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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 2 of the Intranasal Insulin study, the majority of work accomplished falls under bullet points a) and b). 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, Sep. 2017 and Sep 2018). 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.

The conduction of the trial started with the enrollment of our first participant on 09FEB2018. Enrollment has been continuous, at a rate of approximately 1 participant per week. This estimation does not include the months of August and September 2018, when the enrollment of new participants was precluded by a nation-wide shortage of bacteriostatic sodium chloride, the compound necessary for the dilution of the syringes containing 10 International Units of insulin for intranasal use. This issue has been resolved.

At this point we have enrolled 26 participants; 10 of them completed the treatment phase and 3 have recently had their 5th scheduled visit and will complete the study in Jan 2019. Also, 9 eligible candidates have scheduled their baseline visits for Nov-Dec 2018. Additionally, there are more than 30 potentially eligible participants who manifested their interest in joining the trial and are currently reviewing the IRB-approved consent. In addition to this, we have built a list of more than 80 potentially eligible candidates who we are continuing to contact in a systematic fashion.

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 research coordinators 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 new research coordinator in Aug 2018. 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?

We have been actively working to enhance recruitment. In addition to chart screening, calling eligible subjects and our continuous efforts conducting in-person recruitments within the MS Center on each clinic day, we have worked on the following recruitment strategies:

We posted advertisements on the National MS (NMS) Society website, which generated awareness of the trail among potential candidates from other institutions. This proved to be highly beneficial, with many patients contacting us upon seeing the advertisement.

Also, we submitted a request to the IRB to perform home-based Number Processing Speed Test (PST) screening for our MS patients with iPads (Air, Air 2, and iPad 2017), since the PST app is now available on those tablets. This will enable us to remotely screen potential subjects that have transportation and/or mobility limitations.

Lastly, we are also planning to send out “dear doctor” letters to local physicians informing them about the study and also letting them known if their patients enroll in the Intranasal Insulin study. This will help advertise the study to physicians both within and outside of the Hopkins network.

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 are in the initial phase of the study yet.

5. CHANGES/PROBLEMS: We experienced two problems that caused major delays with study initiation and two additional challenges that originated during the progression of the study: 1) change of device manufacturer that postponed the date of first enrollment; 2) recognition prior to trial enrollment that the study drug had an odor, necessitating a change in research to accommodate a more properly-blinded placebo; 3) sodium chloride shortage, which temporarily prevented new enrollments, and 4) a change in the structure of the CRU, whereby fees are now charged for room use, nursing services, and DXA scans. 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.

During discussions with the Hopkins investigational drug pharmacy and insulin users unrelated to the trial, 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 if 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 change substantially reduces the likelihood of unblinding in the trial.

A nation-wide shortage of bacteriostatic sodium chloride 0.9% used for one of the arms of our study (dilution and conservation of the syringes containing 10 International Units for intranasal use) jeopardized the double-blind aspect of the study. After reaching out to all their known suppliers in our area, including DC, Virginia and Delaware, and contacting all the internal and local pharmacies without success, the investigational drug pharmacy notified the rest of team of the ongoing shortage on 07AUG2018. Consequently, from 07AUG2018 to 20SEP2018 we were unable to enroll new participants in the study. As the supplies arrived on 20SEP2018, we restarted scheduling enrollment of new participants.

Finally, due to changes in NIH funding, the CRU where we had been conducting all of the insulin study visits has now charged substantial fees for use of the space, nursing support, and DXA scans. We are working to resolve whether some relief of charges can be accomplished, but in the meantime are completing only baseline scans in the CRU and are seeing study participants otherwise in our clinic's research space.

Three participants dropped out the study due to personal reasons and/or schedule incompatibility.

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	10%
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	8%
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	1%
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	53%
Project contribution: has performed work in the area of study execution, coordination, and logistics planning; assembled regulatory documents, managed IRB changes in research.		
Pablo Ravenna	Research Coordinator	13%
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