Study Protocol, including Statistical Analysis Plan

Official Title:

Does CERC-501 Attenuate Stress-precipitated Smoking Lapse?

Brief Title:

"Does CERC-501 Attenuate Stress-precipitated Smoking Lapse?" (Sherry McKee, PhD, PI)

ClinicalTrials.gov ID: NCT02800928

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Protocol and Statistical Analysis Plan for

"Does CERC-501 Attenuate Stress-precipitated Smoking Lapse?"

(NCT02800928): Sherry McKee, PhD, PI (Yale University)

Scientific Background

There is a significant unmet medical need for treatments that reduce the abuse and dependence of addicting drugs, including tobacco, alcohol, cocaine and opiates. In recent years, opiate antagonists such as naltrexone and nalmefene have been shown to be effective treatments for alcohol and opioid abuse. The effects on tobacco users is equivocal, with well-established effects in short-term laboratory studies of subjective effects, but lack of clear sustained effect on abstinence, perhaps due to the chronic negative effects of mu opioid receptor blockade.

Accumulating evidence indicates that selective antagonism of kappa-opioid receptors (KORs) may provide therapeutic benefit in the treatment of depression. A therapeutic role for KORs in major depressive disorder (MDD) is based upon an emerging scientific literature showing that KORs and the endogenous ligand dynorphin are highly expressed within the prefrontal cortico-striatal loop, which mediates reward and affective states.[1] KOR antagonists have been shown to block stress-induced potentiation of cocaine and conditioned place preference, an animal model of drug relapse.

CERC-501 (previously known as LY2456302) is a high-affinity, selective KOR antagonist being developed for the treatment of substance abuse and MDD, by blocking aversive signaling cascades in the brain triggered by chronic psychological or physical stress.

In a mouse model of precipitated nicotine withdrawal, CERC-501 decreased anxiety-like behavior, somatic signs of withdrawal and hyperalgesia. However, the effects on anxiety and pain behavior had a U-shaped dose response curve, suggesting that doses that selectively block KOR will have the greatest overall effect on symptoms clinically.

In three previous human trials, CERC-501 has been shown to be safe and well tolerated at single oral doses up to 60 mg. At multiple daily doses of 10 mg or less, CERC-501 provides substantial blockade of KOR as assessed in positron emission tomography (PET) imaging studies with minimal effect on mu opiate receptors as assessed by fentanyl-induced miosis.

The current study will evaluate the effect of CERC-501 on the latency to start smoking and the number of cigarettes smoked during the smoking self-administration period after a 18-hour period of abstinence. Subjective measures of cravings, positive and negative mood, and withdrawal symptoms will also be assessed.

Study Objective

The primary objective of this study is to:

To demonstrate that CERC-501 10 mg/day compared to placebo will increase the ability to resist smoking, and reduce subsequent ad-lib smoking following overnight nicotine deprivation and personalized stress imagery in subjects who are heavy smokers.

Study Design and Methods

This is a double-blind, placebo-controlled, two-period, cross-over design examining 10 mg/day CERC-501 compared to placebo in subjects who are cigarette smokers currently not seeking treatment for tobacco use disorder, who currently smoke at least 10 cigarettes per day. Half of the subjects in each group will receive CERC-501 10 mg first in Period 1 and the other half will receive placebo first in Period 1. Each subject will "crossover" to the opposite treatment during Period 2. The crossover design (within-subject analysis) allows the subject to be their own control. Efficacy for CERC-501 on smoking behavior will be assessed in two ways: 1) crossover comparison of CERC-501 10 mg versus placebo; 2) parallel comparison of CERC-501 10 mg versus placebo in Period 1. Gender will be a stratification variable and approximately 50% of the sample will be female.

Sequence 1: CERC-501 10 mg for Period 1 and placebo for Period 2

Sequence 2: Placebo for Period 1 and CERC-501 10 mg for Period 2

After the screening period, subjects will be randomized in a 1:1 manner to one of two sequences (CERC-501 [10 mg] followed by placebo or placebo followed by CERC-501 [10 mg]). Subjects will return to the clinic daily Monday through Friday for supervised study drug administration. On Saturday, Sunday, and holidays the subject will self-administer the study drug. All efforts will be made to have subjects come in for daily medication visits, but if a subject is unable to return for supervised study drug administration, they will be allowed to self-administer the drug. Each period of the crossover treatment consists of a 7-day out-patient treatment period followed by a single in-patient testing day on Day 8. Subjects will participate in a laboratory session following the McKee Smoking Lapse Test[2] and be discharged from the Hospital Research Unit (HRU) to undergo approximately 7 (+3)-day washout period followed by the second period of the crossover design and approximately 7-day follow up visit.

Each laboratory session will consist of an overnight nicotine deprivation period, followed by personalized imagery (stress). After the imagery procedure, subjects will have the option of initiating a tobacco self-administration session or delaying initiation by 5-minute increments for up to 50 minutes in exchange for monetary compensation. Subsequently, the tobacco self-administration session entails a 1-hour period in which subjects can choose to smoke using a smoking topography system. Primary outcomes measures include the time to the first cigarette

(i.e., ability to resist smoking) and the number of cigarettes smoked. Subjects complete a follow-up appointment (approximately 7 +3 days from the second lab session) to evaluate the durability of effects.

Eligibility Criteria

Inclusion Criteria

1. Provides written informed consent and agrees to complete required clinic visits
2. Male or female 21 to 60 years of age inclusive
3. Body mass index (BMI) 18.5 to 40 kg/m2 inclusive
4. Smokes at least 10 cigarettes per day on average for the past 6 months
5. Fagerstrom score ≥3 at screening
6. Currently not seeking smoking cessation therapy
7. Urine dip test for cotinine concentration >150 ng/mL
8. In otherwise good general health without any unstable medical conditions (as determined by medical history, medication history, physical examination, 10- or 12 lead ECG, vital signs, and clinical laboratory testing)
9. Able to read, write, and speak English
10. Females must be either:
    a. Post-menopausal (amenorrhea for at least 12 consecutive months), surgically sterile -or-
    b. Women of childbearing potential (WOCBP) must meet the criteria below:
        i. Uses an acceptable double-barrier method of contraception as determined by the Investigator -and-
        ii. Is not lactating, has a negative serum beta human chorionic gonadotropin pregnancy test at screening and a negative urine pregnancy test prior to dosing on Days 1 and 8 of each treatment period.
        11. Male subjects must agree to use a condom if partner is of childbearing potential

Exclusion Criteria

1. Have used tobacco or other nicotine containing products other than cigarettes (e.g., nicotine patches, pipe, cigars, snuff, chewing tobacco or e-cigarettes) within the past 30 days
2. Any substance use disorder other than nicotine or caffeine as assessed by the Structured Clinical Interview-IV Axis I Disorders (SCID) for Diagnostic[3] and Statistical Manual of Mental Disorders (DSM)[4]
3. Current neurological conditions that interfere with study conduct, assessment or treatment in any significant fashion
4. Any lifetime history of bipolar I, II; schizophrenia or any other psychotic disorders; personality disorders, impulse control disorders as assessed by the SCID-IV

5. Current psychiatric conditions that interfere with study conduct, assessment, or treatment in any significant fashion, such as major depressive disorder (MDD), eating disorders, post-traumatic stress disorder, etc. We will screen for worsening of symptoms of depression and/or suicidality at each medication appointment and lab sessions by having participants complete the Beck Depression Inventory (BDI) and the Columbia-Suicide Severity Rating Scale (C-SSRS)[5]. If there is a worsening of symptoms of depression and/or suicidality, the participants will speak a licensed psychologist for evaluation.
6. Recent active or past history of gastric disease such as peptic ulcer disease, gastritis, upper gastrointestinal bleeding, or any gastrointestinal malignancy or precancerous condition
7. Active, comorbid disease that might limit the ability of the subject to participate in the study as determined by the Study MD (i.e., poorly controlled diabetes mellitus, congestive heart failure, etc.)
8. Clinically significant clinical laboratory test taken during screening
9. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN)
10. Human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C positive as determined by serology testing at Screening
11. Positive ethanol breath test at screening or prior to dosing on Days 1 and 8 of each treatment period
12. Positive urine drug test at screening or and/or prior to dosing on Days 1 and 8 of each treatment period except for cannabis
13. History of severe allergies or multiple adverse drug reactions
14. Known hypersensitivity to CERC-501
15. Current use of a proton pump inhibitor or histamine 2 blocker
16. Use of any investigational medication within 2 months prior to the start of this study or scheduled to receive an investigational drug other than the study drug during the course of this study
17. Current use of any psychoactive medications including: antipsychotics, benzodiazepines, mood stabilizers, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor (SSRI/SNRI) or other antidepressants mood stabilizers

Statistical Considerations

PRIMARY AIM 1. Using a double-blind, placebo-controlled parallel-group design, this Phase II study will randomize 20 daily smokers to either 10 mg/day CERC-501 or placebo (n=10 per group). Following titration to steady state levels, we will evaluate medication effects on stress-induced changes in smoking behavior in the laboratory. Primary Hypothesis 1. During the laboratory component, 10 mg/day CERC-501 compared to placebo will increase the ability to resist smoking, and reduce subsequent ad-lib smoking following overnight nicotine deprivation and personalized stress imagery. Linear mixed models with medication condition (10mg/day or

0mg/day) as a within subject factor will be used to evaluate, in turn, time to smoking, and amount smoked collected in the laboratory.

References

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