AWARD NUMBER: W81XWH-16-1-0693

TITLE: Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis

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REPORT DATE: Oct 2019

TYPE OF REPORT: ANNUAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Annual	09/30/2018 - 09/29/2019

4. TITLE AND SUBTITLE
Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0693

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified		**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Table of Contents

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 cognitive 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.

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 which solidified guaranteed designated 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 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 slow but continuous, at a rate of approximately 1 participant per seven to ten days. 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 was resolved and has not reoccurred.

During Year 3 of the Intranasal Insulin study, the majority of work accomplished falls under Major Task 2.

As of 10/29/19, we enrolled 62 participants out of our goal of 105. At this point, 37 participants had completed the treatment phase and 27 participants completed the entire study. Also, 8 eligible candidates had scheduled their baseline visits in the next several weeks. Additionally, there were several potentially eligible participants who expressed their interest in joining the trial and are currently reviewing the IRB-approved consent. Several more potentially eligible participants are in the process of scheduling their baseline visits.

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 2019. 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 and Green Spring Station on each clinic day, we have worked on the following recruitment strategies:

1) We developed a letter to send to community physicians to help with referrals.

2) We updated the Insulin Flyers and web postings to reflect the current coordinator to contact and the protocol changes.

3) We began contacting potential participants who were ineligible according to old criteria and those who were undecided about their participation.

4) We were granted permission to hand out study flyers at the National MS Society annual walk and plan on doing this in the upcoming year.

4. IMPACT: Nothing to report at this time as no interim analyses were planned.

5. CHANGES/PROBLEMS:

We continued to experience difficulty with recruiting, which was mostly related to strict exclusion criteria related to pre-existing medications. We initially created the exclusion criteria to target participants not taking medications that may alter cognitive performance. However, we realized that a substantial proportion of people with MS who experience cognitive impairment ARE taking one or more of the exclusionary medications, which limited enrollment but also suggested that our results will not be generalizable to the typical cognitively-impaired MS patient population if these exclusion criteria were not changes. As such, we decided to simplify the criteria to ensure that people with MS who are taking a medication that could impact scores are taking a stable dose thereof for at least 6 weeks. These decisions were agreed upon and finalized with our neuropsychologist study team members. In addition, the THC and CBD compounds along with smoking exclusion criterion were relaxed in order to expand recruitment efforts.

Regarding the MS disease modifying therapies inclusion/exclusion criteria, rather than having subjects be untreated/on the same MS therapy for at least 6 months, with no anticipated change in the following year, we changed the criteria to allow subjects to be untreated/or who have been on the same MS therapy for at least 2 months.

Also, most patients did not express enthusiasm about doing the optional lumbar puncture (LP) part of the study. Hence, since we do not anticipate being able to recruit successfully a meaningful number of participants for the optional LPs, we decided to remove this portion from the study. It was felt that having a very small sample size of patients undergoing an LP would likely not provide sufficient interpretable data to justify the invasive procedure.

Four 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	25%
Project contribution: has performed work in the area of advising and training Sr. research coordinator on the use of neuropsychological assessment tests.		
Pablo Ravenna	Research Coordinator	100%
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