

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.

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Fort Detrick, Maryland 21702-5012

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| 14. ABSTRACT In this reporting period, year 4 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. Eight patients were enrolled in year 4 with a total of 33 patients randomized to date. In the fifth year of the project, the major objective will be to complete follow up assessments, database lock and unblinding, and perform analyses according to specifications. | | | | | |
| 15. SUBJECT TERMS PTSD; SRX246; Vasopressin 1a receptor antagonist; Phase II proof of concept clinical trial | | | | | |
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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 4 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 |
|--|------------------------------|
| <i>Milestone Achieved: Local IRB renewal at WCMC</i> | Completed 10Sep2019 |
| <i>Milestone Achieved: DSMB renewal</i> | Completed 06Jun2019 |
| <i>Milestone Achieved: HRPO renewal</i> | Completed 28Dec2018 |
| <i>Milestone Achieved: Personnel hired and trained,</i> | Completed 04Jun2018 |
| <i>Milestone Achieved: 8 Patients Enrolled this Reporting Period</i> | Completed 29Sept2019 |

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 2019 and the first quarter of 2020 we expect to:

- a. Complete follow up assessments**
- b. Complete subject recruitment**
- c. Database lock and unblinding**
- d. 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

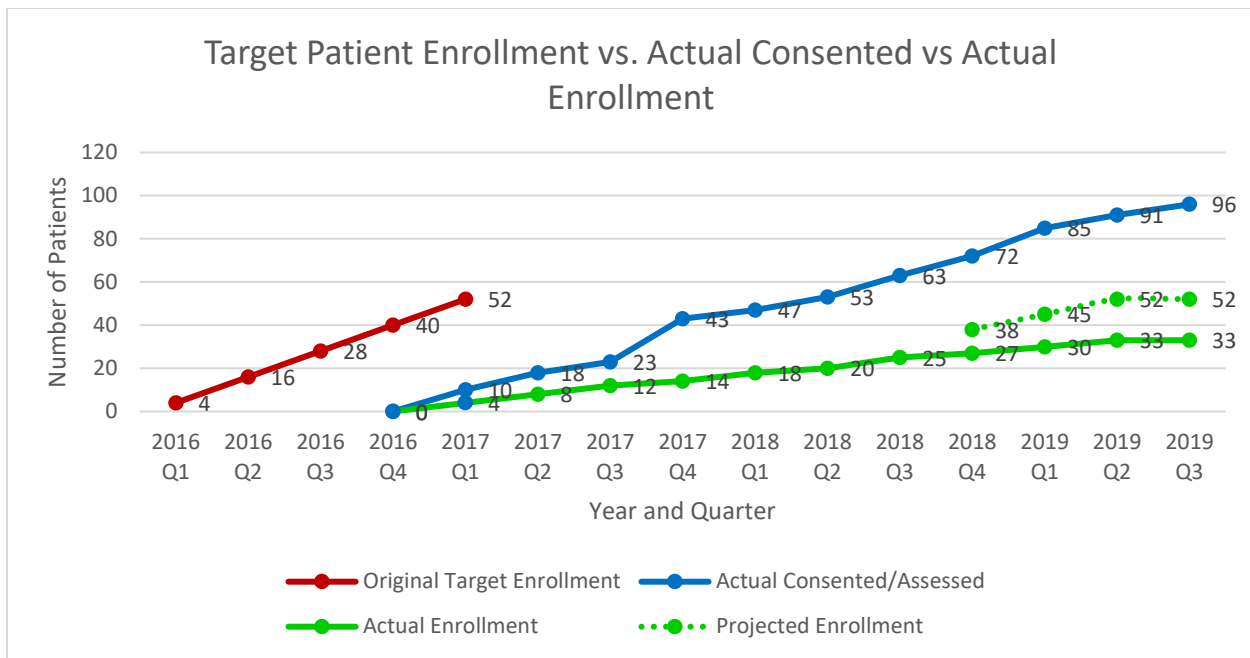
5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

We expanded our advertising efforts (including online postings, flyering and community events) over the past year. These efforts have been successful in generating new study contacts (a total of 173 study contacts have been made in the past year between 10/1/18-9/29/19), As such, we continued to try to recruit subjects through new methods, while maintaining our otherwise successful efforts. Specific new methods included greater staff presence at veterans' events and outpatient medical clinics, continued efforts to generate direct referrals from colleagues, and utilizing websites, such as ResearchMatch. Additionally, we have particularly increased our recruitment efforts through our engagement with the Emergency Department and the William Randolph Hearst Burn Center at NewYork-Presbyterian/Weill Cornell Medical Center. Consistent with prior years, there have been a high number of medical exclusions, hence we continue to need to contact and screen many more individuals than would be eligible.



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: 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

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: 4
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: 2
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: Mariel Emrich
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?

- **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
- 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 the past year (10/1/18-9/29/19) during the period covered by this annual report, 173 people have inquired about the study, 138 were offered the opportunity to be screened for the study; of these 96 participated in the phone screen, and 32 were assessed in person. The following exclusion reasons are not mutually exclusive: 5 were ruled out due to medical co-morbidities; 6 were ruled out due to drug use, 7 were ruled out for psychiatric reasons; 3 were ruled out for other causes. 8 were randomized to treatment.
 - 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



PI: Neal G. Simon, Ph.D.

Org: Azevan Pharmaceuticals

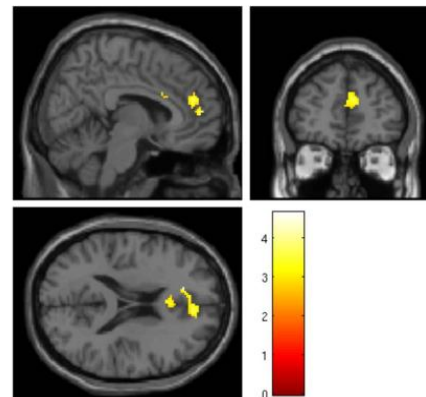
Award Amount: \$2,013,415

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.



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 Renewal Secured

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

CY19 Goal – Randomized Control Trial and Data Analysis

Database lock, unblinding, completion of analyses

Dissemination of findings

Comments/Challenges/Issues/Concerns

• Recruitment and retention delayed timeline

of 1012 month extension (2019-2020) approved

Budget Expenditure to Date

Projected Expenditure: \$2,013,415 Actual Expenditure: \$1,736,950

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 | \$76,475 |