils. Alternate forms will be used at different time points in the study to reduce the potential for practice effects.

7.5.5.3 Brief Visuospatial Memory Test - Revised

The Brief Visuospatial Memory Test- Revised is a visuospatial learning and memory task which includes 6 shapes displayed in an array (Benedict, 1997). Standard administration includes 3 learning trials where the participant is allowed to view the page with the 6 figures for 10 seconds and then they are asked to draw the shapes as accurately as they can in the correct location on the page. The test also includes a 20-25 minute delay where participants are then asked to recall the figures previously learned. This is followed by a 12 item yes-no recognition task, which includes the 6 figures they were initially exposed to and 6 foils. Alternate forms will be used at different time points in the study to reduce the potential for practice effects.

7.5.6 Inhibition

7.5.7 Stroop Color and Word Test

The Stroop Color and Word Test measures cognitive flexibility and inhibition of an overlearned or automatic response. During the first trial (Word), the examinee is asked to read the words green, blue, or red printed in black ink as quickly as they can. During the second trial (Color), there are XXXXs printed in green, blue, or red ink and the examinee is asked to and name the ink color as quickly as they can. The third trial (Color-Word) includes the words with the names of colors, but the ink does not match the print and the examinee is asked to report the color of the ink, inhibiting the response to read the word. For example, the word "red" is printed in green ink, and the correct response for the third trial is "green" (Golden and Freshwater, 2002). Each condition is 45 seconds in length.

7.5.7.1 Letter 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 (Heaton et al., 2004). Sixty seconds are allowed for each letter.

7.5.7.2 Category 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 in 60 seconds.

7.5.8 Mood

7.5.8.1 Beck Depression Inventory- Second Edition

This self-report measure is widely used in research and clinical practice to measure the presence and severity of depressive symptomatology (Beck et al., 1996). The measure consists of 21 items assessing symptoms of depression experienced within the previous two weeks. Each item contains four statements reflecting various degrees of symptom severity.

7.5.9 Apathy Scale

The examiner will ask the participant about the severity of a variety of symptoms of apathy experienced within the previous four weeks (Starkstein et al., 1992). The measure includes 14 items with 4-point Likert scale ratings. This measure was specifically designed for patients with Parkinson's disease and has been recommended for use in Parkinson's disease by the Movement Disorder Society Task Force on apathy and anhedonia (Leentjens et al., 2008).

7.5.10 Suicidality

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale to evaluate suicidality. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent" (Interian et al., 2018). The C-SSRS will be administered by trained raters at specified time points, as indicated in table 2 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.

Table 3: Schedule of Assessments

Assessment/ Procedure	**Visit 1: Screen**	**Visit 2: Baseline/Initial Treatment (fasting)**	**Phone Visit 1: Safety Check after 1 week**	**Phone Visit 2: Safety check after 2 weeks**	**Visit 3: Final Treatment / Safety (fasting)**	**Phone Visit 3: Safety Check**	**Early Withdrawal**
			☎	☎		☎	
Schedule – Week and Windows	Week -2	Week 0	Week 1	Week 2	Week 3	Week 4	
		±5 days	±5 days	±5 days	±5 days	±5 days	
Informed consent	**X**						
Review of inclusion/exclusion criteria	**X**	**X**					
Medical History, demographic	**X**						
Physical/neurological exam	**X**				**X**		
UPDRS	**X**	**X**			**X**		
Vital signs	**X**	**X**			**X**		
Orthostatic vital signs		**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**
Glucose Finger Stick		**X**					
Fasting glucose		**X**			**X**		**X**
Insulin Level		**X**			**X**		**X**
HbA1c	**X**						
Thyroid Stimulating Hormone (TSH)	**X**						
Vitamin B12	**X**						
Pregnancy Test (in females)	**X**				X		**X**
Randomization		**X**					

Working Memory: WAIS-IV Digit Span		X			X		
Processing Speed and Set-Shifting Trailmaking Test Part A and B		X			X		
Visuospatial Ability Judgement of Line Orientation		X			X		
Learning and Memory Hopkins Verbal Learning Test- Revised		X			X		
Inhibition Stroop Color and Word Test		X			X		
Verbal Fluency Letter Fluency		X			X		
Verbal Fluency Category Fluency		X			X		
Mood Beck Depression Inventory- Second Edition		X			X		
Learning and Memory Brief Visuospatial Memory Test - Revised		X			X		
Learning and Memory Logical Memory		X			X		
Apathy Scale		X			X		
MoCA	X				X		
C-SSRS		X			X		X
Study Drug administration training	X	X					
Hypoglycemia rescue training	X	X					
Concomitant mediations		X			X		
IN INSULIN compliance			X	X			
Adverse events		X	X	x	X	X	X

8 Investigational Product(s)

8.1 Description of Investigational Product

The research staff will utilize the following investigational products:

- Intranasal delivery route
- Regular insulin (Novolin-R; Insulin Full Prescribing Information)
- SipNose Device (Sections 2, 5.2, 5.3, and Investigator's brochure)

8.2 Handling and Storage

The study drug (insulin/saline) will be given to participant/care partner after training for administration.

The study drug will be kept at study site per label recommendations and institutional Standard Operational Policy, specifically, but not limited to temperature controlled secure area.

Participants will be instructed to keep unopened study drug according to label recommendations.

The study drug will be stored at room temperature. To ensure that a stable temperature and/or conditions are maintained, site staff will verify and document refrigerator temperature at a minimum of three times per week or monitored continuously if automated systems such as temp trak are used. An electronic log will be securely stored at the HealthPartners Neuroscience Center. Study staff will be responsible for safeguarding and maintaining the master log. In the event of a medical emergency

requiring a blind break, unblinded study staff will be contacted to relay the appropriate information only to those responsible for the patient's immediate medical care (e.g. ED physician).

8.3 Packaging and Labeling

Actual pharmacy-product indicator will be decided by unblinded staff in order to maintain investigator objectivity.

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

- Protocol identifier/IRB approval/account/study number
- Quantity statement
- Participant 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 (see below) 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

Any subject with insulin-dependent diabetes taking insulin will be excluded from the study. Subjects taking medications that may negatively affect their cognition may be excluded from the study at time of screening. Exceptions will be made if such treatment is discontinued within 30 days or if the subject only takes low or infrequent doses of the medication that are unlikely to affect cognition, at the investigators discretion. These medications include anticholinergics, and centrally acting antihistamines (e.g. Benadryl), opiates, benzodiazepines, barbiturates, muscle relaxants.

10 Subject Completion and Withdrawal

10.1 Subject Completion

Subjects completing all 3 study 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 before randomization so as to maintain an n=30.

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 participant 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 SipNose Failures and Malfunctions

Device Quality Control. All failures and Malfunctions of the device must be documented on the Device Malfunction/Performance Form. All performance issues and malfunctions will be reported to SipNose and in the clinical results (e.g., final report).

12 Data Analysis and Statistical Considerations

12.1 Statistical Analysis Overview

Due to the small sample size of this study, statistical analysis will be mainly exploratory and descriptive: t-tests (or Mann-Whitney u-tests if normality of the data is not met) are used to compare the difference of a continuous measure between groups (such as patient age at baseline, various efficacy measures), and contingency tables and chi-square tests are used to compare the difference of a categorical variable (such as patient gender at baseline, various safety and adverse events).

To minimize the potential confounding effects of gender and MOCA score on the treatment effect, we will use stratified block randomization when assigning patient to one of the four study groups. The stratification factors will be gender (male/female) and MOCA score (low <22/30 and high>23/30). We will use block size of four.

12.2 Statistical Analysis of Primary Aim – safety, tolerability and adverse events

To assess safety and tolerability of the study drug at varying dose levels, AEs and SAEs will be categorized and summarized by study group. We will descriptively note if any group was more likely to have experienced a particular AE/SAE or generally experienced more AEs/SAEs throughout the course of the study; if we notice a significant 'spike' associated with a particular dosing group for a certain event, we'll construct a chi-square test to see if it's statistically significant. We will also assess the number of and reason for early withdrawals in each study group.

We will also monitor two key safety measures: 1) a fasting glucose < 70 mg/dL and 2) an unintended weight loss of >5% (relative to the patient's weight at visit 2). The number of participants in each group who experience either or both of these events will be counted and descriptively compared. We will then compare the change in fasting glucose and weight at Visit 2 (Baseline/Initial Treatment) and Visit 3 (Final Treatment/Safety). In the event of an early withdrawal, measures taken at the early withdrawal visit will be used in place of Visit 3 data. We will descriptively note if any dosing group was more inclined to experience one or both of these safety events. In a similar fashion, if we notice a significant 'spike' associated with a particular dosing group, we'll construct a chi-square test to see if it is statistically significant.

Secondarily, we will report the incidence of mild, moderate, and severe hypoglycemia overall and by group. Mild hypoglycemia will be defined as 54 mg/dL ≤ fasting glucose < 70 mg/dL; moderate hypoglycemia is 40 mg/dL ≤ fasting glucose < 54 mg/dL; and severe hypoglycemia is fasting glucose < 40 mg/dL.

12.3 Statistical Analysis of Second Aim – efficacy measures

For each of the efficacy outcome measures, we will report mean differences and 95% confidence intervals between Visit 2 (Baseline/Initial Treatment) and Visit 3 (Final Treatment/Safety) for each study group. In the event of an early withdrawal, measures taken at the early withdrawal visit will be sued in

place of Visit 3 data, if possible. Possible trends in cognitive function, motor function, and mood and apathy scores will be addressed.

We will look at the individual components and domains assessed by the chosen cognitive, motor, mood, and apathy measures to determine if any appear to be more sensitive to IN insulin. We will also explore the data for components that have a larger dose response. That is, they increase or decrease as the dose-level increases.

12.4 Statistical Power

As stated above, due to the sample size limitation of this study, no particular statistical power is under consideration during the study design phase with the intent to detect a meaningful clinically significant difference between study groups for any of the primary or secondary outcome measures; statistical analysis of this study will be mainly exploratory and descriptive.

The overall goal of the study is to identify a safe dose intranasal insulin with trends towards the secondary outcomes. Three different doses (and placebo) will be used, with the highest number of subjects (9) in the group with the highest dose, a model previously used by Finger at al. (2014).

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 the Struthers Parkinson's Center at HealthPartners. They will serve as an advisory panel to the Struthers Parkinson's Center at HealthPartners. The DSMB will be comprised of a non-affiliated neurologist, an unblinded investigator, an endocrinologist and a statistician. The 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.
- Regular DSMB meetings are planned after the first 15 patients, and after 30 patients have completed their treatment

During the course of the trial, the DSMB will review accumulating safety data to monitor for incidence of treads 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 (interim analysis) is complete. Study staff will not be unblinded in regards to individual subject's randomization status until after database lock.

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. SipNose devices 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.

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