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TITLE: Pharmacology of Anal Application of Oxymetazoline in Humans

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8. PERFORMING ORGANIZATION REPORT

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

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

14. ABSTRACT
Fecal incontinence in patients with spinal cord injury is a devastating disease, causing increased morbidity and mortality, especially due to its relation to pressure ulcers in the buttock area and to severe infections. In spinal cord injury, neural signals that travel through the spine, cannot reach their designated muscles. Lack of signals to the rectal sphincter muscle cause fecal incontinence, as this muscle is no longer contracted.
The purpose of this project was to investigate the drug effect of oxymetazoline, applied intra-anally, on safety, drug levels and bowel movements in healthy subjects. The results show that at the highest dose found safe; (1) the drug levels were within FDA approved acceptable range, and (2) reduction in the frequency of bowel movements and increased sphincter pressure were observed. These results; (1) establish the safety and potential efficacy of anal application of oxymetazoline; (2) show that contraction of the sphincter with this drug, results in fewer bowel movements; and (3) will enable RDD Pharma to advance to clinical studies in patients with fecal incontinence due to spinal cord injury.

15. SUBJECT TERMS
Fecal Incontinence; Spinal Cord Injury; Oxymetazoline

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	10	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

RDD Pharma is developing a novel formulation and method of use for the Oxymetazoline, intended as a first-in-concept therapeutic for management of spinal cord injury (SCI) associated fecal incontinence (FI). Based on the pathophysiology of FI, it is evident that restoring resting anal sphincter pressure to normal levels is expected to reduce morbidity and to improve the overall health condition of these patients. This study is a safety and pharmacokinetic study in healthy humans, as per FDA guidance and under an IND.

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

Spinal cord injury; Fecal incontinence; Oxymetazoline

3. **ACCOMPLISHMENTS:**

k

Specific Aims	Timeline (Months from t=0)	Site
Specific Aim #1: *Formulation, release, and stability testing of a GMP clinical batch of OX intended to support Phase 1 clinical trials*	1-12	1
Subtask 1: Formulation	1-3	1
Subtask 2: Product Release (for clinical testing)	3-4	1
Subtask 3: Stability testing of GMP-grade Oxymetazoline	1-12	1
Specific Aim #2: *Physiologically-based PK (PBPK) modeling*	1-4	4
Specific Aim #3: *Preparation and compilation of IND documentation to support FDA-regulated Phase 1 studies of OX in healthy volunteers*	1-2	5
Subtask 1: Generation of IND application and submission to FDA	1-4	5
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Specific Aim #4: *Establish the acute tolerance, and PK of single and multiple dose intra-anal administration of OX in healthy human volunteers*	8-10	2,3
Specific Aim #5: *Analysis of clinical trial results in order to compile study reports and prepare for an FDA meeting*	11-12	4

What was accomplished under these goals?

Major activity #1: *Formulation, release, and stability testing of a GMP clinical batch of OX intended to support Phase 1 clinical trials*

Specific Objective #1: Four different formulations of Oxymetazoline gel were prepared (Emerson Resources Norristown, PA) and were put on test. The best formulation was used for manufacturing of the investigational product.

Specific Objective #2: Product Release (for clinical testing) Expected in Quarter #4 – once 1-month stability of the clinical batch is available (see next specific objective).

Specific Objective #3: Stability testing of GMP-grade Oxymetazoline started on the 18th of May 2018. Results of 6 months accelerated stability (21Nov2018), show a stable formulation. Results of non-accelarated stability (28May2019) show a stable formulation.

Major Activity #2: *Physiologically-based PK (PBPK) modeling* – Completed

Specific Objective #1: PK modeling. Potential human PK of Oxymetazoline was estimated utilizing modeling of PK data from preclinical model species: rat, minipig. According to the model results, topical anal oxymetazoline in humans up to a dose of 10mg once daily may be supported by the rat (oral+anal) and mini-pig (anal) NOAEL (no adverse effect level) data.

Major Activity #3: *Preparation and compilation of IND documentation to support FDA-regulated Phase 1 studies of OX in healthy volunteers.* - Completed

Specific Objective #1: Generation of IND application and submission to FDA

IND submission date – 30th of May 2018.

Specific Objective #2: FDA IND approval – "Study may proceed" letter received from FDA on 17 Jul 2018.

Specific Objective # 3: Local IRB approval – IRB protocol approval: 29 Mar 2018.

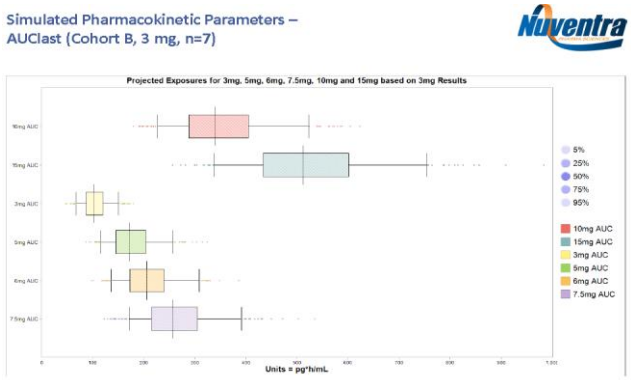
Specific Objective # 4: HRPO approval – Received: 16 Aug 2018.

Major Activity #4: *Establish the acute tolerance, and PK of single and multiple dose intra-anal administration of OX in healthy human volunteers* – First cohort of patients were dosed on 30 Aug 2018. One of the subjects enrolled to the first cohort (1 mg/day) exceeded an AUClast greater than 4110 pg*hr/mL which was a cohort-specific stopping criterion, and the study was suspended by the sponsor. The information was reviewed by the Agency and it was mutually agreed to dose an additional 12 subjects with 1 mg of oxymetazoline gel. A PARTIAL CLINICAL HOLD letter reflecting this decision was issued on October 16, 2018 and on November 10, 2018 these additional 12 subjects were enrolled to the study. The data from all 16 subjects was reviewed by the Agency and on January 31, 2019, a CONTINUE PARTIAL CLINICAL HOLD letter was issued by the Agency granting the sponsor permission to enroll 8 additional subjects to a daily dose of 3 mg/day. Dosing of these subjects started on 28 February 2019, and data was submitted to the Agency for review on May 06, 2019. On June 06th 2019, the FDA determined that the dose of 3 mg/day is safe and that RDD Pharma may use it in future studies.

Major Activity #5*: Analysis of clinical trial results in order to compile study reports and prepare for an FDA meeting* – Completed

Table 2. Day 1 and Day 10 Pharmacokinetic Parameters for Cohort B (n=8 on Day 1; n=7 on Day 10) Continued

Cohort B (n=7): 3 mg, Day 10							
	Tlag (h)	Tmax (h)	Cmax (pg/mL)	Tlast (h)	Clast (pg/mL)	AUClast (pg*h/mL)	Racc
mean	NC	NC	8.41	NC	5.29	105	1.35
median	0	6	7.21	24	3.18	93.4	1.24
minimum	0	0	3.83	24	2.78	77.8	0.58
maximum	0	24	16.20	24	9.28	159	2.06



Bowel Movement – Time till first bowel movement after drug application				
Minutes (SD)	369 (346)	494* (291)	322 (260)	509** (352)

BM = bowel movement
*p=0.03 when compared to baseline
**p=0.02 when compared to baseline

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?

Nothing to Report

4. IMPACT: What was the impact on the development of the principal discipline(s) of the project?

RDD Pharma is developing a new formulation of Oxymetazoline (OX), intended to treat fecal incontinence (FI) in patients with spinal cord injury (SCI). FI is a devastating complication occurring in 75% of patients with SCI. Bowel dysfunction among SCI patients significantly impacts quality of life, and results in restrictions on diet and outdoor mobility. Furtheremore, FI in SCI patients increases morbidity and mortality, due to its relation to pressure ulcers in the buttock area and to severe infections.
Normally, a muscle contracts in response to a neural stimuli generated in the brain and travels through the spinal cord until it reaches the designated muscle. Injury to spinal cord, distrupt these neural signals that travel through the spine, and they do not reach their target muscles. The anal sphincter is a circular muscle that engulfs the anal canal and is the most important factor in preventing stool slippage. Normally, it is in a contracted state, and it relaxes only during defecation. Lack of neuronal signals to this muscle cause fecal incontinence, as this muscle is no longer contracted. Current treatment options for FI are lacking and there are no approved medicinal products. Based on the symptoms associated with FI, it is evident that restoring the sphincter contraction to normal levels is expected to reduce mortality and to improve the overall health condition of these patients. OX is well known drug capable of inducing a long lasting (> 10 hours) contraction in muscles. RDD hypothesis is, that local application of OX will result in increase anal sphincter contraction and reduction in the number of FI episodes.
In this project, RDD has demonstrated the safety and pharmacological properties of topical OX in escalating doses in healthy humans. Furtheremore, although tested in normal subjects without fecal incontinence, during the treatment period, subjects experienced less bowel movements in comparison to the time period before the drug was applied. The reduction in the bowel movements was statistically significant and was associated with an increase in the contraction of the anal sphincter in the hours after the drug was applied.
The data generated in this study will be used in order to design clinical studies, in patients, with the ultimate goal of having OX approved for the treatment of FI in SCI patients.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

The results of this study will be shared with the FDA in order to design the clinical studies needed to validate these results in patients. Validation of these safety and efficacy results in SCI patients will ultimately result in the introduction to the market of the first drug indicated for the treatment FI in SCI patients.

What was the impact on society beyond science and technology?

The proposed research project addresses bowel dysfunction after SCI and therefore meets the FY16 SCIRP "Areas of Encouragement". The 2016 domestic incidence and prevalence of SCI is estimated at 17,000 and 282,000 , respectively, of whom 75% experience FI, necessitating the utilization of diapers by more than 1/3 of this population. The population at greatest need for meaningful clinical intervention thus has a domestic prevalence of 70,000. Bowel dysfunction among SCI patients has an extensive impact on daily life activities, and in particular, restricted diet (80%) and restricted outdoor ambulation (64%). Neurogenic bowel dysfunction is a major physical and psychological problem for persons with SCI, as changes in bowel motility, sphincter control, coupled with impaired mobility and hand dexterity, result to make bowel management a major life-limiting problem. As bowel dysfunction following SCI is a major source of morbidity it is not surprising that improving bowel function alone or bladder/bowel functions are rated among the highest priorities among individuals with SCI.
The presence of FI in SCI patients is closely correlated with anxiety and depression. FI causes shame and embarrassment in patients with SCI due to the leakage of stool and the resulting odor. Gastrointestinal problems in patients with SCI extend beyond quality of life issues: it is the fourth leading cause for re-hospitalization and 4.9% of deaths in the SCI population are directly attributed to diseases of the bowels. Fecal incontinence was also found to be a contributing factor to urinary tract infection and decubitus ulcers. The average bacterial counts in perineal cultures from SCI patients were 10 times greater than in controls and the dominant strains indicate fecal soiling . These infections have become increasingly difficult to treat, due to increasing antibacterial resistance in these organisms. Wilczweski found that fecal incontinence is only second to bed surface as a contributing factor to pressure ulcers 5. Overall, FI in SCI patients is a major source for direct and indirect morbidity and mortality. By introducing to the market a drug that will reduce FI episodes, SCI patients will benefit from reduced mortality, imoproved health and improved quality of life.

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

Delays occurred due to:

(1) Request by FDA to change the study design. Study design was revised so that prior to dosing an entire cohort, a small sample of subjects with receive one dose of the drug, and safety and PK data will be assessed by an independent pharmacovigilance monitor, the Principal Investigator and the sponsor's medical monitor.

(2) One of the subjects enrolled to the first cohort (1 mg/day) exceeded an AUClast greater than 4110 pg*hr/mL which was a cohort-specific stopping criterion, and the study was suspended by the sponsor. The information was reviewed by the FDA and it was mutually agreed to additionally dose 12 subjects with 1 mg of oxymetazoline gel. A PARTIAL CLINICAL HOLD letter reflecting this decision was issued on October 16, 2018 and on November 10, 2018 these additional 12 subjects were enrolled to the study. The data from all 16 subjects was reviewed by the Agency and on January 31, 2019, a CONTINUE PARTIAL CLINICAL HOLD letter was issued by the Agency granting the sponsor permission to enroll 8 additional subjects to a daily dose of 3 mg/day. Dosing of these subjects started on 28 February 2019, and data was submitted to the Agency for review on May 06, 2019. On June 06th 2019, the FDA determined that the dose of 3 mg/day is safe and that RDD Pharma may use it in future studies.

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

Significant changes in use or care of human subjects

One of the subjects enrolled to the first cohort (1 mg/day) exceeded an AUClast greater than 4110 pg*hr/mL which was a cohort-specific stopping criterion, and the study was suspended by the sponsor. The information was reviewed by the FDA and it was mutually agreed to dose an additional 12 subjects with 1 mg of oxymetazoline gel. A PARTIAL CLINICAL HOLD letter reflecting this decision was issued on October 16, 2018 and on November 10, 2018 these additional 12 subjects were enrolled to the study. The data from all 16 subjects was reviewed by the Agency and on January 31, 2019, a CONTINUE PARTIAL CLINICAL HOLD letter was issued by the Agency granting the sponsor permission to enroll 8 additional subjects to a daily dose of 3 mg/day. This amended protocol was approved by the study IRB committee and The U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). Dosing of these subjects started on 28 February 2019, and data was submitted to the Agency for review on May 06, 2019. On June 06th 2019, the FDA determined that the dose of 3 mg/day is safe and that RDD Pharma may use it in future studies.

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: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **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:	*Nir Barak, MD*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Dr. Barak has provided has designed the clinical protocol and development plan for the Phase 1 Study and is the primary interface with FDA and the clinical research unit conducting the study.*
Name:	*Ariel Kamsler, PhD*
Project Role:	*Sub Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Dr. Kamsler has provided oversight of the GMP drug manufacturer of the oxymetazoline, clinical testing laboratories, and regulatory affairs consultants.*

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

COLLABORATIVE AWARDS: Non apllicabale
QUAD CHARTS: Non Applicable

9. APPENDICES: None