AWARD NUMBER: W81XWH-15-1-0645

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

PRINCIPAL INVESTIGATOR: Neal G. Simon, Ph.D.

CONTRACTING ORGANIZATION: Azevan Pharmaceuticals, Inc.

REPORT DATE: OCTOBER 2020

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**
OCTOBER 2020	Annual	30 Sept 2019 – 29 Sept 2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0645

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)

Simon, Neal G., Ph.D.
Difede, JoAnn, PhD

E-Mail: ngsimon@azevan.com

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

Azevan Pharmaceuticals, Inc.
116 Research Drive
Bethlehem, PA 18015

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

In this reporting period, year 5 of the project, the major milestones met included obtaining renewal from the responsible local Institutional Review Board (IRB) and the Human Research Protections Office (HRPO) and the DSMB. No new patients were enrolled in year 5 with a total of 33 patients randomized to date. Azevan received a 3 month extension in order to lock database, unblind, and perform analyses.

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**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Page

1. INTRODUCTION:

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:

***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 5 of the project, our major milestones were to obtain local IRB renewal; local DSMB renewal; HRPO renewal; continue recruitment of participants and complete enrollment. Our progress and accomplishments are shown below.

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 renewal at WCMC	Completed 28Aug2020
Milestone Achieved: DSMB renewal	Completed 24Jun2020
Milestone Achieved: HRPO renewal	Completed 28Dec2018
Milestone Achieved: Personnel hired and trained,	Completed 04Jun2018

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**
- **Ongoing meetings among study assessors with regard to inter-rater reliability for the psychiatric assessment**

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

During the remainder of 2020, we expect to:

a. **Database lock and unblinding**
b. **Perform analyses according to specifications**

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

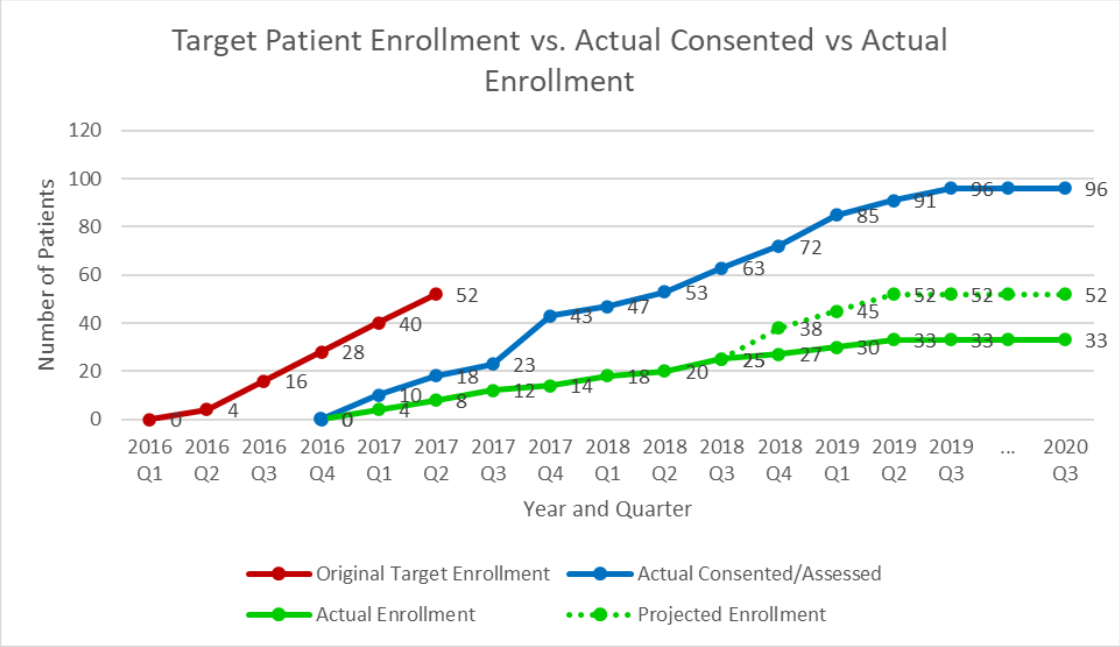
What was the impact on technology transfer?
Nothing to Report. However, this grant was made to Azevan Pharmaceuticals, a small company, thus the technology is already in the private sector.

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
Nothing to Report



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

Difede, et al: Challenges in Implementing a Clinical Trial Using a First-In-Class Medication Targeted to Treat PTSD. Military Health System Research Symposium, August, 2018.

Simon, et al: SRX246: A First-In-Class Vasopressin 1a Receptor Antagonist in Phase II Trials for Mood and Behavioral Disorders. American Society for Clinical Psychopharmacology, Miami, May 2017.

• 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:	**Lisa Spielman, PhD**
Project Role:	**Statistician; hired as an independent consultant**
Nearest person month worked:	**1**
Contribution to Project:	**Provides data management, evaluation planning, and statistical analysis**

Weill Cornell Personnel

Name:	**JoAnn Difede, Ph.D.**
Project Role:	**PI**
Nearest person month worked:	**0***
Contribution to Project:	**Responsible for assuring that specific aims and technical objectives are met in coordination with co-PIs**
Name:	**Janna Gordon-Elliott, 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:	**0***
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:	**0***
Contribution to Project:	**Responsible conducting all study clinical assessments**
Name:	**Mariel Emrich**
Project Role:	**Research Assistant**
Nearest person month worked:	**0***
Contribution to Project:	**Responsible for all aspects of the study management including recruitment, scheduling, and data management**

***0% funded percent effort, since this year was the no-cost extension. Dr. Andrew McAleavey left WCM on 8/31/20.**

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?

- **Work with Weill Cornell Medical College Clinical and Translational Sciences Center outpatient laboratory to assess participants**
- **Gain local IRB approval**
- **Continue recruitment activities following IRB and HRPO approvals**
- **Establish new recruitment avenues through the New York-Presbyterian Hospital Weill Cornell Medicine Emergency Department**

What was accomplished under these goals?

- **Work with Weill Cornell Medical College to assess participants**
- **Successfully collaborated with Clinical and Translational Science Center (CTSC) at Weill Cornell to assess patients using blood draws and physical examinations for duration of report period.**
- **Successfully collaborated with Weill Cornell's research pharmacy to dispense medication and randomize participants throughout report period**
- **Retained Dr. Erica Jones as study cardiologist to read and evaluate electrocardiogram (ECG) results**
- **Gained IRB approval on November 22, 2017 for continuing review**
- **An amendment was submitted to the local IRB on January 17, 2017 and was approved on January 23, 2017**
- **An amendment was submitted to the local IRB on March 29, 2017 and was approved on April 19, 2017**
- **An amendment was submitted to the local IRB on June 3, 2017 and was approved on June 27, 2017**
- **An amendment was submitted to the local IRB on August 2, 2017 and was approved on August 8, 2017**
- **An amendment was submitted to the local IRB on September 21, 2017 and was approved on September 29, 2017**
- **An amendment was submitted to the local IRB on April 18, 2018 and was approved on May 1, 2018**
- **An amendment was submitted to the local IRB on October 21, 2018 and was approved on October 30, 2018**
- **An amendment was submitted to the local IRB on November 27, 2018 and was approved on December 14, 2018**
- **An amendment was submitted to the local IRB on February 21, 2019 and was approved on March 22, 2019**
- **An administrative amendment was submitted to the local IRB on April 10, 2019 and was approved on May 7, 2019**
- **An amendment was submitted to the local IRB on May 29, 2019 and was approved on June 14, 2019**
- **An amendment was submitted to the local IRB on February 19, 2020 and was approved on April 11, 2020**

- **Hire and train additional assessors**
  - **In 2017, Drs. Amy Rubenstein, Melissa Peskin, and Colleen Becket-Davenport were successfully trained to conduct study assessments, to cover during Dr. MacAleavey's parental leave.**
- **Recruitment activities**
  - **In total, 549 people have inquired about the study, 403 were offered the opportunity to be screened for the study; of these 279 participated in the phone screen, and 96 were assessed in person. 33 were randomized and 28 had begun treatment. The following exclusion reasons are not mutually exclusive: 22 were ruled out due to medical co-morbidities; 23 were ruled out due to drug use, 24 were ruled out for psychiatric reasons; 6 were ruled out for other causes. 8 were randomized to treatment. 16 participants have now completed treatment and 16 have completed their follow-up phone call one week after completion.**

- **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 CHART: See attached.**

9. APPENDICES: **QUAD CHART**

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:** $2,013,415

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.

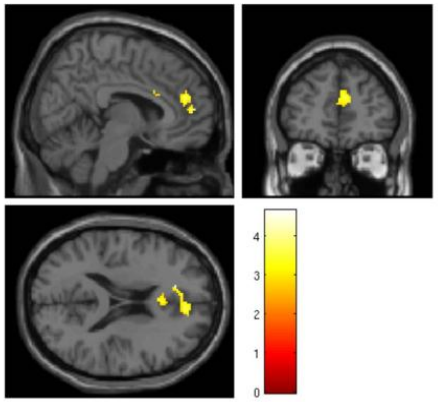
Approach

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.

Timeline and Cost

Activities	CY15-CY16	CY17	CY18	CY19	CY20
Study Set Up					
Randomized Control Trial					
Data Analysis					
Dissemination					
Estimated Budget ($K)	**$731,565**	**$538,427**	**$307,913**	**$359,035**	**$3,981**

Updated: December 1, 2020



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: Database locked, analysis in progress

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*
☑Screen, randomize patients, execute protocol tasks over 18 weeks
☑Cornell IRB renewal ☑ DSMB renewal ☑ HRPO renewal

CY18 Goal – *Randomized Control Trial*
☑ Cornell IRB renewal ☑ DSMB renewal ☑ HRPO renewal
☑Continue to Screen, randomize patients, execute protocol

CY19 Goal – *Randomized Control Trial*
☑Continue to Screen, randomize patients, execute protocol

CY20 Goal – *Randomized Control Trial and Data Analysis*
☑ Database lock, unblinding
☐ Analysis and Dissemination of findings

Comments/Challenges/Issues/Concerns

- Recruitment and retention and COVID-19 delayed timeline
- 3 month extension granted

Budget Expenditure to Date
Projected Expenditure: $2,013,415 Actual Expenditure: $2.009,434