

STUDY TITLE: Combination Nicotine Patch / Lorcaserin for Smoking Cessation

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Combination Nicotine Patch / Lorcaserin for Smoking Cessation

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PURPOSE OF THE STUDY:

This study proposes to investigate the potential efficacy of a combination of two FDA-approved agents, nicotine patch and lorcaserin, for smoking cessation treatment. The nicotine patch which provides a sustained low dose of nicotine is a nicotine receptor agonist. Lorcaserin, a serotonin 5-HT2C agonist, is a drug that is FDA-approved for weight loss, and has also recently been shown to be efficacious in a Phase II trial for smoking cessation (Shanahan et al, 2015). Given that these drugs act through distinct mechanisms it is hoped that the combination will prove more efficacious than either drug alone.

The aims of this small-scale (N=60) clinical trial are as follows:

- 1) To compare the efficacy of the nicotine patch / lorcaserin combination treatment vs. the nicotine patch alone in terms of leading to a reduction in ad libitum smoking behavior, withdrawal symptoms and time-to-lapse in a simulated quit-smoking situation;
- 2) To assess the tolerability of the combination treatment in terms of side effect frequencies and adherence to taking the medications;
- 3) To obtain an estimate of the smoking abstinence rate 10 weeks after a target quit-smoking date in smokers receiving combination treatment. Because the dichotomous outcome of abstinence vs. smoking is relatively insensitive from a statistical standpoint, no attempt will be made in this study to directly compare abstinence rates with the nicotine patch / lorcaserin combination vs. the nicotine patch alone. Instead, all participants will ultimately receive the combination treatment when making a quit-smoking attempt, yielding a larger sample with which to estimate the abstinence rate using combination treatment. This estimate will be compared with historical data on abstinence rates in a similar population of smokers;
- 4) To assess weight gain after quitting smoking. Lorcaserin has been shown in the above-cited Phase II study to prevent weight gain, with subjects at Week 12 losing a small amount of weight relative to baseline (-0.41 kg), as compared to gaining +0.73 kg on placebo treatment. We predict that there will be, on average, no weight gain in this study, in contrast to historical data from recent clinical trials in our Center consistently finding a weight gain of approximately 2 kg in abstinent smokers at week 12 after quitting smoking.

The results pertaining to tolerability and efficacy obtained in this study will serve as useful pilot data for a future grant application that would propose to conduct a well-powered clinical trial comparing combination treatment to each agent alone and to placebo.

BACKGROUND & SIGNIFICANCE:

Cigarette smoking remains the leading cause of preventable disease and death in developed countries, due principally to its contributions to heart disease, chronic obstructive pulmonary disease (COPD), and cancer (Lando & Wilson, 2010). The annual death toll in the U.S. from diseases caused by smoking has been increasing steadily and is estimated to be the highest ever, 540,000/year (Carter et al., 2015). Importantly, smoking cessation leads to a substantial reversal of the risks borne by smokers (Kenfield et al., 2008). However, no new medications have been approved for smoking cessation treatment since FDA approval of varenicline in 2006. In fact, the rate of decrease in the prevalence of smoking has slowed in recent years, with over 45 million Americans continuing to smoke (CDC, 2014). Thus there is an urgent need for more effective therapeutic approaches that can be tailored to specific subpopulations of smokers and for guidance to medical providers.

Previous studies have reported that smoking abstinence rates are increased when nicotine skin patch treatment is initiated prior to the target quit smoking date, as compared with conventional treatment beginning on the quit date. Rose et al (2009) showed that continuous abstinence rates were approximately doubled by pre-cessation nicotine patch treatment (22% vs. 11%). The treatment which was well tolerated mainly benefited smokers with lower levels of dependence. The authors hypothesized that smoking in the presence of continuous levels of nicotine attenuated the reinforcing effects of cigarette smoking and led to a decline in dependence on inhaled nicotine, thus facilitating cessation.

Lorcaserin (Belviq) is a selective serotonin 2C (5-HT2C) receptor agonist which decreases body weight by selectively mimicking the effects of serotonin at the 5-HT2C receptor. Serotonin is a monoamine neurotransmitter which acts on the central nervous system to reduce food intake. The FDA approved Belviq in 2012 for chronic weight management in adults with a BMI of >30 kg/m² or >27 kg/m² with a comorbid condition.

Bubar et al (2007) reported that the 5-HT2C receptor may be important in inhibiting dopaminergic neurons (which are important for drug reinforcement) in the ventral tegmental area. This inhibition of dopaminergic neurons suggests that lorcaserin HCl may have an effect on smoking cessation (Higgins et al, 2013). Two investigators have studied the ability of lorcaserin to inhibit nicotine self-administration in rats.

In a study conducted by Levin et al (2011)., lorcaserin HCl (0.625 mg/kg subcutaneous [SC]) was found to decrease nicotine self-administration ~50%, with no sign of

attenuation of effect after 10 doses; at this dose, there was no effect on food-motivated responding and no generalized locomotor hypoactivity. In a separate study conducted by Higgins et al (2012), lorcaserin HCl reduced feeding behavior and self-administration of nicotine in the same dose range (0.6-1 mg/kg SC).

A recent Phase II trial conducted by Shanahan et al (2015) demonstrated that lorcaserin was efficacious for smoking cessation. Smokers who received lorcaserin 10mg bid had a continuous abstinence rate (CAR) of 15.3% while those that received 10mg daily had a CAR of 8.7%. The placebo group had a CAR of 5.6%. The combined benefit of smoking cessation and prevention of associated weight gain, which many smokers report as a concern when quitting smoking, addressed two significant challenges in the fight against the leading preventable cause of illness and early death.

DESIGN & PROCEDURE:

Design Overview

The study will comprise a randomized, double-blind parallel-arm controlled clinical trial to ascertain whether combination nicotine patch + lorcaserin will be more effective than nicotine patch alone as a treatment for reduction of ad libitum smoking behavior and time-to-lapse in a simulated quit-smoking situation during the first 2 weeks. After the first 2 weeks, all participants will receive the same combination treatment for the remainder of the study. The study will include N=60 randomized participants. This study will include a screening visit, a baseline visit, a laboratory visit, a visit one day prior to the Target Quit Date (TQD), 4 post quit visits, and a 6 month follow up visit (for eligible participants). Participants will be randomized to receive nicotine patch + lorcaserin or nicotine patch + placebo for the first 2 weeks. The nicotine patch will be administered according to the standard dosing regimen of 21mg daily. Lorcaserin will be administered at a dose of 10 mg twice a day, a dose used in weight loss treatment. Ad libitum smoking will be assessed weekly using daily diary recordings of cigarettes smoked per day as well as the objective index of expired air carbon monoxide (CO) levels measured at the study visits. After 2 weeks, a laboratory session will be conducted in which withdrawal symptoms will be assessed as well as the ability to delay smoking in a simulated smoking lapse paradigm validated by McKee et al. (2012). In this paradigm smokers are allowed to smoke but are offered a monetary incentive to delay smoking; the amount of this incentive decreases over time during the session. The outcome measure is the time-to-lapse, which has been shown to increase following smoking cessation medications such as varenicline and bupropion, and decrease following manipulations which are known to trigger relapse, e.g., stress, alcohol consumption. Following the laboratory session, the group that receives nicotine patch + placebo will be switched to receiving nicotine patch + lorcaserin and the nicotine patch+ lorcaserin group will continue receiving nicotine patch+ lorcaserin, for an additional 2 weeks leading up to a scheduled target quit-smoking date (TQD). Treatment with nicotine patch + lorcaserin will continue for an additional 10 weeks after the TQD for all participants, followed by

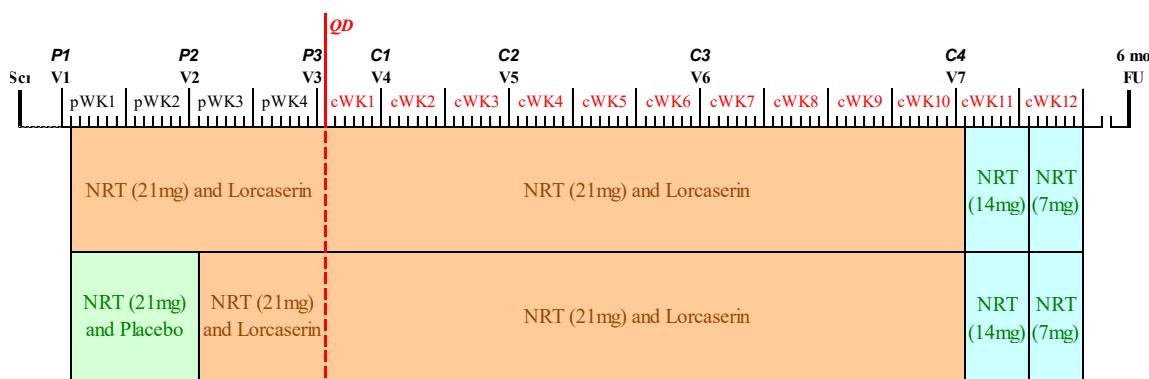
two weeks during which the dosage of the nicotine patches will be tapered (one week of 14mg patches and one week of 7mg patches).

The treatment groups are as follows:

Group A: 21mg nicotine patch + lorcaserin 10mg twice daily for the 14 week study period followed by a 2 week taper of the nicotine patch (14mg for 1 week; 7mg for 1 week).

Group B: 21mg nicotine patch + placebo for the first 2 weeks; 21mg nicotine patch + lorcaserin 10mg twice daily for the next 12 weeks followed by a 2 week taper of the nicotine patch (14mg for 1 week; 7mg for 1 week).

The Study timeline is shown below:



Blinding

In order to maintain a double-blind assignment to treatment conditions, subjects receiving nicotine patch alone (Group B) will receive placebo lorcaserin tablets during the first two weeks.

Screening and Session Procedures

Interested potential subjects will respond to advertisements by contacting our Center to be phone screened. Potential subjects will be given a brief description of the study and will be asked questions to assess eligibility and interest. Eligible subjects interested in participating will be scheduled for the medical history and physical examination screening visit.

After granting their informed consent, potential subjects will be given the HIPAA Notice of Privacy Practices. They will also complete a medical history form and will have their blood pressure, pulse, weight, height, temperature and expired air CO measured.

Subjects will provide smoking history information, a saliva sample, blood (maximum of 20mL) for tests to measure general health, and urine for urinalysis and illicit drug testing. Women of child bearing potential will also have a serum pregnancy test. The study physician or one of his assistants will perform a physical examination and an ECG. The

initial target Quit Day for all the subjects will be established at screening. The screening visit will last approximately 2 hours.

Blood and urine specimens will be sent to LabCorp for processing. The results of laboratory blood and urine tests will not routinely be given to participants to send or be sent to their physician to include in their medical record. However, if the subject's lab results are outside the acceptable range for participation in the study the Physician/P.A. will send the subject a medical exclusion letter and a copy of the lab results. Participants who are accepted into the study but need medical follow up due to minor abnormalities in lab results will also be informed by letter from the Physician/P.A. A copy of the laboratory results will be included with the letter, which will also indicate that the condition does not interfere with his/her participation in the study.

The time commitment for subjects is 16 weeks: 4 weeks of pre-cessation treatment before the scheduled Quit Day and 12 weeks of additional post-Quit Day treatment, plus one follow-up session at six months (if eligible) after the Quit Day.

Questionnaires will be completed within REDCap on a desktop computer in the Center office. The technician will log on to the REDCap site and will open the questionnaires for the subjects. Subjects will only have access to their questionnaires. Access to any other websites will be blocked by Psychiatry Information Technology.

Session P1

The first study visit will take place approximately one week after the screening visit. Subjects will complete baseline questionnaires and will be randomized to either Group A (nicotine patch + lorcaserin) or Group B (nicotine patch + placebo). Subjects will be tested for exhaled air carbon monoxide and smoking related chemicals in the saliva. They will also have their blood pressure, heart rate and weight measured. Females of child bearing potential will also complete a urine pregnancy test which must be negative in order to continue study participation. Subjects will also complete questionnaires rating craving, withdrawal symptoms, side effects, and sensory experience.

Subjects will be given a supply of study medications (depending on randomization) to use for 2 weeks and will receive verbal and written instructions on how to take them.

Subjects will also be given diaries to record medication use and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring.

Subjects will be called within three days after the first day of treatment to make sure that medications are being used as directed.

Session P2

The second study visit will take place 2 weeks after the first visit. Subjects will be tested for exhaled air carbon monoxide and smoking related chemicals in the saliva. Subjects

will also have their blood pressure, heart rate and weight measured. In addition, they will also complete questionnaires rating craving, withdrawal symptoms, side effects, and sensory experience.

A laboratory session will be conducted at this visit. Participants will be asked to refrain from smoking after midnight the night before the session. After an additional 2 hour period in which subjects refrain from smoking, withdrawal symptoms will be assessed as well the ability to delay smoking in a simulated smoking lapse paradigm validated by McKee et al (2012). In this paradigm smokers are allowed to smoke but are offered a monetary incentive to delay smoking, which decreases over time in the session.

Subjects in both Group A and Group B will be given a supply of study medications (nicotine patch + lorcaserin). Following the P2 laboratory session, the group that received nicotine patch + placebo will be switched to receiving nicotine patch+ lorcaserin, and the nicotine patch+ lorcaserin group will continue receiving nicotine patch+ lorcaserin, for an additional 2 weeks leading up to a scheduled target quit-smoking date (TQD).

Subjects will also be given diaries to record medication use and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring.

Session P3 (the day before Quit Day)

The third study visit will take place 2 weeks after the second visit (and one day prior to the Quit Day). Subjects will be tested for exhaled air carbon monoxide and smoking related chemicals in the saliva. Subjects will also have their blood pressure, heart rate and weight measured. Females of child bearing potential will also complete a urine pregnancy test which must be negative in order to continue study participation. They will also complete questionnaires rating craving, withdrawal symptoms, side effects, and sensory experience.

Subjects will be dispensed a sufficient supply of nicotine patches and lorcaserin to last until the next scheduled visit.

Subjects will also be given diaries to record medication use and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring. In addition, they will be given forms to be completed on their Quit Day. They will be asked to return these forms at their next visit.

Sessions C1-C4

Session C1 will take place 1 week after Session P3. Session C2 will take place 2 weeks after C1. Session C3 will occur 3 weeks after C2, and Session C4 will occur 4 weeks after C3.

Subjects will be tested for exhaled air carbon monoxide and smoking related chemicals in the saliva. Subjects will also have their blood pressure, heart rate and weight measured. In addition, they will also complete questionnaires rating craving, withdrawal symptoms, side effects, and sensory experience.

At Sessions C2 and C3 females of child bearing potential will complete a urine pregnancy test which must be negative in order to continue study participation.

At Sessions C1-C3 subjects will be dispensed a sufficient supply of nicotine patches and lorcaserin to last until the next scheduled visit. At session C4 subjects will be given instructions for tapering off of the patch. They will be given a 1 week supply of 14mg nicotine patches and a 1 week supply of 7 mg nicotine patches. A technician will call them 2 weeks after the C4 session to follow up on the patch tapering process.

Subjects will also be given diaries to record medication use and the number of cigarettes smoked each day and will be instructed to return the diaries at the next visit. They will also be asked to return any unused medications for proper disposal and compliance monitoring.

Six-month Follow-up

Study participants will be contacted by phone, letter or email six months after their Quit Day and asked about their current smoking behavior, as well as their smoking behavior since their last session. Those subjects who report continuous or point abstinence (no smoking in the previous seven days) and have not used any smoking cessation aid will be asked to return to the laboratory for a brief follow-up session. This session will include an expired air CO reading; blood pressure, heart rate and weight measurements; collection of a saliva sample; and completion of several questionnaires.

SUBJECT IDENTIFICATION:

We propose to enroll up to 360 smokers in order to identify 60 participants who meet all criteria to be accepted into the study and to be randomized into one of two treatment conditions. When the 60th subject is randomized into the study, we will discontinue new recruitment efforts for the study. If there are individuals who already have screening or baseline appointments scheduled, these appointments will be honored. Thus, it is possible that our final sample will exceed 60 participants by some small number.

Inclusion Criteria

- Are 18-70 years old;
- Smoke an average of at least 10 cigarettes per day;
- Have smoked at least one cumulative year;
- Have an expired air CO reading of at least 10ppm;
- Body weight of ≥ 50 kg (110 lbs.) and ≤ 170 kg (375 lbs);
- Able to read and understand English;

- Express a desire to quit smoking in the next thirty days.

Potential subjects of child bearing potential must agree to use acceptable contraception during their participation in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Potential subjects must agree to avoid the following during their participation in this study:

- participation in any other nicotine-related modification strategy outside of this protocol;
- use of tobacco products other than cigarettes, including pipe tobacco, cigars, e-cigarettes, snuff, and chewing tobacco;
- use of experimental (investigational) drugs or devices;
- use of illegal drugs;
- use of exclusionary medications.

Exclusion Criteria

- Hypertension (systolic >140 mm Hg, diastolic >100 mm Hg, coupled with a history of hypertension); subjects with no previous diagnosis of hypertension may have a screening blood pressure up to 160/100.
- Hypotension with symptoms (systolic <90 mm Hg, diastolic <60 mm Hg).
- Participants with a history of hypertension may, however, be allowed to participate in the study if the study physician or physician assistant determines that the condition is stable, controlled by medication, and in no way jeopardizes the individual's safety.
- Coronary heart disease with symptoms (e.g., chest pain, shortness of breath);
- Heart attack in the past year;
- Cardiac rhythm disorder (irregular heart rhythm);
- Chest pain in the last month (unless history, exam, and ECG clearly indicate a non-cardiac source);
- Symptomatic cardiac (heart) disorder (including but not limited to valvular heart disease, heart murmur, heart failure);
- Liver disease or kidney disorder that requires medication or a change in diet or lifestyle;
- Major gastrointestinal illness (e.g. Celiac disease, Crohn's dx Ulcerative Colitis) that require medication;
- Active ulcers in the past 30 days;
- Currently symptomatic lung disorder/disease that requires oxygen;
- Major brain disorder (including but not limited to stroke with residual deficit, brain tumor, and seizure disorder);
- Migraine headaches that occur more frequently than once per week;
- Recent, unexplained fainting spells;

- Problems giving blood samples;
- Diabetes (unless controlled by diet and exercise alone and screening glucose is less than 180mg/dl and HbA1c is less than 7%);
- Current cancer or treatment for cancer in the past six months (except basal or squamous cell skin cancer);
- HIV, Hepatitis B, or Hepatitis C
- History of Tuberculosis or recent positive PPD
- Other major medical condition;
- Current symptomatic psychiatric disease (with the exception of anxiety disorders, OCD and ADHD);
- Psychosis, bipolar disorder, or psychiatric hospitalization within the past 12 months;
- Suicidal ideating (thinking about ways to commit suicide) (within the past 10 years) or lifetime occurrence of attempted suicide;
- Current depression - The Patient Health Questionnaire PHQ-9 for Depression will be used to screen for current (within 2 weeks) depression. Potential subjects who score >9 (or who score >0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way")) will be excluded from study participation, and, at the discretion of the study physician, referred to appropriate psychiatric treatment;
- Bulimia or anorexia;
- Pregnant or nursing mothers
- BMI of < 18.5 kg/m² or > 38 kg/m²;
- Prior use of fenfluramine or dexfenfluramine
- Use (within the past 30 days) of:
 - Illegal drugs (or if the urine drug screen is positive for THC, Cocaine, Amphetamine, Opiates, Methamphetamines, PCP, Benzodiazepines, or Barbiturates), unless recent use of prescription Opiates or Benzodiazepines were taken for management of acute symptoms (e.g., tooth extraction, recent surgery).
 - Experimental (investigational) drugs;
 - Psychiatric medications including antidepressants (SSRIs, SNRIs, TCAs, MAOIs, St. John's Wort), lithium, anti-psychotics or any other medications that are known to affect smoking cessation (e.g. clonidine);
 - Phentermine, triptans, tryptophan, linezolid, dextromethorphan, opiates (unless taken for management of acute symptoms), tramadol, or dopamine agonists;
 - Any agents that have documented correlation with increased incidence of valvulopathy and/or pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide) (or anticipated use during the study);
 - Wellbutrin, bupropion, Zyban, Chantix, varenicline, nicotine patch, nicotine replacement therapy or any other smoking cessation aid.
- Concurrent use of a serotonergic agent/combination associated with severe serotonin syndrome (within the past 30 days);
- Use of cigars, cigarillos, pipes, Hookah, dissolvable nicotine, snuff, chewing tobacco, or e-cigarettes within the past 30 days;
- Self-report of consuming more than 6 alcoholic drinks on 1 or more days per week;
- Significant adverse reaction to lorcaserin or nicotine patch in the past.

- Current participation or recent participation (in the past 30 days) in another smoking study at our Center or another research facility.
- Current participation in another research study.

Assessment of Eligibility

Potential subjects who do not have a self-reported diagnosis of the above listed conditions may be excluded if the study physician or physician assistant determines that the history, physical findings, ECG, or laboratory studies reveal information that may jeopardize the subjects' safe study participation. For medical conditions that do not appear above, the study physician will be consulted, and if the medical condition does not jeopardize safe study participation, then the subject may be enrolled.

SUBJECT RECRUITMENT AND COMPENSATION

Subject Recruitment

Smokers with no major health problems will be recruited from communities in and around Durham, North Carolina. Recruitment will occur through newspaper, flyers, and internet advertisements and by word-of-mouth. Potential subjects will be pre-screened on the phone by a member of the Duke CSC. If potential subjects meet the pre-screening study requirements and are still interested in participation, they will attend a physical screening session at the Duke CSC, located at 2424 Erwin Road, Suite 201, Durham, NC 27705. In order to have a physician or physician assistant perform the physical screening, it may be necessary to conduct part of the screening visit at Duke Clinic. Subjects would either be escorted on foot by a member of study staff for our Center to Duke Clinic, or be met by a member of study staff at Duke Clinic. This part of the screening may be scheduled on a different day. If after this visit it is determined that they qualify for participation, they will attend subsequent study visits at the Duke Center for Smoking Cessation located at 2424 Erwin Road, Suite 201, Durham, NC 27705.

Subject Compensation

Subjects will be reimbursed up to \$417.42 for attending seven study visits and one follow up visit. There will be a payment of \$40 per study visit attended. In addition, subjects will receive a payment of \$10 for each of the 7 sessions attended in which they return their completed take-home forms (brief questionnaires which describe withdrawal symptoms and record smoking behavior and medication use). Subjects will also receive additional compensation up to \$7.42 (per Sherry McKee protocol) for completing the laboratory session (P2). Subjects who do not complete each visit will still receive payment for the sessions attended. Thus, subjects who attend seven visits and hand in their take-home forms each time will receive a total payment of \$350 plus the amount earned in the P2 laboratory session. Subjects who come back for a follow up session six months after their Quit Day will receive an additional \$60. Subjects will not be compensated for the screening session.

CONSENT PROCESS

Because of the nature of this study and the amount of questionnaires that subjects are expected to complete, we do not recruit potential subjects who do not read, are blind or who do not read/understand English. We are not equipped to validate alternate versions of our questionnaires, most of which are not published. Questionnaires cannot be administered orally by a translator or by Technicians to illiterate or blind subjects because the data obtained would not be comparable to self-administered questionnaires.

RISK/BENEFIT ASSESSMENT

Continuing to smoke carries significant health risks. Subjects enrolling in this study are attempting to quit smoking, and will receive two FDA-approved medications. The nicotine patch is approved for smoking cessation. Lorcaserin is approved for weight loss. A Phase II study conducted by Shanahan et al (2015) recently showed that lorcaserin is efficacious for smoking cessation. To date, hundreds of thousands of individuals have used lorcaserin with no major adverse events (death, permanent injury, hospitalization) reported (personal communication with Dr. Shanahan, former CEO of Arena Pharmaceuticals). With smoking prevalence in society of 18.3% (higher in prior years) (CDC 2014) it is estimated of these it is reasonable to assume that a substantial proportion of individuals using lorcaserin has used the medication in combination with nicotine provided through tobacco use. Because of this, we do not anticipate adverse drug interactions with the combination of lorcaserin and nicotine provided via patch.

Potential side effects of Nicotine patch: Insomnia and abnormal dreams are common and expected side effects associated with 24-hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include lightheadedness, dizziness, nausea, fainting and vomiting. A less likely side effect of nicotine patches is somnambulism.

Potential side effects of Lorcaserin HCl:

Most likely

- Headache
- Dizziness
- Fatigue
- Nausea
- Dry mouth
- Constipation
- Cough
- Back pain

- Low blood sugar (hypoglycemia in participants with diabetes)

Less likely

Lorcaserin HCl may also cause other, potentially serious side effects, including:

- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions.
- Valvular heart disease
- Changes in your attention or memory
- Depression or thoughts of suicide
- Low blood sugar (hypoglycemia)
- (For Men) Painful erections (priapism)
- Slow heartbeat
- Decreases in your blood cell count
- Increase in prolactin
- Pulmonary hypertension (high blood pressure in the lungs)

Increases in the proportion of animals with tumors of some tissues, including breast, brain, thyroid gland, liver, skin and nerve sheath, were found in rats, but not mice, given lorcaserin HCl for 2 years at doses which produced blood levels higher than in humans. The relevance of tumors in rats to humans is unknown.

Subjects will be monitored throughout the duration of the study for side effects and severe adverse effects (SAEs). They will be instructed to report any side effects to the study technicians, who will communicate these reports immediately to the medical staff. The most appropriate course of action will be determined, which may include options for dose reduction or termination of treatment. Participants will be reminded that they have the option to withdraw from the study at any time. Subjects will also be given the 24 hour emergency contact numbers in the event that side effects or adverse events occur between sessions. SAEs will be reported to the IRB and will be monitored until resolution or stabilization.

Needle stick / Blood drawing: The risks associated with venipuncture are minimal, and include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

SERIOUS ADVERSE EVENT REPORTING PLAN

The Principal Investigator will report all serious adverse events relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office, and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

COSTS TO PARTICIPANTS

There are no costs to participants for taking part in this study. All the study costs, including any study medications and procedures related directly to the study, will be paid for by the research grant awarded to Duke University. The active lorcaserin and placebo lorcaserin tablets will be supplied by Eisai. The nicotine patch will be purchased from Duke Outpatient Pharmacy.

DATA ANALYSIS & STATISTICAL CONSIDERATIONS

The primary outcome measure will be the time-to-lapse during the laboratory session. McKee et al. (2012) reported an effect size of ~0.8 on this measure, and obtained significant results assessing the therapeutic effects of bupropion and varenicline with n=20 per group. With n=30 per group in the proposed study, and using a one-tailed alpha=0.05 (the hypothesis is one-tailed inasmuch as there would be no interest in pursuing the development of lorcaserin unless an increase in time-to-lapse is demonstrated), we should obtain over 90% power to detect a comparable effect. Secondary outcomes that will be compared between groups include the percent reduction in ad libitum smoking during the first 2 weeks, and withdrawal symptoms reported after 2 hours of smoking abstinence in the laboratory, measures that have been sensitive to treatment in our previous studies of nicotine replacement therapy (NRT) and other treatments. The two treatment groups will be compared on these measures using ANOVA-based statistical methods.

Continuous abstinence from smoking during weeks 7-10 after the quit date will also be tabulated, and 90% confidence intervals will be calculated. Abstinence will also be correlated with the reduction in ad libitum smoking in the first 2 weeks to determine whether smoking reduction may be a useful early marker of therapeutic efficacy. Among smoking-abstinent participants, weight gain relative to baseline will also be assessed, and 90% confidence intervals will be calculated.

Tolerability of treatment will be assessed by tabulating side effect frequencies and degree of adherence to taking medications (percent of total doses taken, assessed by self-report diaries and counts of returned medications at each session).

DATA & SAFETY MONITORING

Description of BP monitoring procedures after study enrollment

After study enrollment, if blood pressure during return sessions is above 160/100, then the following actions will be taken to enhance subject safety:

- If BP >210/100 with symptoms of malignant hypertension: stop experiment interventions and refer to appropriate medical treatment. Resume participation and continue to be monitored if BP is no greater than 140/100.

- If BP > 160/100 for 2 consecutive sessions, then CSC will provide either weekly BP checks or request that the participant have his/her BP checked weekly by PCP, local pharmacy, or home machine and call us with results. The physician assistant will discuss these results with the study physician.
- A blood pressure memo to file form will be completed if BP>160/100 for 3 readings per center approved procedure.

Data Safety Monitoring Plan (DSMP)

We plan to exclude potential participants who take drugs that could interact with lorcaserin by increasing the risk of serotonin syndrome.

To address potential safety issues in addition to collection of the primary study outcomes, severe side effects and adverse events potentially associated with the study will be examined, recorded and then reported to the IRB in a manner consistent with Duke HRPP policies. The principal investigator will be responsible for monitoring data collection and safety of this study.

Data collection for this study will be carried out at the Durham clinical site of the Duke Center for Smoking Cessation (CSC). All members of the study team will complete research integrity (“code of conduct”) and CITI (Collaborative Institutional Training Initiative) Human Research Curriculum and clinical laboratory safety training as required by Duke University Medical Center. All study staff who are involved in data collection, management, and processing will be thoroughly trained following standards of procedures prior to working on this project.

Study staff responsible for data collection will use a checklist for completion for each study visit of each participant. Missing Data Forms, along with explanations should missing data occur, will be completed by the study staff for each study visit.

Microsoft Access will be used for logging subject information (Enrollment Log, Visit Log, etc.). Data will be entered by the study staff. The key study personnel will further examine the computerized data entries and original records for accuracy and completion.

Emergency Unblinding

This is a blinded protocol such that all participants and all study personnel except for the Clinical Research Coordinator and the Research Program Leader are blinded to group allocation. During specific circumstances it will be necessary to unblind other study personnel, such as study team medical personnel. Emergency unblinding will occur under the discretion of the study physician (or one of the study physician assistants) in any situation in which unblinding is deemed necessary to ensure or promote the safety of a study participant. The decision to unblind for safety reasons may occur for a number of reasons and it is not possible to enumerate all potential circumstances. Examples of reasons for unblinding to ensure participant safety include situations in which it is necessary to know which study drugs the subject was taking in order to manage the side effect(s), advise the subject on the risk of future negative drug reactions, uncover potential safety information about the drug, and/or determine whether the adverse event

is study related. In those situations, the Clinical Research Coordinator or Research Program Leader will inform the study physician (or physician assistant handling the event) of that subject's treatment condition. If unblinding occurs, that subject's data will be censored and will not be included in final data analyses.

DATA STORAGE & CONFIDENTIALITY

Any PHI collected prior to documentation of informed consent will be de-identified if the potential subject does not qualify for this study. Please refer to the "Request for Waiver of Documentation of Informed Consent".

Prior to any physical screening procedures, subjects will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations. Study records that identify subjects will be kept confidential as required by law. Blood and urine specimens will be sent to LabCorp for processing. Name, date of birth, and gender will be included with each specimen. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS) (except to LabCorp). For records disclosed outside of DUHS, subjects will be assigned a unique code number. The key to the code will be kept in a locked file in the PI's office separate from the locked file where the study records are stored.

During data collection, data for active subjects are kept at our offices located in Durham, NC.

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