Study Protocol, including Statistical Analysis Plan

Official title:
Development of a Novel Therapeutic for Smoking Cessation

Brief title:
"Test of Novel Drug for Smoking Cessation" (Kenneth Perkins, PhD, PI)

ClinicalTrials.gov ID: NCT02217527

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Protocol and Statistical Analysis Plan for

"Development of a Novel Therapeutic for Smoking Cessation"

(NCT02217527): Kenneth Perkins PhD, PI (Univ Pittsburgh)

Scientific Background

Purpose of study: We have partnered with Janssen Research and Development (Johnson & Johnson) to test if an α7 nicotinic acetylcholine receptor (nAChR) positive allosteric modulator (PAM), JNJ-39393406, will promote smoking cessation. Preclinical efficacy/feasibility studies were performed based on highly convincing preliminary data showing that activation of α7 nAChRs decreases rats' motivation to work for nicotine (Brunzell and McIntosh, 2012). A novel, efficient procedure for predicting therapeutic efficacy of smoking cessation drugs (Perkins and Lerman, 2014) will evaluate JNJ-39393406's efficacy in healthy smokers.

Stimulation of α7 nAChRs as a strategy for smoking cessation: Selective stimulation of α7 nAChRs is an innovative strategy for smoking cessation treatment. The highly selective α7 nAChR PAM, JNJ-39393406, could assist individuals in quitting with fewer side-effects than currently available therapeutics. The JNJ-39393406 α7 nAChR PAM proposed ought to work more efficiently and more specifically than an α7 agonist drug in promoting smoking cessation. The JNJ-39393406 PAM does not activate α7 nAChRs on its own, but in binding to an allosteric site (different from the nicotine/ACh binding site) selectively enhances nicotine and ACh activity at the α7 nAChRs. Hence, administration of JNJ-39393406 would be expected to be efficacious for smoking cessation. α7 nAChR PAMs are less likely than a full agonist to lead to neuroadaptations (e.g. of α7 nAChRs) that could result in adverse effects or affect dosing; therefore, JNJ-39393406 would also be expected to exert fewer side-effects than a selective full agonist of α7 nAChRs.

Study Objectives

Aim: To test the proof of principal that JNJ-39393406 promotes smoking cessation. We have developed, tested, and validated an innovative and efficient Phase 2a screening procedure that optimally combines the validity of randomized clinical trials with the practicality of lab- based medication studies. As detailed elsewhere (Perkins & Lerman 2014), it employs a within-subject, cross-over design comparing active versus placebo effects on quitting smoking to maximize statistical power without a large sample. We have demonstrated the sensitivity of this approach in identifying efficacy for biochemically-verified (CO) abstinence in all 3 of the first- line FDA-approved cessation medications, as well as its specificity in identifying lack of efficacy for abstinence in a medication known to not aid cessation. Using this procedure, we will evaluate effects of JNJ-39393406 vs. placebo on short-term smoking abstinence in smokers who already have a high interest

in quitting soon. We predict that, compared with placebo, JNJ-39393406 will increase days of abstinence, identifying initial evidence of efficacy for smoking cessation.

Our main dependent measure is days of very stringent biochemically validated (expired CO<5 ppm) 24-hr smoking abstinence, with post-quit withdrawal and cognitive function as secondary measures. Potential for adverse side-effects will be assessed at each visit. We hypothesize that the number of days of abstinence will be significantly greater for JNJ-39393406 vs. placebo.

Study Design and Methods

Random assignment: Upon entry into the study, subjects will be randomly assigned in double-blind fashion to medication order (active drug then placebo, or vice versa) within the cross-over design. We will use permuted-block randomization to assign subjects to these medication order conditions. The same order assignment will not be repeated more than 3 consecutive times, to prevent an imbalance in the sequence of these orders.

Medication: Active JNJ-39393406 (50 mg tablets), abbreviated here "JNJ" (IND #122957) and matching placebo (both from Janssen Research and Development LLC) will be encapsulated by the WPIC Investigational Drug Service (IDS) research pharmacy. Staff and participants are blind to medication assignment by IDS (i.e. double blind). To start the dose run-up, participants will take one capsule of JNJ-39393406 (50 mg), or identically appearing placebo, once on day 1, incrementing by 50 mg daily to reach 200 mg by day 4. The full dose involves two capsules, each twice per day (100 mg b.i.d. for JNJ), in the a.m. and evening, over the remaining 7 days of that medication condition, including the 5-day practice quit period (Mon-Fri), when they will come to the lab each day to provide CO validation of quit status, plus provide self-reported withdrawal and possible adverse effects. One day will also include computerized test of cognitive processing (see below). One week of *ad lib* smoking follows the first quit attempt phase prior to the dose run-up week with the other condition, to allow separate 3-week tests of each in aiding smoking abstinence.

Procedure: Participation for each subject will be 6 weeks after randomization, involving two 3-week phases, one for each drug condition in this double-blind, crossover procedure. For each phase, visits occur on Mon and on Thurs of the first 2 weeks and Mon-Fri of the third week. CO is assessed upon arrival to each session, along with MNWS withdrawal. Each phase begins with a week of *ad libitum* smoking (baseline, week 1), with drug regimen started on Mon a.m. of week 2 while continuing to smoke (dose run-up). On week 3, they are instructed to try to abstain as of Sun am through the mid-day Fri visit, with CO assessments of quit status on Mon-Fri of week 3. On Mon of week 3, all completed testing of cognitive function (CPT). After Fri of week 3, all then ad lib smoke for at least a week to repeat this 3-week phase for the other condition: smoking without drug (i.e. washout; week 4), next dose run-up (week 5), and trying to quit during Mon-Fri (week 6).

Measures:

Smoking outcome. During the "quit week" (week 3) of each condition, the primary outcome of 24-hr abstinence is assessed daily on Mon-Fri by expired-air carbon monoxide (CO) <5 ppm.

Secondary outcomes. Also examined daily are abstinence symptoms on the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes *et al*.1991), with each item scored on a 0-100 VAS. In addition, we will assess the Penn Continuous Performance Task (CPT) assessing sustained attention (Kurtz *et al.,* 2001; Gur *et al.,* 2010) on Mon of each quit week. Also assessed daily (Mon-Fri) of the two "quit" weeks (weeks 3 and 6) are medication blinding and side-effects, rated on a 0 to 3 scale (none, mild, moderate, severe). Potential adverse effects will also be assessed by repeat of EKG and lab tests (see end of screening in Eligibility section below) on Fri of week 3 on each condition.

Eligibility Criteria

Randomized will be 60 dependent smokers aged ≥ 18 and < 66 (about 30 women, 30 men) with a high interest in quitting smoking (defined below), i.e. those shown in our prior research to be more sensitive to cessation medication efficacy. All subjects will be smokers with a high interest in quitting soon (within 3 months). Subjects also will be those who have smoked at least 10 cigarettes per day for at least 1 year, with no current use of non-tobacco nicotine products. To obtain 60 participants, we expect to screen about 80 male or female smokers, aged ≥ 18 and < 66 years, living in Allegheny or neighboring counties of the greater Pittsburgh metropolitan region, who do not have significant health problems. We will also assess the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al. 1991) and other smoking characteristics, but will not select based on these factors. We selected these inclusion criteria because they approximately fit the current FDA-approved indications for smoking-cessation medications, and because we are interested in responses to this active compound, JNJ-39393406, among dependent smokers with an interest in quitting, those most likely to use such medications to help them quit smoking.

Screening will also include assessment of alcohol use via the AUDIT (Saunders *et al*. 1993), as those with scores indicating dependence are excluded. Self-report of no more than 15 drinks/week and 3 drinks on any day in the past week are required. Those not ineligible at screening will receive a physical exam by study physician, including EKG, bloodwork to check liver and kidney function (CBC, etc.), illicit drug screen (other than THC), urine pregnancy test (women), and interview to assess history of psychiatric disorders, suicidal ideation, current major health problems (e.g. heart disease, diabetes) or contraindicated medications (e.g. fentanyl, cyclosporine, pimozide, quinidine).

Statistical Considerations

Analyses will be conducted using IBM SPSS 24.0. Preliminary analyses of variance (ANOVAs) examine effects of sex and of medication order between phases. The primary outcome, number of days abstinent per assessment week (range of 0-5 days), will be analyzed using paired t-tests. Medication condition (active JNJ, placebo) is the within-subjects factor. Generalized estimating equations (GEE) assesses differences between conditions for the secondary outcome of withdrawal, limited to only responses from days in which smoking abstinence is confirmed. Results of cognitive testing are to be examined using paired t-tests for the CPT. Medication condition is a within-subjects factor. Similar to analyses of withdrawal, to detect potential efficacy of conditions on cognitive testing unconfounded by recent smoking, cognitive responses will be analyzed only when CO<10 on both the JNJ and placebo testing sessions, as in prior research (e.g. Perkins, Karelitz, *et al*. 2013b).

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