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PRINCIPAL INVESTIGATOR: Tracy Nolen, DrPH

CONTRACTING ORGANIZATION: Research Triangle Institute, Research Triangle Park, NC

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14. ABSTRACT

The goal of the Pharmacotherapies for Alcohol and Substance Use Disorders Alliance (PASA) is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD). In the eighth year, the consortium continued to support two clinical trials, the PT150 PK study and the Davis and Petrakis multi-site study. The PT150 PK study completed enrollment and the Davis and Petrakis study completed enrollment and primary results manuscript was published.

15. SUBJECT TERMS None listed.

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1. Introduction

The Pharmacotherapies for Alcohol and Substance Use Disorder Alliance (PASA) is funded by the Congressionally Directed Medical Research Programs (CDMRP) as part of its Alcohol and Substance Use Disorder Research Program (ASUDRP). The goal of the PASA is to fund research for developing new medications that can improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to post-traumatic stress disorder (PTSD) and other psychological disorders. Research proposed can be for an alcohol use disorder (AUD), substance use disorder (SUD), or both an AUD and SUD.

Clinical trials that include military service members and Veteran populations are highly desirable because these comorbidities are common in these populations. Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. FDA approved pharmacotherapies are available for AUD, OUD, and PTSD. While traumatic brain injury (TBI) is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies.

Under a Cooperative Agreement, RTI International is partnering with the CDMRP to solicit, select, and operationalize research studies that support the goals of PASA.

PASA has three aims under the primary objective to develop medications to treat ASUD in the context of the reciprocal relationship between ASUD, the physiological state of stress, and the subjective state of anxiety as manifested in PTSD) and other psychological disorders. The three broad aims are:

- ***Aim 1****: Discover: Test new chemical entities and repurpose existing medications in strictly pre-clinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.*
- ***Aim 2****: Phase 1 First-in-Human Safety: Conduct clinical trials of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.*
- ***Aim 3****: Phase 2 Efficacy: Conduct multiple site clinical trials to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications*

2. Keywords

- alcohol and substance use disorder (ASUD)
- alcohol use disorder (AUD)
- substance use disorder (SUD)
- opiate use disorder (OUD)
- post-traumatic stress disorder (PTSD)
- pharmacotherapy

3. Accomplishments

In Year 8, the PASA Core research program continued activities related to management, oversight, and close-out of the ongoing clinical studies funded under PASA1.

- Enhanced operationalization of ongoing PASA-funded studies via:
    - AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150:
        - Ongoing management, including 3 DSMB reviews.
        - Working on CDISC compliant dataset and documentation development for regulatory reporting requirements with efficiencies made via use of standards developed for prior PT-150 study.
        - Completed enrollment, working on clinical study report and primary manuscript.
- Supported reporting out of completed PASA-funded studies via:
    - Completing study conduct, analyses and published primary manuscript for AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD/Dr. Davis.
        - Primary manuscript published during this reporting period (07/19/2023).

3.0.a Primary objectives and milestones for the eighth year were:
A PASA objective is to efficiently manage and monitor studies that lead to accurate, quality data for publication and dissemination. This is achieved through PASA management responsibilities such as regularly scheduled check-ins, follow-ups, data accountability, statistical analysis, quality control and assurance, and other oversight activities.

Consistent with the 3 Aims of this program as detailed in the Introduction, the overall focus of the PASA project is in (i) aiding in establishing priorities and endpoints for each project; (ii) providing scientific guidance in achieving project goals; and (iii) facilitating the navigation of challenges incurred in study conduct toward successful and timely completion of objectives. PASA ensured close communication with all research sites and tracked status through shared internal documentation.

For year 8, the PASA1 focus was close-out and completion of the remaining previously funded clinical trials.

3.0.b Accomplishments under the goals include:

- Monitored and supported ongoing studies.
- Closed out one clinical trial.

3.0.c Training and professional development provided:
The PASA data coordinating center (DCC) staff performing study related activities on PASA are responsible for complying with training requirements set forth by RTI and federally mandated regulations. All PASA DCC staff performing study related activities train on the PASA and RTI standard operating procedures (SOPs). Exceptions to this requirement are for staff who solely manage either the PASA website or manage the financial/subcontracting processes. Individual staff are responsible for providing documentation of current training for central PASA files.

For study site staff, PASA monitors that personnel are adequately trained on all relevant study documents, as warranted per their study role, including but not limited to the study protocol, manual of procedures (MOP), electronic data capture system (EDC), and other applicable study procedures, materials and tools.

3.0.d Dissemination to communities of interest:
PASA hosts a public and private website [https://pasa-research.org]. The private side of the website is password protected and has role-based access for unaffiliated individuals, PASA-affiliated individuals, and funded researchers. An expertise directory, study specific templates, tools, dashboards, and trackers are accessed via the private side of the portal. The public side of the website allows dissemination of public information on PASA, including updates on completed research and information on funding opportunities.

PASA personnel disseminate study results and data through regulatory submissions to the FDA, study specific manuscripts, conference workshops and presentations, and other modes of public dissemination (e.g., the website).

3.0.e Plans for next reporting period to accomplish goals and objectives:
PASA leadership will continue to provide comprehensive support to close out the currently funded study, over the next reporting period. Areas of focus include the completion of required regulatory reporting (e.g., clinical study report and CDISC compliant datasets) and dissemination of data via a primary manuscript.

3.1 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517) (completed enrollment, clinical study report and primary manuscript pending)
The primary purpose of this Phase I, single center drug study is to evaluate the safety and tolerability of PT150 in combination with alcohol and to determine the amount of PT150 and alcohol in blood (i.e., the pharmacokinetic (PK) interactions between alcohol and PT150) in 10 non-treatment seeking participants.

The objective of this study is to assess the possibility of any adverse interactions between alcohol and PT150. While PT150 might be effective in the treatment of AUD, because alcohol can affect the way that PT150 is metabolized in the body, the study team first need to determine 1) that it is safe to take PT150 in combination with alcohol, and 2) the amount of PT150 and alcohol in blood after PT150 has reached steady state.

3.1.a Primary objectives and milestones for the year were:
The primary objective includes assessing if measures of concentration and timing of PT150 levels in the blood differ between the PT150 challenge (challenge on Day 8 and continually observed through Day 9) in combination with alcohol (ethanol beverage) compared to the steady-state PT150 challenge, absent alcohol challenge, on Day 7.

Secondary objectives are to determine if measures of concentration and timing of BAL in the blood differ between the active alcohol challenges only (Day 1/baseline) and PT150 challenges in combination with alcohol challenges (Day 8). Other secondary outcomes include evaluating health and safety outcomes as well as withdrawal from alcohol.

All goals were accomplished during the past year. The 10th and final study participant completed study procedures on 09/29/2023.

A routine audit by the MEDVAMC Compliance Office yielded no findings and reflected the research team's dedication to ensuring that the study is conducted in accordance with regulatory policies and procedures. Administrative goals for the year include specimen shipment

to various collaborators, with a goal to complete the shipment of all study samples by 10/31/2023. Final database lock is set to occur by 11/30/2023.

3.1.b Accomplishments under the goals include:
The research team consented 16 potential participants this year. Of those, 10 were enrolled into and completed the study.

3.1.c Training and professional development provided:
Baylor College of Medicine and the Michael E. DeBakey VA Medical Center regularly provides training courses for research personnel. Trainings seminars at Baylor College of Medicine are conducted by the Office of Research and Sponsored Programs Office and are Society of Clinical Research Associates (SOCRA) approved training programs.

3.1.d Dissemination to communities of interest:
Study closeout, clinical study report and CDISC-compliant datasets for FDA submission, and manuscript finalization and submission for publication will occur during next quarter.

3.1.e Plans for next reporting period to accomplish goals and objectives:
All recruitment goals have been accomplished. FDA clinical reports and manuscripts will be prepared during the next quarter.

3.2 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD (closed, with manuscript publication this reporting period)
The use of medications that result in kappa opioid receptor (KOR) antagonism represents a novel potential treatment for Veterans and Service Members with comorbid alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). The combination of buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, and naltrexone, which blocks the mu receptor, yields a pharmacological net effect of a KOR antagonist. The use of buprenorphine in a non-opioid dependent population has ethical implications given its risk of addiction, which has led to the idea to combine it with naltrexone in order mitigate the potential for misuse. KOR antagonists are being developed by the pharmaceutical industry, but until available for investigator-initiated trials, the combination of buprenorphine and naltrexone allows for a proof-of-concept study until a formulated KOR-antagonist becomes commercially available.

Further, preclinical studies suggest KOR antagonism is important for drinking behavior, stress induced reinstatement of drug and alcohol consumption. Clinical studies have shown that KOR antagonists have therapeutic effects in treatment-resistant depression compared to placebo. For these reasons, there is substantial interest in the development of KOR antagonists for indications such as AUD and PTSD.

3.2.a Primary objectives and milestones for the year were:
The over-arching objective of this study was to evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid AUD and PTSD.

- ***Aim 1:*** *To evaluate the efficacy of SL-BUP + XR-NTX in the treatment of comorbid moderate-to-severe AUD and PTSD based on a response in both AUD and PTSD outcomes.*
- ***Aim 2***
  - ***2a:*** *Examine the baseline association between fear extinction and PTSD symptom severity in participants with comorbid AUD and PTSD.*
  - ***2b:*** *Examine the baseline association between Psychophysiological Reactivity to a Trauma-Relevant Stimuli and PTSD symptom severity.*

    - ***2c:*** *Examine the baseline association between Psychophysiological Reactivity to Alcohol-Cues Stimuli and measures of alcohol craving.*
- ***Aim 3:*** *Examine the association of baseline fear extinction, stress reactivity, and treatment outcomes.*
- ***Aim 4:*** *Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at week 8. An early indication of signal detection can be used in the future to enhance precision medicine treatment decisions.*

3.2.b Accomplishments under the goals include:
Data were analyzed and a primary manuscript was published.

3.2.c Training and professional development provided:
No training was required as enrollment into the study was halted on 03/24/2022 (due to futility).

3.2.d Dissemination to communities of interest:
07/19/2023: The research team published their primary manuscript in the Al*cohol: Clinical and Experimental Research* Journal.

> *Davis LL, Petrakis IL, Pilkinton PD, Nolen T, Vandergrift N, Hirsch S, Norrholm SD, Kosten TR. Comorbid alcohol use disorder and post-traumatic stress disorder: A proof-of-concept randomized placebo-controlled trial with buprenorphine and naltrexone combination treatment. Alcohol Clin Exp Res (Hoboken). 2023 Jul 19. doi: 10.1111/acer.15155. PMID: 37468230.*

3.2.e Plans for next reporting period to accomplish goals and objectives:
Study has completed; no further goals to accomplish.

4. Impact

4.0 PASA Core
The work, findings, and specific products of the projects sponsored through PASA are ongoing, but collaboration on required regulatory reports, manuscripts and presentations has provided quality data to push innovations forward. As PASA continues to finalize and publish regulatory reports and additional manuscripts, this strengthens PASA's impact. PASA has continued to develop working relationships with several VAMCs, for conducting PASA clinical studies, across the USA. PASA has leveraged knowledge across studies conducted within PASA, as well as knowledge from clinical trials conducted outside of PASA, to help inform funding decisions for compounds being studied within PASA.

4.1 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)
The study has completed and the study team is developing the clinical study report and primary manuscript.

4.2 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD
The study enrollment was closed as of 03/24/2022, and the results were published in a peer-reviewed journal during this reporting period (07/19/2023).

5. Changes/Problems

5.0 PASA Core

The co-PI for this contract was changed from Dr. Nathan Vandergrift to Dr. Ryan Whitworth.

Regulatory approvals from FDA and DoD advisory boards and local IRB and VA R&D committees remain on track for successful resolution of all projects.

5.1 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

The research team modified the BCM protocol at the request of The Office of Research Oversight and Research Compliance Services. This modification addressed parameters regarding the Certificate of Confidentiality (CoC) and the inclusion of research data into the participant's medical record. Amendments regarding the CoC were approved on 06/30/2023. The research team also modified the master protocol to expand the inclusion/exclusion criteria the provide clarification on permissible medications. The protocol was updated to reflect the following changes:

- A change is permissible (contraceptive methods for female participants).
- A completion bonus for participants who complete Day 9 study assessments.

The research team encountered some protocol deviations relating to sample collection times during the review period. A summary of protocol deviations are as follows:

- Sample collection for the following participants occurred outside of the allowable +/- 10-minute window during in-patient days: 01C053; and 01C057.
- 1 participant (01C053) did not consume the total volume of the alcohol drink on Day 7 of enrollment.

The local IRB reviewed protocol deviations relating to sample collection in August of 2023, and determined no action be taken at the local level.

5.2 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

Enrollment, recruitment and randomization ended on 03/24/2022 due to results of a futility analysis. The project has completed all deliverables, including the publication of their primary manuscript this reporting period (07/19/2023), therefore, no issues anticipated since the study is closed.

6. Products

6.0 PASA Core

Specific products that have resulted from these projects during the reporting period include conference papers, presentations, and publications.

Presentations

- None this reporting period.

Publications

- Comorbid Alcohol Use Disorder and Post-Traumatic Stress Disorder: A Proof-of-Concept Randomized Placebo-Controlled Trial with Buprenorphine and Naltrexone Combination Treatment; Lori L Davis, Ismene L Petrakis, Patricia D Pilkinton, Tracy Nolen, Nathan Vandergrift, Shawn Hirsch, Seth D Norrholm, Thomas R Kosten; Alcohol Clin Exp Res (Hoboken) . 2023 Jul 19. doi: 10.1111/acer.15155. https://pubmed.ncbi.nlm.nih.gov/37468230/

7. Participants and Other Collaborating Organizations

RTI International - Management Core

Last Name, First Name	Project Role	Level of Effort
Nolen, Tracy	Principal Investigator	8%
Whitworth, Ryan	Co-Principal Investigator	7%
Kendrick, Amy	Lead Project Manager	18%
Abella, Julie	Financial/Subcontracts Manager	11%
Arafat, Dana	Financial/Subcontracts Manager	1%
Beverly, Jennifer	RFA Support	1%
Bradley, Lauren	Research Coordinator	1%
Chang, Samantha	Programmer	4%
Gatto, Gregory	Regulatory Affairs Lead	5%
Gizlice, Selen	Statistician	5%
Ham, Michael	Website admin/developer	2%
Hirsch, Shawn	Statistician	4%
Hudspeth, Julie	Financial Analyst	1%
Nowak, Kayla	Statistician	15%
Smith, Emily	System Analyst	1%
Talbert, Jennifer	Research Coordinator	12%
Tang, Yan	Programmer/Analyst	1%
Thomas, Brittany	System Analyst	1%
Tillman, Stefanee	Statistician	2%
Turner, Eugene	Clinical Data Manager	3%
Vandergrift, Nathan	Statistician	1%
Williams, Alexis	Research Coordinator	7%
Williams, Kristi	Research Coordinator	2%

Baylor College of Medicine - Management Core

Kosten, Thomas	Co-Principal Investigator	25%
Domingo, Coreen	Site Coordinator	75%

Baylor College of Medicine

AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

Verrico, Christopher	Principal Investigator	50%
Kosten, Thomas	Co-Principal Investigator	0% (no cost)
Vaughan, Adetola	Study Coordinator	50%
Sibley, Alexandra	Co-Investigator	0%
Vennaman, Sandy	Research Nurse	20%

Veterans Medical Research Foundation

AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)- Labs

Dewleen Baker, then Risborough, Victoria	Principal Investigator	8%
Patel, Anjana	Project Manager	2%

*Dr. Baker retired as of 06/30/2023 and Dr. Risborough transitioned into PI position.

Tuscaloosa Research & Education

AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of AUD and Comorbid PTSD

Davis, Lori	Co-Principal Investigator	20%
Petrakis, Ismene	Co-Principal Investigator	20%
Norrholm, Seth	Co-Investigator	5%
Pilkinton, Patricia	Co-Investigator	10%
Brittney Washington-Ball	Study Coordinator	100%
Newcomb, Jenelle	Primary Study Coordinator	90%
Serrita, Jane	Independent Assessor	14%
Marlo Mccaw	Back-up Study Coordinator	50%
Shalonda Barnes	Back-up Coordinator	<5%
Emily Pisani	Back-up Study Coordinator	5%
Lucienne Levy	Back-up Study Coordinator	34%
Palmissano, Alexandra	Independent Assessor	<5%
Ralevski, Elizabeth	Co-investigator	<5%
Yoon, Gihyun	Co-investigator	<5%

*Subcontract ended on 03/31/2022. However, the above numbers are included because it was the effort reported when the contract was in effect (which is within this reporting period).

7.1. AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

7.1.a. What individuals have worked on the project?

Dr. Christopher Verrico (PI): Responsible for all trial activates conducted at the Michael E. DeBakey VA Hospital and Baylor College of Medicine; responsible for reviewing and confirming participant eligibility.

Dr. Thomas Kosten (Co-PI): Responsible for performing and overseeing study related procedures; responsible for making important study related decisions in compliance with the ethical conduct of the study.

Dr. Alexandra Sibley (Co-I): Responsible for obtaining medical history; conducting screening and post study physical exams; evaluates study related test results; responsible for assessing adverse events.

Ms. Adetola Vaughan (Study Coordinator): Responsible for managing day-to-day conduct of the study; responsible for ensuring that the research is conducted in compliance with the study protocol as well as federal, state and institutional guidelines and regulations; responsible for making changes to the IRB and communicating changes to the IRB.

Ms. Sandy Vennaman (Research Nurse): Responsible for in-patient care of research participants, venous sample collection; assess the research participant's health and review of adverse events.

7.1.b. Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

Dr. Dewleen Baker retired 06/30/2023 and Dr. Victoria Risborough replaced Dr. Baker's role in the biospecimen analysis for this project.

7.1.c. What other organizations have been involved as partners?

San Diego VA, UCSD, and Palisades Therapeutics have been active partners for this project.

7.2. AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of AUD and Comorbid PTSD

7.2.a. What individuals have worked on the project?

Dr. Lori Davis (Co-PI): no change
Dr. Ismene Petrakis (Co-PI): no change
Dr. Seth Norrholm (Subject Matter Expert: Psychophysiological Testing): no change
Dr. Patricia Pilkinton (Co-I): no change
Dr. Brittney Washington-Bell (Primary Study Coordinator): Efforts ended in October 2021
Ms. Jenelle Newcomb (Primary Study Coordinator): no change
Ms. Jane Serrita Jane (Primary Independent Assessor): no change
Ms. Marlo Mccaw (Back-up Study Coordinator): no change
Ms. Shalonda Barnes (Back-up Study Coordinator): no change
Ms. Emily Pisani (Back-up Study Coordinator): no change
Ms. Lucienne Levy (Back-up Coordinator): no change
Ms. Alexandra Palmissano (Independent Assessor): no change
Dr. Elizabeth Ralevski (Co-I): no change
Dr. Gihyun Yoon (Co-I): no change

7.2.b. Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

As of 07/19/2023, the research team completed all contractual requirements (with the publication of this project's primary manuscript).

7.2.c. What other organizations have been involved as partners?

Alkermes (Vivitrol and placebo) and Tonix Pharmaceuticals (sublingual placebo) were partners for the duration of the study.