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TITLE: Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis

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14. ABSTRACT

Cognitive dysfunction is common and devastating to people with multiple sclerosis (MS). To date, multiple pharmacologic interventions have been tried for MS-related cognitive dysfunction with disappointing results. Hence, there is an urgent need to identify or develop novel therapies that can help improve cognitive function in MS. This clinical trial is designed to evaluate the safety, tolerability, and efficacy of intranasal insulin in cognitively impaired people with MS. The study will also evaluate the impact of intranasal insulin on measures of oxidative stress, axonal injury, cellular stress, and energy metabolism in MS. The design of this phase I/II, randomized, double-blind, placebo-controlled trial is as follows; 105participants will be randomized (1:1:1, stratified by relapsing versus progressive MS) to intranasal insulin 10 international units (IU) twice a day, 20 IU twice a day, or placebo for 24 weeks. Insulin will be administered intranasally to allow direct delivery of the medication into the central nervous system. Standardized cognitive assessments will occur at baseline and throughout the 24-week trial, as well as for a period of 24 weeks after discontinuation of the intervention, to evaluate the impact of insulin on cognitive performance as well as the longevity of the treatment response. If intranasal insulin does appear to be safe and shows some evidence of helping cognition in MS, we will pursue a larger clinical trial to confirm our results. Intranasal insulin may provide a safe way to improve cognition and, ultimately, overall disability in people with MS, leading to better quality of life for patients and their caregivers.

15. SUBJECT TERMS					
Multiple Sclerosis, Cognitive Impairment, Neurodegenerative diseases, Intranasal Insulin, Symbol Digit Modalities Test, Minimal Assessment of Cognitive Function in Multiple Sclerosis					
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1. INTRODUCTION: Cognitive impairment is common in and devastating to people with multiple sclerosis (MS). MS is a common, chronic, central nervous system (CNS) disease characterized by inflammation, demyelination, and neurodegeneration. One of the most devastating symptoms of this disease is impaired cognitive function, which is common and present in over 60% of individuals with MS. Attention, memory, executive functioning, and especially processing speed are cognition areas negatively affected by MS. Intranasal insulin has been shown to help alleviate some cognitive impairment in other neurodegenerative diseases like MS. Insulin is critical for helping with regulation of multiple CNS functions including brain metabolism, learning and memory. Insulin is present at high levels in the brain and when these levels are decreased, there may be learning and memory impairments. Moreover, insulin's anti-inflammatory effects may also impact brain health via suppressing molecules that may provoke ongoing CNS inflammation and damage in disease states. This clinical trial is designed to evaluate the safety and tolerability of intranasal insulin in people with MS. In addition, this trial is going to evaluate if intranasal insulin improves cognition in people with MS, as assessed by standardized cognitive assessment tests.

2. KEYWORDS: Multiple Sclerosis, Cognitive Impairment, Neurodegenerative diseases, Intranasal Insulin, Symbol Digit Modalities Test, Minimal Assessment of Cognitive Function in Multiple Sclerosis

3. ACCOMPLISHMENTS:

What were the major goals of the project?
Specific Aims: 1) To evaluate the safety and tolerability of intranasal insulin in people with MS; 2) To evaluate if intranasal insulin improves cognition in people with MS; and 3) To evaluate the impact of intranasal insulin on measures of oxidative stress, axonal injury, cellular stress, and energy metabolism in MS.

Below are the lists of tasks as stated in the Statement of Work (SOW):

a) **Major Task 1: Obtain Regulatory Approval and Complete Study Start-Up**
b) **Major Task 2: Conduct Pilot Trial**
c) **Major Task 3: Perform Clinical Data Analyses and Prepare Abstracts and Manuscript**
d) **Major Task 4: Perform Biomarker Studies, Analyze Data, and Prepare Abstracts and Manuscript**
e) **Major Task 5: Finalize Materials for Data Sharing**

What was accomplished under these goals?
The accomplishments of each stated tasks corresponds with each bullet point above.

During Year 1 of the Intranasal Insulin study, the majority of work accomplished falls under bullet point a). We received Johns Hopkins IRB approval on 09JUN2016 and HRPO approval on 09MAR2017. In addition, activities involving study start-up were initiated. They included the compilation of study documents for the regulatory binder: protocol, informed consent form, curriculum vitaes, etc. FDA forms 1571 & 1572 were also completed and filed (including submission of annual progress reports for IND 127655 in Sept. 2016 and Sep. 2017). Study case

report forms such as the eligibility checklist, medical history form, relapse assessment form, and physical exam forms were finalized.

We also finalized the reservation of study space by completing an ICTR Clinical Research Unit (CRU) application and now have a space to complete subject study visits. Other insulin logistics included meeting with CRU staff to discuss what was required of their research staff in assisting with collection of labs, and dexa scans.

We also conducted meetings with the Hopkins Investigational Drug Pharmacy to discuss management, dispensation and randomization of study products (treatment and placebo). In addition, we have had several meetings with the manufacturer of the intranasal devices used in this study including a meeting for device training. On 12OCT2017, we received approval on the intranasal demo device from Johns Hopkins Clinical Engineering.

The study has also been registered on clinicaltrials.gov under the following identifier number: NCT02988401.

Lastly, we have chart screened over 400 patients, 100 of which appear to be eligible for the study and will be logged in our "screening and enrollment log".
Bullet points b) through e) are a work-in-progress and cannot currently be reported on since the trial has not commenced.

What opportunities for training and professional development has the project provided?
The project has allowed for training on how to administer the neuropsychology battery, Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). The MACFIMS has to be administered at 5 out of 6 study visits and includes seven cognitive assessments including the Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Paced Auditory Serial Addition Test (PASAT), Brief Visuospatial Memory Test – Revised (BVMT-R), Judgement of Line Orientation (JLO), Delis–Kaplan Executive Function System (DKEFS), and California Verbal Learning Test (CVLT-2). Our trained neuropsychologist has performed work in the area of advising and training the senior (Sr.) research coordinator on the use of the neuropsychological assessment tests.

Additionally, the project has provided an opportunity for phlebotomy training. A certificate of completion in routine venipuncture and butterfly procedure for adults in a clinical setting was obtained and awarded to the Sr. research coordinator in Nov 2016. At each study visit, at least 40 mls of blood needs to be obtained for biomarker evaluation and future research use. Therefore, this training was necessary for study blood draws.

The Intranasal Insulin study members were also trained on the proper use and cleaning techniques of the Kurve ViaNase III N2B devices. The device manufacturer held an hour-long webinar to review the device instructions for use (IFUs) and to answer any questions that we had on operating the devices.

How were the results disseminated to communities of interest?
Not applicable

What do you plan to do during the next reporting period to accomplish the goals?
During the next reporting period, we plan to enroll at least two participants per week. There was a major delay in receiving the intranasal devices which impacted the start of our study. However,

with aggressive chart screening, we already have a list of more than 100 potentially eligible participants. Eligible subjects with an interest in participating in the trial will be consented using the IRB-approved written consent form and subsequently enrolled. There are currently 20 pre-consented participants.

4. IMPACT: Nothing to report at this time; We are not at a point where we can discuss the impact of the study results since we have not started enrolling in the study yet.

5. CHANGES/PROBLEMS: We experienced two problems during study start-up that caused major delays with study initiation: 1) change of device manufacturer; 2) study drug odor. The initial device manufacturer's fees were too exorbitant and much more than the original projected cost; therefore, we changed device manufacturers from Impel Neuropharma to Kurve Technology. After this change, there were additional unanticipated delays in receiving the study devices due to construction of Kurve's new ViaNase III N2B model device. In addition, changing the device manufacturer necessitated a change in plans for diluting the insulin in order to get the lower-dose insulin treatment arm of 10 IU.

The first batch of devices arrived at our study office on Tuesday, October 24. Therefore, we are currently awaiting the latest approval from the Johns Hopkins IRB on our most recent change in research.

During discussions with the Hopkins investigational drug pharmacy, we learned that although this was not reported in some of the phase 2 trials that used saline, insulin has a "band-aid" like smell which is related to the diluent. In order to preserve study blinding (odor could un-blind participants and study team members), we needed to investigate whether a placebo diluent product was available that smells similar to the active medication (insulin). After contacting several companies, investigational drug pharmacies, and other clinical trial sites, we found that Eli Lilly & Company have diluent that is similar in odor to Novolin. This diluent has been ordered and we are awaiting shipment.

Significant changes in use or care of human subjects
Nothing to report

6. PRODUCTS: The ViaNase III N2B device is a product that was developed for the purpose of the clinical trial. The investigational device works as an electronic atomizer that delivers a nasal spray of the drug into the nasal passages of patients.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel	**Role**	**Percent Effort**
Ellen Mowry	PI	9%
Project contribution: has performed work in the area of study management and oversight (including drafting/revising protocol and IRB documents, advising Sr. research coordinator, and negotiating with device manufacturer).		
Scott Newsome	Co-PI	9%
Project contribution: has performed work in the area of study management and oversight (including drafting/revising protocol and IRB documents, advising Sr.		

research coordinator, and negotiating with device manufacturer).		
Meghan Beier	Co-Investigator	13%
Project contribution: has performed work in the area of advising and training Sr. research coordinator on the use of neuropsychological assessment tests.		
Sandi Cassard	Research Manager	7.5%
Project contribution: has performed work in the area of study management and oversight (including drafting/revising protocol and IRB documents, advising Sr. research coordinator		
Ama Avornu	Sr. Research Coordinator	58%
Project contribution: has performed work in the area of study execution, coordination, and logistics planning; assembled regulatory documents, managed IRB changes in research.		

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to report

What other organizations were involved as partners? Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

- Nothing to report

9. APPENDICES N/A