

Technical Abstract: A Randomized, Placebo-Controlled Trial of the Dopamine- β -Hydroxylase (DBH) Inhibitor, Nopicastat, for the Treatment of PTSD in OIF/OEF Veterans

BACKGROUND: Preclinical and clinical studies have shown that PTSD is associated with a substantial increase in noradrenergic (NA) activity and that by reducing the NA activity one can improve PTSD hyper-arousal symptoms in humans, as well as in animal models of PTSD. Compelling evidence exists for exaggerated noradrenergic activity associated with PTSD hyperarousal and re-experiencing symptoms, the findings of PTSD symptom provocation with yohimbine (alpha 2-adrenergic antagonist), and the preliminary results of the therapeutic effects of prazosin (alpha 1-adrenergic antagonist). Nopicastat is a new medication under Phase II development that is a potent dopamine- β -hydroxylase (DBH) inhibitor. A DBH inhibitor's mechanism of action is to decrease neuronal noradrenaline (NA) release by inhibiting DBH conversion of dopamine (DA) to NA. A reduction in NA with nopicastat is hypothesized to reduce the hyper-arousal symptoms in patients with PTSD. This study is based on pilot data with disulfiram, which significantly reduced hyper-arousal symptoms in patients with PTSD. This improvement was evident within one month in those who responded to the disulfiram. Disulfiram's mechanism action also appears to decrease NA release from neurons by inhibiting DBH conversion of DA to NA. Nopicastat is selected for this study since it decreases NA more potently and specifically than disulfiram. The optimal dosage of nopicastat for decreasing NA in humans is 120 mg once daily, since this dose has been shown to result in a sustained and substantial NA reduction from baseline in both healthy controls and patients with hypertension. Clinically, in the experience of the clinical investigators, the most common chief complaint of the OIF/OEF veterans with PTSD is hyperarousal (DSM-IV criterion D symptom cluster) and these symptoms significantly interfere with social, occupational, and interpersonal function. Standard treatments with antidepressants are not fully effective in treating the symptoms of PTSD in the veteran population; thus, new treatments are needed. An intervention, such as nopicastat, aimed at reducing hyperarousal, as well as other PTSD symptoms, would have significant impact of restoring the quality of life in OIF/OEF veterans with PTSD.

OBJECTIVE/HYPOTHESES: The current application proposes to increase the number of sites to five (5), increase the sample size to 120, and reduce the time-line by 15 months. By adding two additional sites and increasing the sample size to 120, the proposed expansion of the previously funded 3-site study substantially improves the statistical power to detect CAPS-D (i.e. hyperarousal cluster) differences between treatment groups that would be deemed clinically meaningful and greatly accelerates the time-line to complete the study. The core funded study (identical design) for N=45/group and was designed with adequate statistical power ($\geq .80$) to detect a treatment effect of .70 standard deviation units on the CAPS-D at endpoint. However, this sample size will not have sufficient power to detect smaller, yet clinically meaningful, effects of treatment. With N=60/group the statistical power will exceed .80 for effects of .45 or greater (ICC .60). In contrast, with N=45/group the design will not have adequate power to detect even an effect of .50 sd units. Therefore we propose increasing the sample size to 60/group. With such a change the study would have sufficient statistical power to detect CAPS-D differences between treatment groups that would be deemed clinically meaningful. More importantly, the addition of 2-sites would reduce the time-line currently targeted to be completed in May 2012 to be completed in the Dec 2010 (i.e. reducing total time-line by 15 months). This reduction in time-line substantially advances drug development of a novel medication for treating a priority condition in the military population.

Primary Hypothesis: Compared to placebo treatment, nopicastat-treated OIF/OEF veterans with PTSD will have significantly reduced PTSD hyperarousal symptoms as defined by the Clinician Administered PTSD Scale (CAPS), subscale D (CAPS-D). Secondary hypotheses: Compared to placebo treatment, nopicastat-treated OIF/OEF veterans with PTSD will have significantly reduced PTSD symptoms (total CAPS); significantly reduced PTSD reexperiencing symptoms (CAPS-B); significantly reduced PTSD avoidance symptoms (CAPS-C); significantly higher rates of PTSD response and remission; and significantly improved quality of life.

SPECIFIC AIMS: The primary specific aim is to assess the global efficacy of nopicastat in the treatment of hyperarousal in PTSD in OIF/OEF veterans. The secondary specific aims are to assess the ability of nopicastat to induce PTSD remission; treat PTSD and other PTSD symptom clusters (Criteria B and D), and improve quality of life and overall functioning. An additional aim is to assess the tolerability and side effects of nopicastat in the treatment of PTSD in OIF/OEF veterans.

STUDY DESIGN: This is a multisite, 6-week prospective, randomized (1:1), double-blind, placebo-controlled trial (RCT) of nopicastat (120 mg/day) monotherapy in the treatment of PTSD in 120 OIF/OEF veterans, followed by an 8-week extension phase of nopicastat treatment. During the open-label phase (weeks 7-14), veterans who have a positive clinical response to the study medication, nopicastat vs. placebo, will be continued on the study medication for a total exposure of 14 weeks, in order to assess further improvement and safety. Those patients who do not have a positive clinical response during the 6 week RCT will be offered the addition of the standard first-line PTSD pharmacotherapy, paroxetine, during the 8 weeks of follow-up treatment (weeks 7-14). Thus, weeks 7-14 offer an opportunity to evaluate longer-term nopicastat efficacy and to compare the treatment response of nonresponders after augmentation with the standard pharmacotherapy. The primary outcome variable is the change from baseline in the criterion C (hyperarousal cluster) subscale of the Clinician Administered PTSD scale (CAPS-C). The secondary outcome variables are the total CAPS, CAPS-B, CAPS-C, and others listed in the full protocol.

RELEVANCE: The project will promote development in the pharmacologic treatment of PTSD and, in combination with the partnering PI's current clinical trials, will significantly contribute to the advancement of treatment guidelines and will address critical PTSD research and treatment gaps. *Importantly, this study is a critical step in drug development for a novel medication for an indication of PTSD, an illness that has a substantial prevalence in the military and civilian populations – representing a sustainable market for this a new drug indication.*