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14. ABSTRACT

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). In the fifth year, the consortium completed activities in support of RFA #4. Manuscript development for PT150 Alcohol Interaction study and 2 pre-clinical studies were initiated. The Davis and Petrakis study protocol continued enrollment. The PK study began preparation activities in anticipation of study launch.

15. SUBJECT TERMS

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1. Introduction

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Clinical trials that include military service member and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is 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 ASUD, OUD, and PTSD. While 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 the PASA Consortium.

The PASA Consortium 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 or TBI. The three broad aims are:

AIM 1. Discover novel medications and combination medications for ASUD

AIM 2. Develop these medications through a rational Phase I proof of concept pipeline

AIM 3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

The subject of the Core research program in Houston at Baylor and the Michael E. DeBakey VA Medical Center (MED VAMC) is to help facilitate the issuing of Requests for Research Applications (RFA) on an approximately yearly basis, with the primary goal of providing new medications for substance use disorders (SUD) with comorbid Post-Traumatic Stress Disorder (PTSD) and/or mild Traumatic Brain Injury (mTBI). The purpose of these proposals should fit within three categories of work:

1. Pre-clinically to discover medications using animal models of SUD, PTSD and mTBI;

2. Clinically to test medications which have completed FDA Phase 1 safety testing, in small human studies for safety and some surrogate efficacy measure (e.g. fear potentiated startle for PTSD, drug choice vs money for SUD) in our SUD patients;

3. Larger outpatient clinical trials for late Food & Drug Administration (FDA) Phase 2 multi-site randomized, placebo-controlled clinical trials for proof and concept of efficacy.

Submitted proposals are then evaluated, including planning grants for the larger clinical trial proposals, in order to ensure feasibility. The feasibility assessment is based on novelty, statistical power, subject availability, study design, and scientific significance aligned with stated specific aims and purpose of the proposal. This is an extensive process and includes biweekly conference calls with the RTI Core resources over several months. During this planning, the scope of the research and its trajectory for commercialization through industry collaboration is assessed and facilitated

though discussions of FDA regulatory requirements and the capacity of the pharmaceutical partner to provide the support needed. Expected levels of support minimally include, provision of medications and placebos, investigator initiated Investigational New Drug (IND) filing by citing IND files of the company, and related follow-through to Phase 3 studies and Non-Disclosure Agreements (NDA) filings, if these PASA-DoD studies are successful.

2. Keywords

- alcohol and substance use disorders
- post-traumatic stress disorder
- traumatic brain injury
- pharmacotherapy
- research consortium

3. Accomplishments

3.0 PASA Core

The PASA Core research program continued in year 5 with awarding new studies from the Requests for Research Applications (RFA) #4 and oversight of ongoing animal and clinical studies.

3.0.a Primary objectives and milestones for the fifth year were:

At the start of year 5, we completed the review process for PASA RFA #4b. RTI received and conducted peer review on 10 applications that were reviewed by the Panel. The Panel agreed with RTI's recommendation and one pre-clinical was awarded funding.

A consortium team objective is to efficiently manage and monitor studies that lead to accurate, quality data for publication and dissemination. This is achieved though core management responsibilities such as regularly scheduled check-ins, follow-ups, data accountability, statistical analysis, quality control and assurance, and other various oversite activities. The Core has worked directly with each project in fine-tuning, clarifying, and adjusting endpoints as dictated by planned outcomes as well as interim data analysis findings. Another objective of the core is to ensure the PASA website remains a living entity with constant updates in order to ensure sites and the consortium meet and maintain efficient feasible deadlines and milestones, as well as provide up to date, useful resources and tools.

One objective that formed over the course of the year, was to track COVID-19 barriers and delays. The prespecified goals of all studies were only partially met during FY20 due to the impact of Covid-19 that has caused multiple delays, particularly to Aims 2 and 3 for late Phase 1 and Phase 2 clinical studies requiring human subjects' interaction. Preclinical Aim 1 studies also incurred delays due to temporary closure of some animal laboratories and limiting the number of personnel who could be in the laboratory at the same time, leading to staggering of shifts and reducing lab time to between 2 to 3 days per week. Consistent with the 3 primary objectives of this program as clarified in the Introduction (section I), the overall focus of the Core project is in (i) providing assistance 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. The PASA core ensured

close communication with all research sites and tracked status through shared internal documentation.

3.0.b Accomplishments under the goals include:

- Completed activities in support of RFA #4.
- Dr. Verrico' s PK study was approved for funding under PASA 1.
- Received IRB approval for PK study.
- Developed systems for PK study.
- Convened DSMB to review active studies.
- Begin activities in support of RFA #5.
- Developed manuscripts for the 2 pre-clinical studies being completed by Drs. Haile and Kosten, and by Dr. Becker and 1 clinical study completed by Dr. Verrico.
- Publish Evaluation of the effect of doxasozin and zonisamide on voluntary ethanol intake in mice that experienced chronic intermittent ethanol exposure and stress manuscript in the journal *Alcohol.*
- Two abstracts accepted for the Military Health Systems Research Symposium (MHSRS).
- Hosted a virtual PASA Consortium wide Investigator Meeting.
- Maintain consortium and study progress despite the outbreak of the COVID-19 pandemic (i.e. transitioned to remote investigator meeting, stayed in close communications with and tracked sites' abilities to continue with study activities, revised protocols and submitted to regulatory entities to allow for telemedicine endeavors, etc.).
- Re-launch Davis and Petrakis study post COVID-19 delays.
- Updated and maintained PASA website as it relates to PASA 1 activities.

3.0.c Training and professional development provided:

The PASA Consortium, under PASA 2, also hosted a virtual Investigator Meeting via Adobe Connect in May 2020. This platform allowed for researchers across PASA 1 and PASA 2 to present current study accomplishments as well as provide an open platform for discussion of potential future research concepts.

Additionally, the studies have provided a training ground for medical students, nursing students, and residents. While training opportunities are currently limited due to COVID restrictions, training is provided in conducting patient physicals and implementing study protocol procedures, particularly as relates to patient monitoring while maintaining adherence to study-related and institutionally mandated documentation specifications. For the Houston site, this has occurred under the overall oversight of Dr. Kosten.

Dr. Kosten, because of his position within the MED VAMC, also sponsors all non-VA trainees through the VA's HR processes that provides necessary support and vetting for their engagement in research as non-VA employees on federal VA premises. This engagement also necessitates completion of multiple research related trainings throughout the year with typically annual refresher courses in the protection and safety of human subjects in research, HIPAA (Health Insurance Privacy and Accountability Act), Privacy and Information Security Awareness, Biosecurity training; to name but a few. These trainings largely occur in an online environment and have continued undisrupted for all research personnel.

3.0.d Dissemination to communities of interest:
The PASA consortium currently hosts a public and private website. The private side of the website is password protected and can only be accessed by specified researchers. Study specific templates, tools, dashboards, and trackers are disseminated via the private side of the portal. The public side also allows dissemination of various public recourses and provides updates and opportunities related to PASA to general society.

The Investigator Meeting is another way pertinent information was disseminated to communities of interest. This meeting allowed for PASA collaborators to discuss their own work as well as that of other researchers. Though the meeting was virtual due to COVID-19, the participants responded highly, stating it was beneficial and productive.

The PASA Consortium has also helped in dissemination of study data through collaboration on study specific manuscripts. Consortium personnel provide support in the development and/or finalization of all manuscripts.

3.0.e Plans for next reporting period to accomplish goals and objectives:
Over the next reporting period, one focus will be on helping studies get back on track due to time lost during this ongoing COVID-19 pandemic. Helping studies rework protocols so that, where possible, amenable aspects of studies shift to a virtual environment in order to continue study activities will be a primary focus. An example of this would be expanding effort on initial phone screens in order to have a ready cohort of participants for in-person screening once study re-start is approved. In some instances, via protocol amendment, it may also be feasible to conduct in-person screenings at non-VA sites. Again, the overall intent would be in creating a cohort of eligible participants for study inclusion in order to move forward in the most expedient manner once current research restrictions are lifted. The core also plans to continue providing excellent support for our funded studies. The core plans to collaborate on manuscripts, encourage more conference participation, and host consortium-wide meetings as needed.

3.1 AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

3.1.a Primary objectives and milestones for the fifth year were:

- Finalize Manuscript
- Publication

3.1.b Accomplishments under the goals include:
The study team finalized the manuscript and published in the journal *Alcohol.*

3.1.c Training and professional development provided:
Attended PASA investigator meeting and presented study data.

3.1.d Dissemination to communities of interest:
The team has published study data. It has been disseminated to communities of interest through publication.

3.1.e Plans for next reporting period to accomplish goals and objectives:
Study has concluded; no additional goals.

3.2 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

The subject of this research was to assess potential pharmacotherapies for PTSD (Post-Traumatic Stress Disorder) and AUD (Alcohol Use Disorder) in animal models of these disorders. The purpose of the experiments conducted during the annual period were to assess the impact of ASP8062, a GABA B allosteric modulator, and a positive control (baclofen) on male and female rats lever pressing for alcohol in an operant self-administration paradigm (AIM2). The purpose of experiments for AIM3 was to determine if ASP8062 and doxazosin (positive control) would block stress-induced increases in oral alcohol self-administration in male and female rats. Results showed ASP8062 blocked both alcohol self-administration and stress-induced increases in alcohol self-administration. Overall, all AIMs for this award have been completed with positive impact. The scope or application of this research has been immediate in that clinical trials focused on assessing ASP8062 for AUD in humans began August 2019.

3.2.a Primary objectives and milestones for the fifth year were:

Complete AIM2 and AIM3 of the study and finalize publication

3.2.b Accomplishments under the goals include:

SUMMARY: AIM2

The effects of ASP8062 (1, 3, and 10 mg/kg) and baclofen (0.3, 1, and 3 mg/kg) were assessed on operant self-administration in male and female rats lever pressing for EtOH (ethyl alcohol,10%, w/v) under a FR2 schedule of reinforcement. Once maintenance responding was established rats received four consecutive days of randomly administered vehicle or ASP8062 followed by randomly administered vehicle or baclofen. Active lever presses, reinforcers earned (dipper presentations) and drug seeking (head entries) on day four of testing were analyzed. Compared to vehicle, both ASP8062 and baclofen significantly decreased all measures in both male and female rats with the highest dose producing the greatest reductions. Overall, the findings indicate ASP8062 robustly decreases EtOH reinforcement in rats to a similar degree as baclofen. Results appear to support further clinical development of ASP8062 as a potential treatment for alcohol use disorder in humans.

SUMMARY: AIM3

The effects of ASP8062 (10 mg/kg) and doxazosin (DOX, 1 mg/kg) were assessed on operant self-administration in male and female rats lever pressing for EtOH (ethyl alcohol,10%, w/v) under a FR2 schedule of reinforcement. Once maintenance responding was established rats were exposed to predator odor stress (bobcat urine) then tested again on days 3, 8, 11 and 15. Three different groups of rats received vehicle, ASP8062 or DOX. Active lever presses, reinforcers earned (dipper presentations) and drug seeking (head entries) on two baseline lever pressing days and days post-odor exposure were analyzed comparing change from baseline. Compared to vehicle, ASP8062 significantly decreased all measures in both male and female rats with the greatest reductions occurring on day 15. DOX also significantly decreased certain measures however not to the extent of ASP8062. Overall, the findings indicate ASP8062 robustly attenuates predator-odor induced increases in EtOH reinforcement in rats. Results appear to support further clinical development of ASP8062 as a potential treatment for co-morbid PTSD and AUD in humans.

3.2.c. Training and professional development provided:
Attended PASA investigator meeting and presented study data.

3.2.d. Dissemination to communities of interest:
AIM 2 data were presented at the MOMRP meeting Ft. Detrick, MD, 09/11/2019 "Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder"

3.2.e Plans for next reporting period to accomplish goals and objectives:
Publish manuscript.

3.3 AS140026-A3b PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

The primary purpose of this Phase I, single center drug study is to complete a within-subjects experimental procedure to assess the effects of PT150 on the subjective effects of alcohol in non-treatment-seeking alcohol-experienced volunteers who are veterans. The study will evaluate the safety of study drug PT150 taken concurrently with alcohol in 10 non-treatment seeking participants by evaluating pharmacodynamics and safety endpoints during alcohol challenge before and after 5 days of PT150 treatments when PT150 has reached steady state.

The objectives of this aim are to compare pharmacodynamic and safety endpoints following an alcohol challenge prior to- and concurrent with PT150 treatment. Participants will undergo two alcohol challenges on day 1 separated by 4 hours (one with alcohol, 0.8g/kg; 16% by volume, and one with placebo beverage, 1% by volume, randomly ordered) and receive active study drug (PT150) from days 1-5 (after alcohol challenge for day 1). On day 5, the study drug dosing will be followed by two more alcohol challenges (alcohol and placebo beverage randomly ordered). Physiologic, subjective effects and BAL will be obtained after the alcohol challenges. Participants will be discharged on day 6.

3.3.a Primary objectives and milestones for the fifth year were:
Primary: Change in alcohol-induced effects between day 1 (before PT150 administration) and day 5 (after PT150 administration) on 1) breath-alcohol level; 2) blood pressure; 3) heart rate; 4) scores on the Positive and Negative Affect Schedule; 5) scores on the Alcohol Urge Questionnaire; 6) scores on the Biphasic Alcohol Effects Scale; 7) scores on the Addiction Research Center Inventory; and 8) adverse events. Change in electrocardiogram abnormalities from baseline (i.e., pre-alcohol administration on day 1) to post-treatment (day 6).

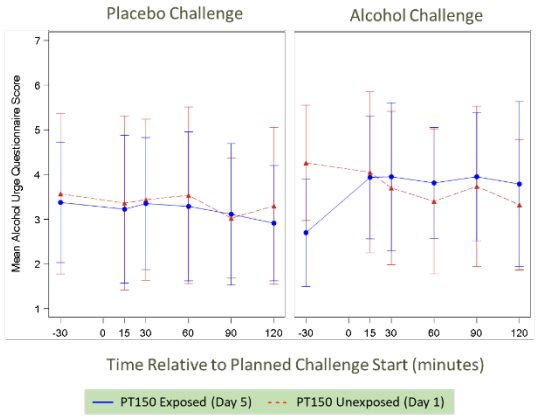
Secondary: Change in alcohol-induced effects between day 1 (before PT150 administration) and day 5 (after PT150 administration) on 1) the Hopkins Verbal Learning Task-Revised; 2) the Dual n-Back task; 3) the Continuous Performance Task-2; 4) the One-Leg Stand test; and 5) the Walk and Turn test.

Administrative goals for the year included reconciliation of data queries; data finalization; and proceeding with the creation of a manuscript. The study team at Baylor College of Medicine continues to collaborate with Dr. Dewleen Baker from the University of California, San Diego and the RTI team to interpret study data and prepare a manuscript for dissemination.

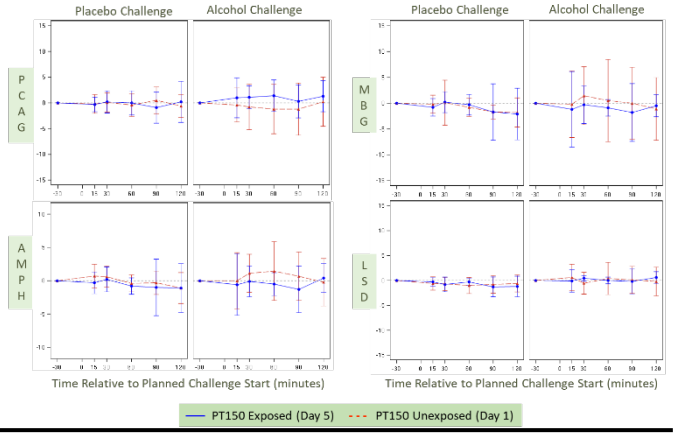
3.3.b Accomplishments under the goals include:

All goals were accomplished during the past year. The 10th and final study participant completed study procedures in JUL-2019. Final data closeout was achieved on 17-February-2020. An abbreviated Clinical Study Report (CSR) was submitted to and accepted by the FDA on 14-September-2020. The CSR. This study provided human safety data needed for the Food and Drug Administration to approve an Investigational New Drug (IND) application to evaluate PT150 as a potential treatment for Veterans with PTSD and co-occurring alcohol use disorder. This study, thereby, paved the way for the recently funded pharmacokinetic study of PT150 as well as the eventual PT150 outpatient study. The results are summarized graphicly below.

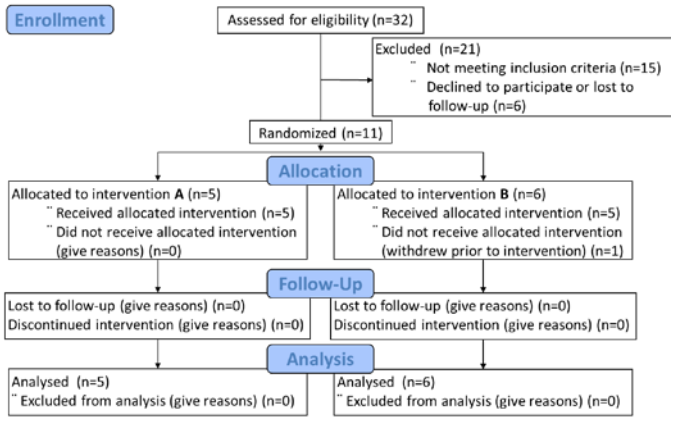
Mean Alcohol Urge Questionnaire (AUQ) Score



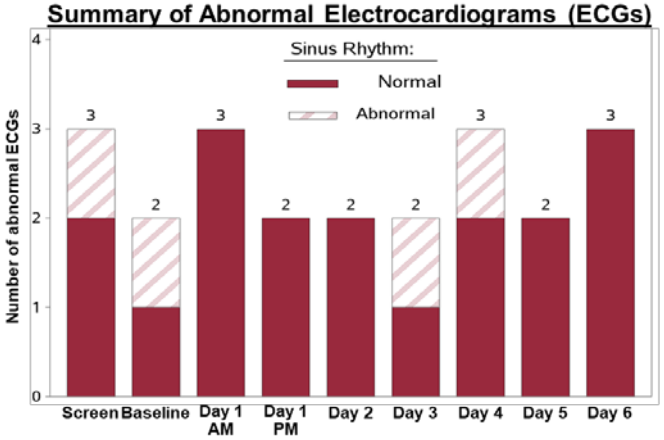
Subjective Effects of PT150 and Alcohol on Mean Addiction Research Center Inventory Sub-scores



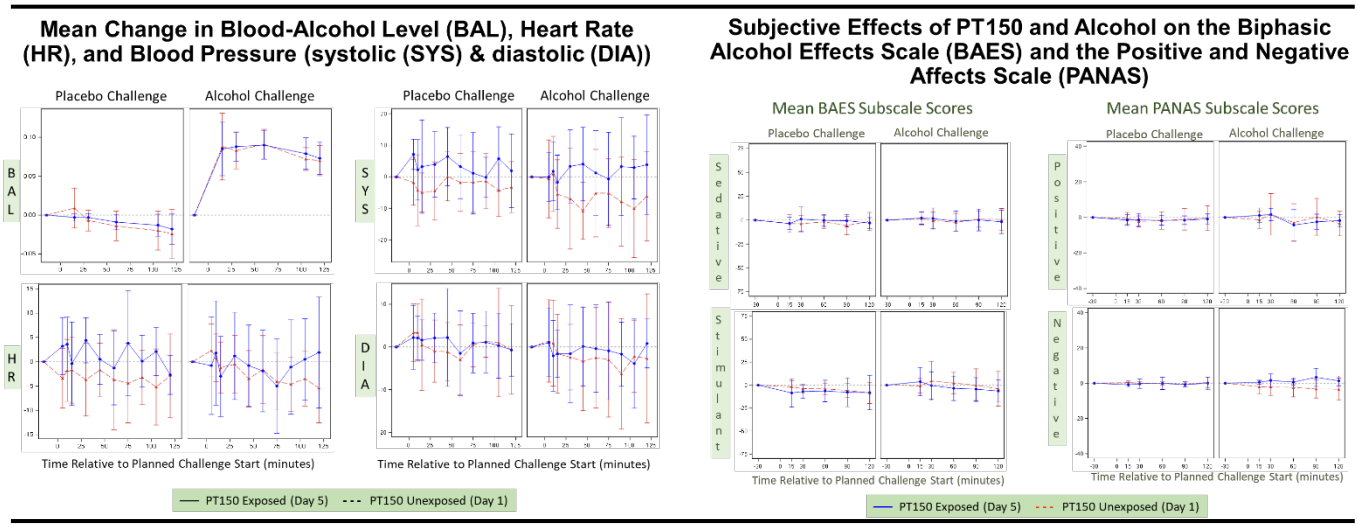
As shown on the right below, of the 32 subjects screened for the study, 11 participants were enrolled and randomized. On average (±SD) the participants were 46 (±11.4) years old (range: 28-63); 91% (10/11) were Male; 73% (8/11) were African American; 27% (3/11) were Caucasian; 18% (2/11) identified as Hispanic or Latino. 1 participant experienced 5 AEs, all were mild severity and not related to the study drug or alcohol/placebo treatment. As shown on the left, 6 participants experienced a total of 22 abnormal ECGs, all were clinically insignificant.



Summary of Abnormal Electrocardiograms (ECGs)



The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the right below for BAL, heart rate and blood pressure. The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the left below for the subscales of the Biphasic Alcohol Effects Scales (BAES), and for the subscales of the Positive and Negative Affect Schedule (PANAS). NOTE: The 'I' bar represents +/- 1 Standard Deviation from the Mean.



The raw means over the course of the placebo challenge and alcohol challenge are shown on the right below for Alcohol Urge Questionnaire (AUQ). The mean change relative to the pre-challenge value over the course of the placebo challenge and alcohol challenge are shown on the left below for the subscales of the Addiction Research Center Inventory (ARCI), which includes the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG; Range 0-15), the Amphetamine Scale (AMPH; Range 0 -11), the Morphine-Benzedrine Group (MBG; Range 0-16) and the Lysergic acid diethylamide Scale (LSD; Range 0-14). NOTE: Time 0 is the start of the beverage challenge, no collections are taken at time 0. The 'I' bar represents +/- 1 Standard Deviation from the Mean.

3.3.c Training and professional development provided:

Baylor College of Medicine regularly provides training courses for research personnel. These training seminars are conducted by Baylor College of Medicine Office of Research and are SoCRA approved training programs.

In addition, several psychiatry residents were involved in the study, providing research training opportunities.

All study personnel also utilized Medidata, an electronic data capture platform, which provided an opportunity to gain proficiency in a research database platform.

Attended PASA investigator meeting and presented study data.

3.3.d Dissemination to communities of interest:

Study closeout occurred in July of 2019. Final AIS study data was downloaded on 17-February-2020. A manuscript describing the study and results dissemination is currently in progress.

3.3.e Plans for next reporting period to accomplish goals and objectives:
Publish manuscript.

3.4 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)
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 purpose 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, we 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. Participants will undergo 10 days of in and out-patient visits while enrolled in the research study. On Day 2 on enrollment the first dose of study drug (PT150) will be given in the amount of 900 mg. The study drug will continue to be given in the amount of 900 mg and administered daily thereafter at approximately 8 AM for the next five days (through study Day 7). Study Day 6 marks the start of the PK assessment phase for PT150 without alcohol, which will continue through Day 7. Day 7 also marks the first day of the PK assessment phase for PT150 with alcohol, which will continue through Day 9. On Day 9, the PK assessment phase for PT150 with alcohol will conclude, and participants will be discharged after health and safety measures. The study aligns with PASA aims for a proof of concept study to assess safety and surrogate markers (extinction learning) of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. The medication is novel and innovative, and the mechanism of action (GR antagonism) for treatment of the key symptoms/behaviors is supported by previous research, including two clinical trials currently underway (PTSD in veterans, AUD is non-veterans) using a drug with a similar mechanism of action. The efficacy is likely via modulation of the stress-axis, which is a logical target for the PTSD+AUD population.

3.4.a Primary objectives and milestones for the fifth 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.

Administrative goals for the year include BCM IRB, R&D committee, and HRPO approval. The execution of a CRADA between Baylor College of Medicine, Poptest and RTI was a major goal during this review period.

3.4.b Accomplishments under the goals include:
In response to the COVID-19 Pandemic, Baylor College of Medicine instituted college wide measures to help limit the spread of the virus and perform responsible conduct of research. Starting March 23, 2020 limited access to research facilities was implemented and all novel

research protocols were suspended indefinitely. The study team plans to resume research activities once research restrictions have been lifted across the institution.

BCM IRB approval was initially granted on 1/29/2019, and again on 4/17/2020 following the submission of multiple amendments to the protocol. R&D committee approval was granted on 3/19/2020. Additional amendments were added to the protocol on 8/28/2020 at the request of the Human Research Protection Office (HRPO) Office of Research Protections (ORP) United States Army Medical Research and Development Command (USAMRDC). The request of additional protocol modifications has delayed HRPO approval. A subcontract between Mayo Clinic, RTI, and Baylor College of Medicine was fully executed on 9/16/2020. A CRADA agreement between BCM, Poptest and RTI is still ongoing.

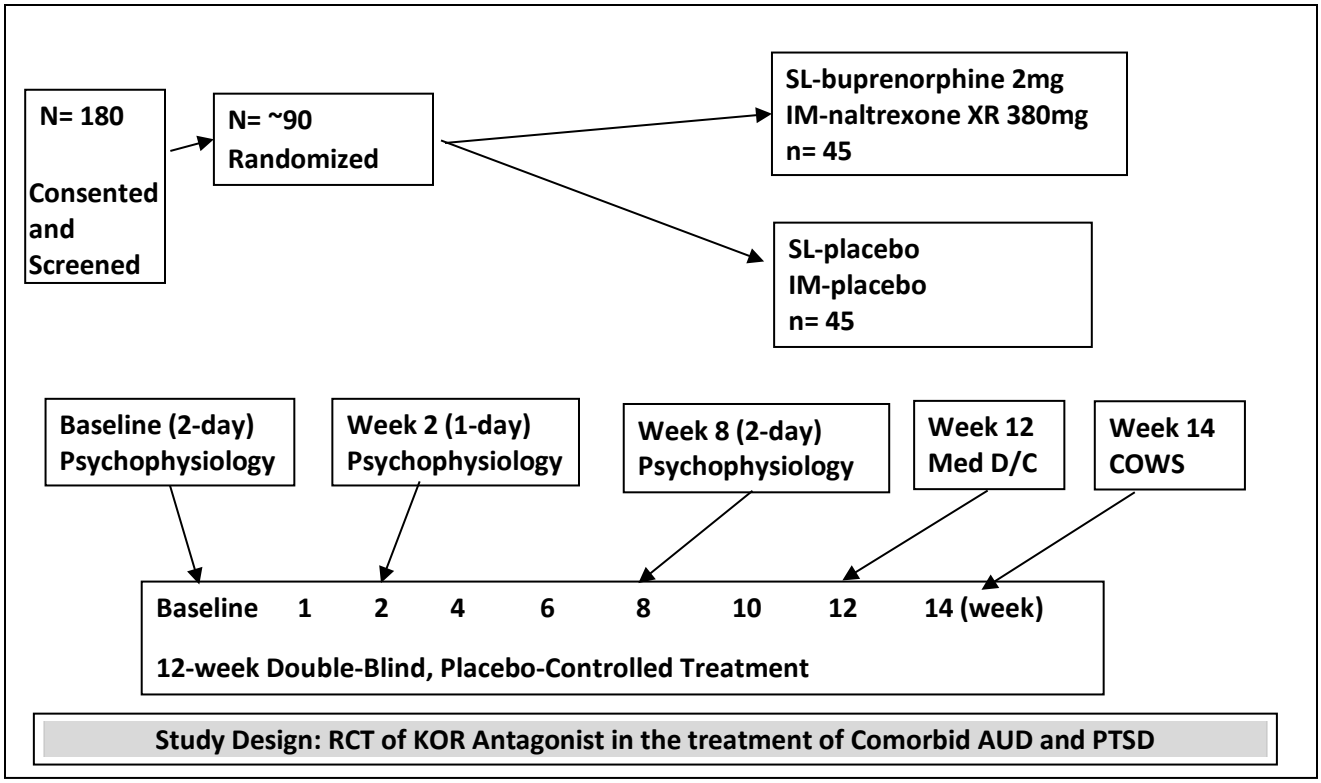
3.4.c Training and professional development provided:
Baylor College of Medicine and the Michael E. DeBakey VA Medical Center regularly provides training courses for research personnel. Trainings seminars at Baylor College of Medicine are conducted by the Office of Research and Sponsored Programs Office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

3.4.d Dissemination to communities of interest:
N/A

3.4.e Plans for next reporting period to accomplish goals and objectives:
Execute CRADA. We anticipate commencement of the study by January 2021. The study team has generated a cumulative list of interested research subjects to recruit from. Once open, those subjects will be contacted and screened for enrollment.

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

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. 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 and the combination of buprenorphine and naltrexone allows for a proof-of-concept study until a formulated KOR-antagonist becomes commercially available. Figure 1 provides an overview of the current research design.



3.5.a Primary objectives and milestones for the fifth year were:
The over-arching objective of this study is 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 2a: Examine the baseline association between fear extinction and PTSD symptom severity in participants with comorbid AUD and PTSD.

Aim 2b: Examine the baseline association between Psychophysiological Reactivity to a Trauma-Relevant Stimuli and PTSD symptom severity.

Aim 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.

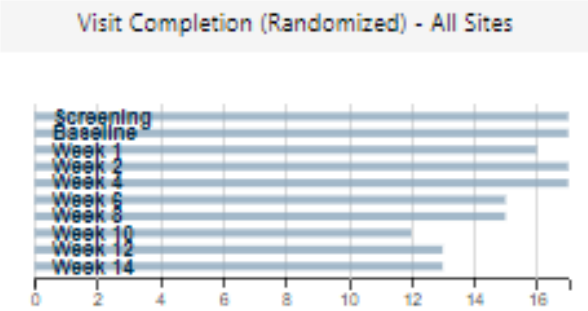
3.5.b Accomplishments under the goals include:
Goal #1: Operationalize the study protocol at all participating sites.
Tuscaloosa (Davis) and West Haven (Petrakis) started FY20 as fully operational. Tuscaloosa opened a satellite site at the Birmingham VA and this site received final regulatory approvals on

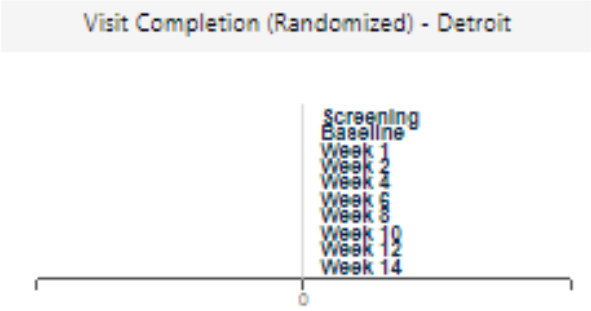
22-Jan-2020. The move of the investigator from Atlanta to Detroit (Norrholm) required the Atlanta site to be closed down and the Detroit site to be initiated. Detroit site received local IRB approval on 05-MAR-2020. Non-pharmaceutical supplies were on station and staff were training on protocol and rating scales by 20-FEB-2020 at the Detroit site. Final approval for Detroit site activation occurred in late SEPT-2020 due to post-COVID administrative hold shipments of study drugs needing to be ordered and received at a time close to actual post-COVID opening of enrollment to avoid drugs expiring before use.

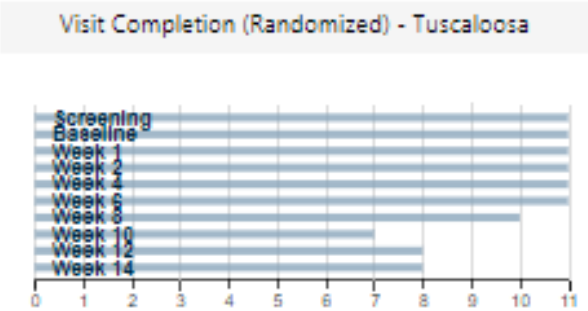
In early MAR-2020, all sites were placed on ADMINISTRATIVE HOLD due to COVID-19 and thus new enrollments were suspended, and in-person visits were minimized as participants previously enrolled were continued in follow-up. The Administrative Holds were lifted at all sites in July/Aug-2020. Supplies, training, and study drugs were refreshed at all sites so that enrollment could officially resume. Recruitment is open, refresher training has been conducted, and all supplies are in place at all sites as of 30-SEPT-2020. Sites will continue to operate using COVID-19 safety measures (minimize in-person visits, wear face masks, maintain social distancing whenever possible, decontaminate high touch surfaces, limit capacity in clinic at any one time, etc.).

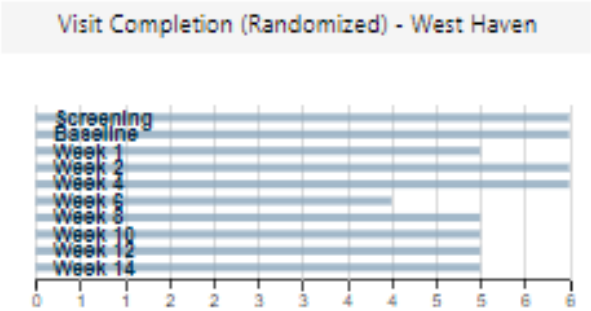
GOAL #2: Randomize 90 participants into the two-arm placebo-controlled study within the allotted enrollment period and retain ≥70% of the randomized sample (n ≥ 63) for the 8-week primary endpoint of the protocol.

Recruitment was not meeting targets at the beginning of FY20. Protocol amendments to improve recruitment and reduce sample size requirements were made by the investigators and approved by DoD, DSMB, local IRBs, and HRPO, including approval to enroll nonveterans, drop the Buprenorphine 8mg arm, add Birmingham VA as a satellite site (22-JAN-2020), and use a commercial recruiting company, called Trialfacts. Recruitment was really starting to pick up at the Tuscaloosa and West Haven site in JAN-2020 and FEB-2020 prior to the COVID-19 pandemic and forced Administrative Hold. After the lifting of the Administrative Hold in JULY/AUG-2020, screening and enrollment resumed at Tuscaloosa and West Haven, but no participants have been randomized since re-opening enrollment.









As shown in the Figure above, as of 30-SEPT-2020,

- First subject enrolled 20-MAY-2019
- 38 consented across both sites
- 17 randomized (11 Tuscaloosa, 6 West Haven)
- 15 completed week 8 (10 Tuscaloosa, 5 West Haven), 88.2% retention
- 13 completed week 14, which is a 76.5% retention rate at week 14.

Based on our new projected enrollment numbers in order to randomize n=90 in the two arm study design by 15-JUN-2021, the investigators would need a total of 10 randomized per month to achieve 90+ enrolled by June 2021 (~3 at each site per month beginning 01-OCT-2020**)**.

GOAL #3. Conduct the Physiological Assessments for Aims 2, 3, and 4.

Prior to COVID-19 pandemic, the 17 participants had already completed the physiological assessments. However, these assessments are currently on hold until safe decontamination protocol of startle booth can be developed and approved by local IRBs. Data for the physiological assessments is being consolidated on the PASA database and is being evaluated for quality so that training and quality improvements measures can be implemented as soon as safety protocol is approved and assessments resume.

3.5.c Training and professional development provided:
Refresher trainings for all sites, as well as for new staff at the Detroit/Wayne State University site were provided:

Start	End	Session 1
8/10/2020	4-5pm ET 3-4pm CT	Protocol Review 1. Aims and Outcomes 2. Treatment Arms 3. Inclusion/Exclusion Criteria 4. Enrollment Goals, Timeline and Recruitment 5. Assessments and Schedule 6. Coordination of the Study Visit Treatment 1. Medication Management 2. Adherence and Retention 3. Drug Accountability (controlled drugs) 4. Maintaining the Blind
		Session 2
8/11/2020	2-4pm ET 1-3pm CT	Labs and Shipping
		CAPS-5
		Session 3
8/12/2020	2-3pm ET 1-2pm CT	Medidata, Randomization, Queries
		Website/Screening Log Document Management • (Regulatory Documents, Source Docs) Reporting Requirements • (Safety, Deviations, Progress reports)
		Session 4
8/13/2020	2-3pm ET 1-2pm CT	Timeline Follow-Back (TLFB) Assessment

Additional one on one training was given to the Detroit staff in September:

1) Session 5: Randomization overview reviewed again with site coordinator and pharmacist
2) Session 6: CAPS-5 training follow-up done with the WSU independent assessor
3) Session 7: Pharmacy manual reviewed again with site coordinator
4) Session 8: Schedule of assessments, organizing visits, visit checklists and visits packets reviewed again with site coordinator

3.5.d Dissemination to communities of interest:
There are no results to disseminate at this time since enrollment and data collection is still ongoing. The investigators were scheduled to present the study rationale and design at the American Society of Clinical Psychopharmacology annual meeting in May-2020, however, the meeting was reduced to a smaller virtual meeting and the symposium was not retained on the shorter agenda.

3.5.e Plans for next reporting period to accomplish goals and objectives:
Goal #1: Operationalize the study protocol at all participating sites.

The investigators will maintain operations at all sites and continue to monitor levels of supplies, study drugs, staffing, and environmental factors. Study supplies and drug expiration dates are

closely monitored so that new supplies and study drugs can be ordered in advance. All new staff members will be immediately trained using archival videos, live web-based training by RTI and Co-PIs, and hands-on training by local site investigators. Regulatory requirements will be closely adhered to and approvals will be sought in advance so that compliance issues do not surface. The budget will be closely monitored to ensure that site resources are stable and sufficient.

GOAL #2: Randomize 90 participants into the two-arm placebo-controlled study within the allotted enrollment period and retain ≥70% of the randomized sample (n ≥ 63) for the 8-week primary endpoint of the protocol.

Assertive recruitment activities will include:

- Daily reach out to clinicians
- WebEx internal in-services
- Chart reviews for clinic patients each week
- Press releases will be issued again
- Flyers and study brochures placed in clinics and community settings
- Mail letters to potential subjects whose names and addresses have been pulled from VA Corporate Data Warehouse (CDW)
- Organize community outreach meeting with NAMI
- Advertise in the newspaper and on social media
- Utilize commercial Trialfacts recruitment services for veterans and nonveterans in the catchment areas of all sites.

Beginning 01-OCT-2020 the sites will collectively randomized 10 participants per month to achieve enrollment goal by June 2021 (~3 at each site per month). The sites will continue the participant engagement tactics to retain ≥70% of the randomized sample through the 8-week primary endpoint visit.

GOAL #3. Conduct the Physiological Assessments for Aims 2, 3, and 4.

COVID-19 safety protocol is being developed, the protocol will be amended, and the amendment will be submitted to local IRBs by 01-DEC-2020 so that the physiological assessments can resume as soon as possible. Refresher training will be given to all staff and quality improvements measures will be put into place prior to resuming protocol activities.

4. Impact

4.0 PASA Core

The work, findings, and specific products of the projects sponsored through PASA are still in progress, but collaboration on manuscripts and publications has provided quality data to push innovations forward. As we continue to finalize and publish additional manuscripts, we strengthen our impact. Another important impact during this reporting period has been with our pharmaceutical company partners. These partners have favorably noted our major accomplishments, innovations, and successes for identifying promising new medications for substance use disorders. We have refined our RFA and project award process to better identify viable projects and to make initial low-funded awards to allow

for better determination of clinical trial needs for potential compounds. We continue to build our template library as well as our website to allow for efficiency and consistency across studies. We have also established excellent working relationships with several VAMCs across the USA for conducting our PASA clinical studies. We have used knowledge across studies conducted within the PASA consortium, as well as knowledge of clinical trials conducted outside of the PASA consortium by our established collaborators, to help inform initial and continued funding decisions for compounds being studied within PASA.

4.1. AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

Results from the experiments conducted have had significant impact. The manuscript has been finalized and published.

4.2. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

Results from the experiments conducted have had significant impact. Manuscript containing the aforementioned data is being generated for publication.

4.3. AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

Results from the experiments conducted have had significant impact. The manuscript is being prepared.

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

The study is still in the stage of start-up, therefore there are no findings available to change practice. There have been no patents or technology transfers developed in this study.

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

The study is still in the stage of enrollment, therefore there are no findings available to change practice. There have been no patents or technology transfers developed in this study. The investigators have noted that participants will respond to advertisement about the study and they report that they had otherwise given up hope for treatment or recovery prior to seeing the opportunity for this research study. Even in the patient is a screen failure, he/she can still be helped by providing education about PTSD and AUD, motivating them to seek treatment, and reconnecting them with treatment otherwise available.

5. Changes/Problems

5.0 PASA Core

The main challenge in the past year has been impact of the COVID-19 pandemic on research. Overall, most of the studies did not experience drastic problems; however, there were some study delays and modifications due to the pandemic. To mitigate study problems as much as possible, the PASA core tracked each site's status and impacted abilities. Though there were some delays, sites are now re-launched and have adapted to the constraints inflicted by COVID. Of important note is that regulatory approvals from FDA and DoD advisory boards and local IRB and VA R&D committees remain on track for successful resolution toward restarting clinical projects once the COVID-19 restrictions are lifted

5.1. AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

No major challenges as study efforts have concluded.

5.2. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

No major challenges as study efforts have concluded.

5.3. AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

Following study close-out, the RTI team identified several queries in the EDC system. Discrepant information involving several subjects needed to be resolved before analysis began. The process of re-reviewing and cross-referencing subject data with the EDC system caused a slight delay in data analysis. All queries were typically resolved within 7-10 days of the initial finding.

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

The COVID-19 pandemic and resulting closures of institutions/organizations has delayed opening the study up for recruitment. We have revised the protocol to include COVID-19 precautions for the subjects and study staff.

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

The protocol was changed to drop the 8mg buprenorphine/placebo arm in order to maximize the efficiency of a smaller sample size and to reduce a concern for side effects caused by the higher dose. The inclusion criterion was changed to allow nonveterans so that the enrollment goal can be met, and more women could be recruited. Birmingham VA was added as a satellite site to increase the number of potential participants. The investigator (Norrholm) moved from Atlanta to Detroit for personal reasons and so there was a site change.

The MAR-2020 COVID-19 shutdown has caused the most substantial delay. After medical centers started to open up their facilities, COVID-19 safety protocols were implemented, and the administrative hold on research was lifted, the investigators have been able to resume recruitment in AUG/SEPT-2020.

The site transition of Dr. Norrholm moving from Atlanta to Detroit caused a significant delay in the third site recruitment. These issues have been resolved and Detroit site is fully operational. The addition of the Tuscaloosa satellite site in Birmingham was intended to mitigate this impact, but COVID-19 shutdown did not allow that strategy time to have full impact. Going forward, the Birmingham site will buffer the three main site's performance and ensure enrollment goals are met.

As stated above, COVID-19 shutdown caused 7 months of no enrollment despite staff being paid. Some of the budget was conserved since Detroit site was not operational for some of this time. The Tuscaloosa site utilized Paycheck Protection Program (PPP) funds to cover $13,210 in coordinator's salary and fringe during slow period due to COVID19. Precautions were taken so as not to "double dip" into Federal funds. In 4th quarter, Tuscaloosa experienced turn over in study coordinators, which meant that salary was not spent and will be applied to the extended period of enrollment. These measures will allow the site to utilize the unspent grant funds to extend the project in keeping with the intended use. RTI is has an approved plan to roll the analytic work into PASA 2, which allows sites to extend enrollment to 15-JUN-2020.

COVID-19 required a change in safety protocols to protect the health of research staff and research participants. These measures were described in detail in the amended protocol and approved by local IRBs.

The COVID-19 safety plan includes:

- Screening for COVID-19 risk before entering medical center
- Wear face mask
- Social distancing as much as possible
- Limit occupancy in clinic
- Telehealth visits as often as possible
- Hold on collection of psychophysiological data
- Allow subjects to record alcohol usage on preprinted calendars in advance
- Allow subjects to be mailed self-reports so these can be completed at home and bring to visits, thus limiting the amount of time in research offices.
- Limit office visits to those which require medication administration and/or lab work, as much as possible.
- Include new mailing letter that addresses COVID-19 concerns.

6. Products

6.0 PASA Core

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

Presentations

Haile, Colin, et al.; Effects of FEN-〖CRM〗^197 conjugate vaccine + dmLT adjuvant with and without buprenorphine on fentanyl nociception in male and female Sprague Dawley rats, Military Health Systems Research Symposium. 2020 August.

Verrico, Christopher, et al.; Pharmacodynamic Interaction Between the Glucocorticoid Receptor Antagonist, PT150, and Ethanol in Healthy Veterans and Civilians, Military Health Systems Research Symposium. 2020 August.

Verrico, Christopher; Pharmacotherapies for Alcohol and Substance Abuse Consortium. A Phase 1 Clinical Trial to Evaluate Pharmacodynamic Interactions after Oral Coadministration of Alcohol and the Highly Selective Glucocorticoid Receptor Antagonist, PT150. 2019 ACNP (American College of Neuropsychopharmacology). 2019 December.

Davis, Lori; Pilkinton, Patricia; Brackett, Stephen; Estes, Sandra; Brown, Ashley; McAlpine, Jessie; Sloup, Sharon; McCall, Kimberly; Leatherwood, Shaquela; Pharmacotherapies for Alcohol and Substance Abuse Consortium. Kappa Opioid Receptor Antagonism in the Treatment of Comorbid PTSD and Heavy Alcohol Use. VISN Research Summit. 2019 November.

Publications

Lopez, M. F., Reasons, S. E., Carper, B. A., Nolen, T. L., Williams, R. L., & Becker, H. C. (2020). Evaluation of the effect of doxasozin and zonisamide on voluntary ethanol intake in mice that

experienced chronic intermittent ethanol exposure and stress. Alcohol. doi:10.1016/j.alcohol.2020.07.005

*others in progress are noted above

6.1. AS140026-A1 Preclinical Analysis of Combined GABA B PAM and Doxazosin Treatments in Stress-Alcohol Drinking Models

Published in *Alcohol* as mentioned above

6.2. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

AIM 2 data were presented for the PASA Consortium online meeting 05/29/2020 "Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder"

In coordination with Astellas (the pharmaceutical company that owns ASP8062) and RTI, a manuscript is in the process of being generated.

6.3. AS140026-A3 PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

Poster presentation was given at the ANCP conference on 12/9/2019

An abstract was submitted to the Military Health System Research Symposium (MHSRS) on 4/8/2020

An abstract was included on the ASADRP Annual Report submitted on 7/23/2020

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

Pharmacodynamic Interaction Between the Glucocorticoid Receptor Antagonist, PT150, and Ethanol in Healthy Veterans and Civilians

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

Pharmacotherapies for Alcohol and Substance Abuse Consortium. Kappa Opioid Receptor Antagonism in the Treatment of Comorbid PTSD and Heavy Alcohol Use

7. Participants and Other Collaborating Organizations

RTI International - Management Core

Nolen, Tracy	Principal Investigator	21%
Baldi, Marjorie	Financial/Subcontracts Mgr	13%
Bradley, Lauren	Research Coordinator	20%
Carper, Ben	Statistician	8%
Crawford, Meg	Research Coordinator	15%
Fain, Katie	Research Coordinator	28%
Hirsch, Shawn	Statistician	2%
Kendrick, Amy	Research Coordinator	25%
LeGrow, Keith	Programmer/Analyst	6%
Nowak, Kayla	Statistician	8%
Riggs, Callie	Financial/Subcontracts Mgr	5%
Roberts, Cheryl	Clinical Data Manager	12%
Tang, Yan	Programmer/Analyst	11%
Turner, Gene	Clinical Data Manager	18%

Vandergrift, Nathan	Statistician	6%
Whitworth, Ryan	Statistician	24%
Williams, Rick	Co-Principal Investigator	11%

Baylor College of Medicine - Management Core

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

University of Houston

Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol use Disorder

Haile, Colin	Principal Investigator	10%
Kosten, Therese	Co-Principal Investigator	10%

Baylor College of Medicine

PT150 (formerly ORG34517) as a potential treatment for alcohol dependence – Alcohol interaction study

Verrico, Christopher	Principal Investigator	50%
Kosten, Thomas	Co-Principal Investigator	15% (no cost)
Vaughan, Adetola	Study Coordinator	15%

Baylor College of Medicine

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

Verrico, Christopher	Principal Investigator	25%
Kosten, Thomas	Co-Principal Investigator	25%
Vaughan, Adetola	Study Coordinator	42.5%

Veterans Medical Research Foundation

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

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

Tuscaloosa Research & Education

Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD Planning Grant

Davis, Lori	Co-Principal Investigator	20%
Petrakis, Ismene	Co-Principal Investigator	20%
Norrholm, Seth	Co-Investigator	20%
Pilkinton, Patricia	Co-Investigator	10%
Brown, Ashley	Primary Study Coordinator	100%
Estes, Sandra	Project Manager, Primary Independent Assessor	50%
McAlpine, Jessie	Study Coordinator	25%
Newcomb, Jenelle	Primary Study Coordinator	100%
Serrita, Jane	Independent Assessor	30%
George, Renie	Independent Assessor	25%
Riser, Manessa	Research Coordinator	75%
Woodford, Jessica	Independent Assessor	10%

7.1. AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

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

Dr. Ray Santullo and the CDMRP PASA Programmatic Panel.
Dr. Paul Blahunka and ASP8062 team at Astellas.

7.2. AS140026-A3b PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

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

Dr. Dewleen Baker at UCSD and the San Diego VA was involved as she originally proposed to evaluate PT150 for PTSD and AUD. The Houston VA was involved after the FDA required phase I studies before Dr. Baker could conduct the outpatient clinical trial of PT150.

DoD Alcohol and Substance Abuse Consortium Award

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PI: Tracy Nolen, DrPH**,** Rick Williams, PhD & Thomas Kosten, MD **Org:** RTI International

Study Research Planning Program RFA

- Reviewed 10 applications and awarded one full study implementation awards for conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials (RFA4b)
- Prepared RFA5 and received Programmatic Panel approval for new expansion award. This award will support the continued research of highly impactful studies that were previously funded by PASA. RFA will be released in study year 3.

Held first PASA Investigator meeting in May 2020. Researchers presented study accomplishments and an open forum was used to discuss potential future research concepts.

Timeline and Cost

Activities	Q1	Q2	Q3	Q4
Complete study review and selection for RFA#4				
Prepare and publish Dr. Becker's pre-clinical study				
Monitor and support Davis and Petrakis Study				
Develop protocol, CRFs and system for PK study				
Monitor COVID-19 impact on studies				
Approximate Cost (k)	$482k	$289k	$531k	$373k

Total Costs: $7,912,668; $3,229,031 remaining

Year 5 Completed Objectives

- Completed study review and selection for RFA#4
- Completed CRF and system design for PT150 PK study
- Continued support of the Davis and Petrakis study
- Published Becker pre-clinical study
- Submitted Clinical Studies Report for PT150 alcohol interaction study

Year 6 Objectives in Progress

- Complete manuscripts for Dr. Haile's pre-clinical study and PT150 alcohol interaction study
- Launch PK study
- Complete enrollment in David and Petrakis Study