AWARD NUMBER: W81XWH-19-1-0770

TITLE: Neostigmine and Glycopyrrolate by Iontophoresis to Induce Bowel Evacuation

PRINCIPAL INVESTIGATOR: Mark A. Korsten

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

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2020	Annual	30 Sep 2019-29 Sep 2020

4. TITLE AND SUBTITLE

Neostigmine and Glycopyrrolate by Iontophoresis to Induce Bowel Evacuation

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0770

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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130 W Kingsbridge Rd
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8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposed research project to determine the correct dose of these medications and the correct ratio of them is anticipated to take two years. Then, during the third year of this grant, the investigators will study the possibility of using wireless iontophoresis devices to induce bowel evacuation. A manufacturer of wireless iontophoresis systems has been in contact with the investigators and shown interest in modifying the current device on the market to one that will be easier to use for someone with SCI, and the device would be designed to be more functionally appropriate to administer these drugs to elicit bowel evacuation. The final step to commercialization would be to obtain approval from the Food and Drug Administration (FDA) to market the wireless iontophoresis device with both medications in a patch system with the indication for constipation.

15. SUBJECT TERMS
NBD, paraplegia, tetraplegia, neostigmine, glycopyrrolate, iontophoresis.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Persons with spinal cord injury (SCI) have neurogenic bowel disorders which is associated with significant morbidity. The negative impact of bowel complications is often at the top of the list of problems reported by persons with SCI. Despite the magnitude of the problem of bowel dysfunction in persons with SCI, and the associated reduction in quality of life, this condition has yet to be effectively treated. The investigators have developed a novel dual drug combination to elicit a safe and predictable bowel evacuation (BE). The primary objective is to determine a lower effective dose to induce BE by transcutaneous administration of NEO by ION.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Neurogenic bowel dysfunction, bowel evacuation, paraplegia, tetraplegia, neostigmine, glycopyrrolate, iontophoresis.

3. ACCOMPLISHMENTS:

What were the major goals of the project?
On September 30, 2020 month 12 of the study was completed. The goals for these 12 months are as follows:
Major Task 1: To prepare to launch study
Subtask 1: Prepare IRB submission and research protocol.
Response: We have submitted and approval of IRB, SRS, R&D, FDA and HRPO.

What was accomplished under these goals?

On 3/19/202, our local IRB was informed by the PI that an administration hold was placed on all his clinical research activities due to the pandemic. On the same day, Dr. Melissa Miller was informed that, because of the pandemic, the PI had placed an administration hold on this study. Dr. Miller informed Dr. Korsten to inform the HRPO of the administrative hold, which was to be performed by the PI in a timely manner.

Major Task 1: To prepare to launch study	**Months**	**Percent Completed**	**Date Completed**
Subtask 1: Prepare IRB submission and research protocol	1-3	100%	
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	100%	
Finalize consent form & human participants protocol	1-3	100%	
Submit amendments, adverse events, and protocol deviations	As needed	Ongoing	Ongoing
Milestone(s) Achieved: Local IRB, SRS, and R&D approval	3-6	100%	Local IRB Approval: 06/26/2019 SRS Approval: 05/14/2019 R&D Approval: 07/08/2019

Milestone Achieved: FDA/HRPO/ACURO approval	3-6		FDA Approval: 06/25/2019 HRPO Approval: 03/04/2020
Major Task 2: Screening Phase – To identify SCI individuals who have bowel evacuation in response to intravenous administration of NEO			Admin Hold placed due to SARS-CoV-2 Date: 03/19/2020
Subtask 1: Recruit, consent, screen, and enroll 30 participants with SCI	7-12		
Approximately 30 participants will be screened by IV drugs administration to identify persons who will respond to NEO + GLY	8-11		
Analyze data to obtain 26 potential participants for further studies	11-12		
Milestone(s) Achieved: Participants who respond to NEO are identified and recruited for transdermal studies	12		
Major Task 3: Study 1 – To administer transdermal NEO + GLY by ION and confirm reproducibility of the findings			Admin Hold placed due to SARS-CoV-2 Date: 03/19/2020
Subtask 1: Transdermal ION administration of NEO + GLY and sequentially collect blood for pharmacokinetic analyses	8-15		
Approximately 24 participants undergo standard dose testing (NEO – 0.7 mg/kg, and GLY = 0.014 mg/kg) by iontophoresis to identify subjects who will have a bowel movement to the intervention. PK data will be collected, and patients will be closely monitored for cholinergic or anti-cholinergic symptoms.	8-15		
Subtask 2: Confirm reproducibility of the findings by repeating transdermal ION administration with 10-12 responders and sequentially collect blood for pharmacokinetic analyses	8-17		
Milestone(s) Achieved: Confirmation of participants` response to ION transdermal administration and reproducibility of findings	18		
Major Task 4: Study 2.1 – To determine a lower effective dose of NEO until failure to achieve bowel evacuation occurs in ≥50% of participants	19-21		
Subtask 1: Administer 75% of the standard transdermal dose of NEO and GLY; sequentially collect blood for pharmacokinetic analyses	19-21		

Approximately 20-22 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	21-23		
Subtask 2: Administer 50% of standard transdermal dose of NEO and GLY; sequentially collect blood for pharmacokinetic analyses	21-23		
Approximately 10-12 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	24		
Milestone(s) Achieved: A minimum optimized dose of NEO that can achieve bowel evacuation is identified	24		
Major Task 5: Study 2.2 – To determine a more optimal dose ratio of NEO to GLY until no or fewer cholinergic or anti-cholinergic symptoms			
Subtask 1: Administer a titrated dose ratio of 8:1 of NEO to GLY and sequentially collect blood for pharmacokinetic analyses	25		
Approximately 20-22 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	25-27		
Subtask 2: Administer a titrated dose ratio of 10:1 (if anticholinergic symptoms were observed) or 6:1 (if cholinergic symptoms were observed) of NEO to GLY and sequentially collect blood for pharmacokinetic analyses	28-30		
Approximately 10-12 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	28-30		
Milestone(s) Achieved: A titrated dose ratio of NEO to GLY without cholinergic or anticholinergic symptoms is identified	30		
Major Task 6: Study 3 – To test a commercially available wireless ION system. Possibly redesign, develop and test a more user-friendly, safe and effective wireless ION system			
Subtask 1: Prepare IRB & FDA submission and HRPO approval for Study 3	24-30		
Submit amendments, adverse events, and protocol deviations as needed. After completion of transdermal ION testing, we may need to submit an amendment	As Needed		

Subtask 2: Possibility of re-designing and developing a wireless system with industry	27-30		
Subtask 3: Administer NEO + GLY by a commercially available wireless ION system and sequentially collect blood for pharmacokinetic analyses	31-32		
Approximately 6-10 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	31-32		
Subtask 4: Administer NEO + GLY by a re-designed wireless ION system and sequentially collect blood for pharmacokinetic analyses	33-34		
Approximately 6-10 participants undergo testing, PK assessment, induction of bowel evacuation and cholinergic and anti-cholinergic symptoms.	33-34		
Subtask 5: Analyze data from wired and wireless ION transdermal delivery	35-36		
Milestone(s) Achieved: Local IRB, SRS, and R&D Approval at JJPVAMC. Wireless ION transdermal device(s) tested, and data analyzed	36		

	Year 1				Year 2				Year 3			
Target enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
			14-16 6-7	14-16 6-7	6-7	6-7	10-11	10-11	10-11	10-11	3-5	3-5
Target number of participants for each study (cumulative)			**14-16** **6-7**	**28-32** **12-14**	**18-21**	**24-28**	**10-11**	**20-22**	**10-11**	**20-22**	**3-5**	**6-10**

KEY:

Screening phase (n=30)	Study 1: ION transdermal testing (n=26)	Study 2.1: Optimize dose of NEO (n=20-22)	Study 2.2: Optimize dose of NEO to GLY (n=20-22)	Study 3: Test wireless ION transdermal system (n=6-10)

Suggested ACURO reporting format:

PROTOCOL (1 of 1 total):
Protocol [ACURO Assigned Number]: E00736. 1a
Title: Neostigmine and Glycopyrrolate by Iontophoresis to Induce Bowel Evacuation
Target required for statistical significance: 24
Target approved for statistical significance: 24
Total subjects to date: 0/30

SUBMITTED TO AND APPROVED BY: 07/08/2019

STATUS:

			Enter information regarding number of subjects					
HRPO Protocol Number	**Protocol PI Name**	**Organization (Site)**	**# Target**	**# Enrolled**	**# Completed**	**# Screened**	**# Recruited**	**Other**
E00736. 1a	Mark A. Korsten	James J. Peters VA Medical Center	24	N/A	N/A	N/A	N/A	N/A

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?
Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Now that the hold has been lifted and risks to the subjects are minimized, the next reporting period should include the following major tasks:

Major task 2: Screening Phase - To identify SCI individuals who have bowel evacuation in response to intravenous administration of NEO.
Major Task 3: Study 1 - To administer transdermal NEO+GLY by ION to confirm reproducibility of the findings.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report.

What was the impact on other disciplines?
Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
On 3/19/2020, our local IRB was informed by the PI that a voluntary administrative hold was placed on clinical research activities due to the current pandemic. Dr. Melissa Miller was also informed that an administrative hold was placed on this study by the PI. Dr. Korsten then informed the HRPO of the administrative hold in a timely manner. The PI lifted the administrative hold in September and clinical research activities are being resumed, with appropriate precautions in place. The major tasks and milestones that were delayed due to the pandemic will be initiated and reported in the next reporting period, now that the administrative hold has been lifted.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report.

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

Significant changes in use or care of vertebrate animals
Nothing to report.

Significant changes in use of biohazards and/or select agents
Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.
Nothing to report.

Books or other non-periodical, one-time publications.
Nothing to report.

Other publications, conference papers and presentations.
Nothing to report.

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Mark Korsten, MD	William Bauman, MD	Anton Sabiev, MD	Shawn Gilhooley, BS
Project Role	Principal Investigator	CO-PI	CO-PI	Research Coordinator
Nearest Person Month Worked	1.1	1.1	0.6	1.7
Contribution to Project	Oversee protocol design, recruitment, data collection, medication administration, subject monitoring, analysis and interpretation of results. PI will also ensure that all	Provide clinical expertise and oversight, while also ensuring that the study is meeting its time and scientific objectives. Dr. Bauman will also assist in analysis and interpretation of results.	Execution of study procedure, administration of study medication, monitoring of subjects, and data analysis/ manuscript preparation.	Initiate submissions to the JJP VAMC R&D committees, subcommittees, and study sponsors. Screen and enroll eligible participants; schedule study visits; maintain screening/ enrollment logs; obtain informed consent and HIPAA authorization from participants; collect,

	aspects of the study are compliant with IRB and provide clinical expertise.			process and analyze data; participant travel and reimbursement, and maintain databases and regulatory documents in accordance with expectations.

Name	Run-Lin Zhang, MD	Qishan Lin, PhD	Erika Gowe, MS
Project Role	Laboratory Technician	Laboratory Technician	Research Coordinator
Nearest Person Month Worked			1.0
Contribution to Project	Organize and oversee the storage of blood samples that are collected during the course of the study. Dr. Zhang will coordinate the shipment of specimen to the contracted laboratory for analyses at specific intervals. In addition, Dr. Zhang will organize blood samples and perform the assays for glycopyrrolate.	Perform assays for neostigmine by mass spectroscopy. Specimen will be de-identified and Dr. Lin will be blinded to the sequence of draw to minimize any bias.	Initiate submissions to the JJP VAMC R&D committees, subcommittees, and study sponsors. Screen and enroll eligible participants; schedule study visits; maintain screening/ enrollment logs; obtain informed consent and HIPAA authorization from participants; collect, process and analyze data; participant travel and reimbursement, and maintain databases and regulatory documents in accordance with expectations.

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.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
N/A

QUAD CHART:

8. APPENDICES:

Nothing to report.