AWARD NUMBER: W81XWH-15-1-0645

TITLE: A POC Clinical Trial for PTSD with a First-In-Class Vasopressin 1a Receptor Antagonist

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CONTRACTING ORGANIZATION: Azevan Pharmaceuticals, Inc.
Bethlehem, PA 18015

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Fort Detrick, Maryland 21702-5012

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In this reporting period, year 1 of the project, the major milestones met included obtaining approval from the responsible local Institutional Review Board (IRB) and the Human Research Protections Office (HRPO); the hiring and training of personnel that will work on the clinical trial; and the acquisition of equipment and methods set-up. In the second year of the project, the major objective will be to recruit and enroll subjects to participate in the clinical study that will test the effect of SRX246, a first-in-class vasopressin 1a receptor antagonist, as a potential new treatment for PTSD.

15. SUBJECT TERMS

PTSD; SRX246; Vasopressin 1a receptor antagonist; Phase II proof of concept clinical trial

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The project will test the clinical efficacy of a novel, first-in-class vasopressin 1a receptor antagonist, SRX246 (160 mg PO BID), as a new treatment for PTSD in an 18-week double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients. In addition, the study also will test in PTSD patients i) the safety and tolerability of SRX246 (160 mg PO BID) and ii) the clinical benefit of SRX246 for the treatment of anger, irritability, and aggression; major depression; disturbed sleep; and quality of life that frequently accompany PTSD.

2. KEYWORDS:

PTSD; SRX246; Vasopressin 1a receptor antagonist; Phase II proof of concept clinical trial

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The primary goal **is to provide the initial determination of the clinical efficacy of a novel, first-in-class vasopressin 1a receptor antagonist, SRX246 (160 mg PO BID), as a treatment for PTSD in an 18-week double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients that compares outcomes in drug vs. placebo arms**

There are several secondary goals. **These include providing determinations in PTSD patients of the i) the safety and tolerability of SRX246 (160 mg PO BID) and ii) clinical benefit of SRX246 for the treatment of major depression, anger, irritability, and aggression, disturbed sleep, and quality of life that frequently accompany PTSD.**

In this reporting period, year 1 of the project, our major milestones were to obtain local IRB and HRPO approval; hire and train personnel; acquire equipment and methods set–up; and then begin the clinical trial study. Our progress and accomplishments are shown below.

What was accomplished under these goals?

Major milestones met during this reporting period are shown in the table below

Major Task 1: Study set-up	**Date Completed/Status**
Milestone Achieved: Local IRB approval at WCMC	**Completed 17Mar2016**
Milestone Achieved: HRPO approval	**Completed 28Sept2016**
Milestone Achieved: Personnel hired and trained, equipment and methods set –up	**Completed 09Sept16**
Study Begins	**Pending**

We were not able to begin the clinical trial portion of the project because there was a delay at HRPO in the processing of our materials and as a consequence, receipt of the required approval. Approval was obtained on September 28, 2016 and the matter is now

resolved. Advertising for subjects and recruiting has begun. The enrollment schedule has been revised to reflect the delay in receipt of HRPO approval.

What opportunities for training and professional development has the project provided?

Weill Cornell Trainings:

- **Held several meetings for establishing policies and procedures manual at local site and training relevant personnel**
- **Several trainings in local data management system REDCap**
- **Trained PI, assessor, study physicians in local EMR system Epic**

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?

In the next reporting period, we will recruit and enroll subjects in order to meet the objectives of the project as stated under "major goals," item 3 above.

During the remainder of 2016 and the first quarter of 2017 we expect to:

a. **Begin participant enrollment (Q4 '16)**
b. **Continue and expand recruitment activities (Q1 '17)**
c. **Apply for and receive approval for IRB Continuing Review (Submission December 2016)**

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. **However, this grant was made to Azevan Pharmaceuticals, a small company, thus the technology is already in the private sector**.

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

There was a delay at HRPO in the processing of our materials and as a consequence, receipt of the required approval to start the clinical trial. Approval was obtained on September 28, 2016 and the matter is resolved. Subject recruiting has now begun. The enrollment schedule has been revised to reflect the delay in receipt of HRPO approval.

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

6. PRODUCTS:

• 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. The technology covering SRX246 was already patented.

• Other Products
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Azevan Pharmaceuticals, Inc. Personnel:

Name:	**Neal Simon**
Project Role:	**PI**
Nearest person month worked:	**2**
Contribution to Project:	**Responsible for assuring that specific aims and technical objectives are met in coordination with co-PI and Site-PI**
Name:	**Michael Brownstein**
Project Role:	**co-PI**
Nearest person month worked:	**2**
Contribution to Project:	**Works with PI and Site-PI to assure that specific aims and technical objectives are met**
Name:	**Eve Damiano**
Project Role:	**Regulatory and drug development efforts**
Nearest person month worked	**2**
Contribution to Project:	**Prepares documents for FDA submission, coordinates all drug development tasks, reviews and contributes to protocol development and adherence**
Name:	**Debra Itzkowitz**
Project Role:	**Operations Manager**
Nearest person month worked:	**2**
Contribution to Project:	**supports PI, co-PI, and regulatory and drug development processes, maintains budget and coordinates financial transactions**
Name:	**Margaret Altemus, MD**
Project Role:	**Medical Monitor; hired as an independent consultant**
Nearest person month worked:	**1**
Contribution to Project:	**Responsible for monitoring and evaluation of adverse events and other safety aspects**

Weill Cornell Personnel

Name:	**JoAnn Difede, Ph.D.**
Project Role:	**PI**
Nearest person month worked:	**3**
Contribution to Project:	**Responsible for assuring that specific aims and technical objectives are met in coordination with co-PIs and Site-PIs**
Name:	**Nancy J. Needell, M.D.**
Project Role:	**Co-I, study physician**
Nearest person month worked:	**0**
Contribution to Project:	**Responsible for the medical evaluation of all patients**
Name:	**James H. Kocsis, M.D.**
Project Role:	**Co-I, study physician**
Nearest person month worked:	**1**
Contribution to Project:	**Responsible for the medical evaluation of all patients**
Name:	**Andrew McAleavey, Ph.D.**
Project Role:	**Co-I, Study assessor**
Nearest person month worked:	**4**
Contribution to Project:	**Responsible conducting all study clinical assessments**
Name:	**Adina Jick**
Project Role:	**Research Assistant**
Nearest person month worked:	**12**
Contribution to Project:	**Responsible for all aspects of the study management including recruitment, scheduling, and data management**

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?
Organization Name: **Weill Cornell Medical College**
Location of Organization: **New York, New York**
Partner's contribution to the project (identify one or more):

Collaboration:

What were the major goals and objectives of the project?

- **Determine protocols and procedures at Weill Cornell for laboratory processing and medication dispensation**
- **Gain local IRB approval**
- **Hire and train research assistant**
- **Begin recruitment activities following IRB and HRPO approvals**

What was accomplished under these goals?

- **Determine protocols and procedures at Weill Cornell for laboratory processing and medication dispensation**
    - **Met with Clinical and Translational Science Center (CTSC) at Weill Cornell to establish procedures for blood draws and physical examinations on May 19, 2016**
    - **Met with Weill Cornell's research pharmacy to establish protocol for dispensation of medication on July 26, 2016**
    - **Retained Dr. Erica Jones as study cardiologist to read and evaluate electrocardiogram (ECG) results**
- **Gain local IRB approval**
    - **Gained IRB approval on March 17, 2016**
    - **An amendment was submitted to the local IRB on August 12, 2016 and was approved on September 14, 2016**
- **Hire and train research assistant**
    - **Adina Jick was hired on 9/12/16 as a Research Assistant at Weill Cornell. She will be facilitating administrative coordination and assisting in recruitment efforts and IRB-related activities.**
- **Begin recruitment activities following IRB and HRPO approvals**
    - **Following IRB approval (9/14/16), we began recruitment activities.**
    - **We are working on a press release with the public relations team at Weill Cornell Medicine announcing the beginning of enrollment and launch of the protocol.**
    - **Site PI has communicated with trauma services across the medical campus and to faculty members and colleagues about the launch of the protocol, including close collaborators at the Burn Center. Cornell team is preparing additional recruitment materials for a variety of social media platforms.**
- **See above section for details on trainings and professional development at Weill Cornell site such as trainings in data management system, electronic medical records system, and policies and procedures.**

8. SPECIAL REPORTING REQUIREMENTS:

QUAD CHARTS: See attached.

9. APPENDICES: None

A POC Clinical Trial for PTSD with a First-In-Class Vasopressin 1a Receptor Antagonist
Log #13077001
Award W81XWH-15-1-0645

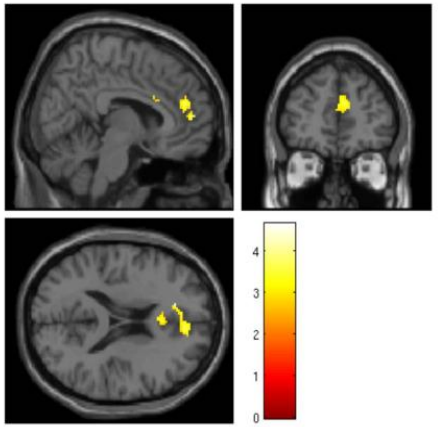
PI: Neal G. Simon, Ph.D. **Org:** Azevan Pharmaceuticals **Award Amount:** $1,577,905

Study/Product Aim(s)

• *Aim 1*: provide the initial determination of the clinical efficacy of SRX246 (160 mg PO BID) as a treatment for PTSD in a 18-week, randomized, double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients that compares outcomes in drug vs. placebo arms
• *Aim 2*: provide determinations in PTSD patients of the i) safety and tolerability of SRX246 (160 mg PO BID) and ii) clinical benefit of SRX246 for the treatment of major depression; anger, irritability, and aggression; disturbed sleep; and quality of life that frequently accompany PTSD.

Approach

We propose to test the *primary hypothesis* that daily oral treatment with SRX246 will result in clinical improvement in PTSD patients based on changes in CAPS score. *Secondary hypotheses*, including the effect of SRX246 on safety and several quality of life measures, also will be tested.



BOLD activity (Placebo > SRX246; yellow) in anterior cingulate and medial prefrontal cortex. SRX246 treatment significantly attenuated BOLD activation following intranasal AVP ($p<0.005$). Comparable attenuation of BOLD signal was seen in amygdala and temporal parietal junction, regions integral to the processing of social and emotional stimuli.

Accomplishments: 1) IRB and HRPO Approval Secured 2) Dr. Neal Simon, PI, attended and presented at the MOMRP PTSD Biomarker IPR

Timeline and Cost

Activities	CY15	CY16	CY17
Study Set Up			
Randomized Control Trial			
Data Analysis			
Dissemination			
Estimated Budget ($K)	**$103,186**	**$500,000**	**$974,719**

Goals/Milestones
CY15 Goal – *Study Set Up*
☑Execute Clinical Trial Agreement; Finalize Protocol and submit to IRB
CY16 Goals – *Study Set Up and Randomized Control Trial*
☑ Cornell IRB Approval; ☑ Establish Data Safety Monitoring Board
☑ Appoint Independent Medical Monitor; ☑ Recruit Study Physician
☑ HRPO Approval; ☑ Site Initiation Visit ☐ Begin patient enrollment
CY17 Goal – *Randomized Control Trial and Data Analysis*
☐Screen, randomize patients, execute protocol tasks over 18 weeks
☐Database lock, unblinding, completion of analyses
☐Dissemination of findings
Comments/Challenges/Issues/Concerns
• Recruitment and retention may impact timeline
Budget Expenditure to Date
Projected Expenditure: $700,000
Actual Expenditure: $374,523

Updated: October 28, 2016