Varenicline and lorcaserin for smoking cessation and weight gain prevention

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General Study Information

Study Title: Varenicline and lorcaserin for smoking cessation and weight gain prevention

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Purpose

Hypothesis:

Weight gain associated with stopping smoking is common and is frequently identified as an important predictor for smoking relapse, but interventions for preventing weight gain after stopping smoking are lacking. Lorcaserin has potential to prevent post cessation weight gain. In this study we will: (1) investigate the impact of a novel pharmacologic agent on weight gain attenuation after stopping smoking; (2) evaluate a product that may have broad appeal among smokers to whom weight gain is a barrier to tobacco abstinence; (3) Investigate a novel smoking cessation combination (lorcaserin and varenicline) in a targeted population;

Aims, purpose, or objectives:

Cigarette smoking is the single most important preventable cause of morbidity, mortality, and excess health care costs in the United States. Among smokers achieving smoking abstinence, weight gain is common and may be an important mediator of smoking relapse. The availability of pharmacotherapy facilitating smoking abstinence and preventing weight gain may prompt more smokers to make quit attempts, enhance long-term smoking abstinence, and prevent the development of overweight or obesity among former smokers.

Varenicline is a partial agonist/antagonist that binds with high affinity and selectivity at $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors. Varenicline is presently the most efficacious pharmacotherapy for increasing smoking abstinence rates, with proven superiority over bupropion SR and suggested superiority over nicotine replacement therapy. However, varenicline does not have a clinically meaningful effect on preventing the weight gain that occurs with smoking abstinence. Combining the beneficial effects of varenicline with a post cessation weight gain intervention might have a significant impact on weight-concerned smokers for whom weight gain is a significant risk factor for smoking relapse.

Lorcaserin is a selective 5-HT_{2C} receptor agonist with a 100-fold selectivity of 5-HT_{2C} compared to the 5-HT_{2A} receptor subtype. Activation of the 5-HT_{2C} receptor subtype in the hypothalamus increases pro-opiomelanocortin (POMC) production leading to weight loss through satiety. Three phase III studies have demonstrated the efficacy of lorcaserin for weight loss in overweight and obese subjects. As a result of the significant weight loss in these studies and the favorable side effect profile, lorcaserin was recently approved by the FDA for weight reduction in overweight and obese patients. No studies have evaluated the use of lorcaserin to reduce weight gain following stopping smoking. In addition, 5-HT_{2C} agonists have been shown to reduce the stimulant, discriminative, and reinforcing effects of nicotine in animal models. No clinical studies have evaluated the use of 5-HT_{2C} agonists for smoking cessation.

After stopping smoking, most of the weight gain occurs in the first 3 months. The mechanism for post cessation weight gain is not fully understood. Combining lorcaserin, with its effects on weight, with varenicline for initiating smoking abstinence may offer a unique clinical approach to the treatment of weight-concerned cigarette smokers. The overarching goal of this line of research is to improve smoking abstinence rates among cigarette smokers by intervening to reduce factors that increase the risk for smoking relapse. Our primary goal in this proposal is not *weight loss,* but rather *an attenuation of the weight gain* commonly observed in smokers who stop smoking.

The primary aim and hypothesis of this study is to assess the efficacy of a 24-week course of lorcaserin for decreasing weight gain after stopping smoking.

Hypothesis: After 24 weeks, lorcaserin will be associated with significantly less weight gain compared to placebo among weight-concerned adult smokers who have quit smoking with varenicline.

The secondary aims and hypotheses of this study are

1. Assess the efficacy of a 24-week course of lorcaserin for attenuating increases in BMI after stopping smoking.
   - *Hypothesis*: At 24 weeks, lorcaserin will be associated with a significantly lower increase in mean BMI than placebo among
   - weight-concerned adult smokers who have quit smoking with varenicline.
2. Assess the efficacy of the combination of 24 weeks of lorcaserin and varenicline on smoking abstinence rates.
   - *Hypothesis*: After 24 weeks, smoking abstinence rates will be significantly higher in subjects receiving lorcaserin compared to placebo when all subjects receive 12 weeks of varenicline

Background:

Smoking, Smoking Cessation, & Weight Concerns: Some individuals smoke with the perception that smoking helps control body weight.[1,2] Smokers gain an average of 5 to 10 pounds in the months following smoking abstinence,[3,4] with heavier and more-dependent smokers gaining more weight.[5,6] The mean weight gain may be as much as 13 pounds at one year[7] and 21 pounds over 5 years.[8] Actual weight gain following smoking abstinence has been associated with smoking relapse.[9] In a large population-based study, 52% of the women and 32% of the men with a previous quit attempt reported that weight gain was one of the reasons for relapse to smoking.[10] In previous research involving the prospective evaluation of a large sample of smokers, 47% of female smokers and 22% of male smokers were classified as having weight concerns.[11]
Smoking cessation also leads to increases in visceral fat, and visceral fat is a risk factor for adverse health consequences. Individuals with larger amounts of visceral and organ adipose tissue have higher rates of insulin resistance, cardiovascular risk, and organ dysfunction.[12] A large prospective cohort evaluating visceral fat area (VFA) measured by abdominal computed tomography observed that former smokers had higher VFA (124.0-132.0 cm^2) than current smokers (120.4 cm^2) or nonsmokers (123.1 cm^2).[13]

Recent evidence has suggested that the distribution of adipose tissue is more predictive of cardiovascular risk than body mass index (BMI) alone.[14] Central adiposity, which appears to be the best surrogate for estimating visceral adipose tissue, can be measured clinically as waist circumference (WC) and waist-to-hip ratio (WHR).

Two large case-control studies have demonstrated that WC and WHR are independent risk factors for cardiovascular mortality.[14,15]

Interventions to prevent weight gain after smokers stop smoking: Approximately 80% of smokers want to stop smoking and 40% attempt to stop each year. More than 90% of these self-initiated efforts are unsuccessful.[4] Intervening to affect factors such as weight gain may improve long-term smoking abstinence rates. Both behavioral and pharmacologic interventions have been evaluated for the prevention of weight gain after smoking cessation. A systematic review concluded that behavioral interventions, including general weight loss advice, are not effective and may reduce smoking abstinence. Studies incorporating behavioral interventions for both weight gain prevention and tobacco dependence suggest that participants may have difficulty complying with two behavioral interventions simultaneously.[16] Thus, the use of a pharmacologic agent to address weight concerns and weight gain while the smoker focuses on the behavioral aspects of stopping smoking offers an attractive clinical option. Varenicline, a partial agonist/antagonist that binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors, is presently the most efficacious approved pharmacotherapy for increasing smoking abstinence rates; however, varenicline does not have a clinically meaningful effect on preventing the weight gain that occurs with smoking abstinence. We have published a pilot study of the combination of varenicline and sibutramine[17]; however, sibutramine has been taken off of the market. We are interested in exploring the novel approach of using lorcaserin for the prevention of postcessation weight gain.

Serotonin Activation and Weight Attenuation: Activation of the serotonin receptor 2 (5-HT_2) has been associated with satiety, hypophagia, and modulation of the effects of psychostimulant addiction.[18,19] Previously available drugs that targeted 5-HT_2 (fenfluramine and dexfenfluramine) were effective in promoting weight loss, however these agents were nonselective. As a result of 5-HT_{2B} receptor activation, some patients developed valvular heart disease and these drugs were subsequently withdrawn from the market. Lorcaserin is a selective 5-HT_{2C} receptor agonist with a 100-fold selectivity of 5-HT_{2C} compared to the 5-HT_{2A} receptor subtype. Activation of the 5-HT_{2C} receptor subtype in the hypothalamus increases pro-opiomelanocortin (POMC) neuron activity leading to weight loss through hypophagia and satiety. In three large phase III studies, there has been no valvular heart disease associated with lorcaserin.

Lorcaserin and Weight Attenuation: Three phase III studies have demonstrated the efficacy of lorcaserin for weight loss in overweight and obese subjects. The first of these studies is the BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) trial which evaluated the efficacy and safety (including safety regarding cardiac valves) of lorcaserin used for weight loss in obese and overweight subjects.[20] A total of 3182 subjects were randomized to receive placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily for 52 weeks.[20] At 52 weeks, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost 5% or more of their body weight ($P<0.001$), corresponding to an average loss of 5.8+/-0.2 kg with lorcaserin and 2.2+/-0.1 kg with placebo during year 1 ($P<0.001$).[20] Among 2472 patients evaluated at 52 weeks and 1127 evaluated at 104 weeks, the rate of cardiac valvulopathy was not increased with lorcaserin compared to placebo.[20] The most frequent adverse events reported with lorcaserin were headache, dizziness, and nausea.[20]

The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study evaluated efficacy and safety of lorcaserin for weight loss in overweight and obese subjects with DM2.[21] A total of 604 patients were randomized to either placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily for 52 weeks.[21] More patients lost ≥ 5% body weight with lorcaserin twice daily

(37.5%; P < 0.001) or lorcaserin daily (44.7%; P < 0.001) versus placebo.[21] Common adverse events were headache, back pain, nasopharyngitis, and nausea. However, serial echocardiograms did not demonstrate valvular heart disease.[21] Lorcaserin was associated with significant weight loss and improvement in glycemic control in patients with type 2 diabetes.[21] As a result of the significant weight loss in these studies and the favorable side effect profile (including no valvular defects), lorcaserin was recently approved by the FDA and is currently clinically available for weight reduction in overweight and obese patients.

Lorcaserin and Smoking Cessation: In addition to the effects on satiety and weight loss, serotonin activation appears to be involved with nicotine effects as well.[22,23] Ketanserin, a 5-HT_{2A} and 5-HT_{2C} antagonist, significantly reduced nicotine self-administration in rats.[23] Lorcaserin has been shown to reduce nicotine self-administration in two animal studies. The first used self-administered subcutaneous doses of nicotine (0.03 mg/kg per infusion) with fixed doses of lorcaserin (0.3125-20 mg/kg) in rats for 2 weeks.[23] Nicotine self-administration was reduced in all doses of lorcaserin compared to placebo. The second study used self-administered subcutaneous doses of nicotine, and all doses of lorcaserin reduced self-administration.[22] Furthermore, lorcaserin produced a dose-dependent reduction of nicotine induced hyperactivity.[22] These studies support the hypothesis that lorcaserin could potentially aid in smoking cessation in addition to attenuate postcessation weight gain. No clinical study has been published evaluating the use of lorcaserin to attenuate weight gain in smokers who stop smoking.

Mechanism of Postcessation Weight Gain: Despite the convincing evidence for the association between smoking cessation and weight gain, the molecular mechanisms involved are not well understood. Energy homeostasis is a complex interaction between adipose tissue and the hypothalamus. The role of leptin and neuropeptide Y (NPY) in obesity has been well established.[24,25] NPY is released by the hypothalamus and gut and is one of the most potent orexigenic (appetite stimulant) neuropeptides known.[24] Leptin is released by adipose tissue and counteracts the effects of NPY and induces appetite suppression.[26,27] Increasing adiposity can lead to increased leptin resistance with increased circulating levels of leptin.[26,27] A recent study has evaluated the role of NPY and leptin in postcessation weight gain.[28] Plasma levels of NPY and leptin in 35 nonsmokers and 31 cigarette smokers before and three months after smoking cessation were evaluated.[28] Compared to nonsmokers, smokers were leaner and had reduced NPY and leptin levels. Smoking cessation resulted in a significant weight gain and increased WC which was associated with increased leptin and NPY.

Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual: 100

Subject population: A total of 100 daily smokers (≥10 cigarettes/day for ≥6 months)

Inclusion Criteria:

1. ≥18 years and ≤65 years of age;
2. smoked ≥10 cigarettes/day for the past 6 months;
3. BMI of 27–39.9 kg/m^2;
4. motivated to stop smoking;
5. weight concerned as shown with the Weight Concern Scale;
6. able to participate fully in all aspects of the study;
7. understand and signed the study informed consent.

8. Subject is in good health as determined by the clinical investigators.

Exclusion Criteria:

1. current nonspecific suicidal thoughts or a lifetime history of a suicidal attempt (defined by the Columbia-Suicide Severity Rating Scale [C-SSRS] as a "potentially self-injurious act committed with at least some wish to die, *as a result of act*.");
2. current moderate or severe depression as assessed by a score of ≥16 on the Center for Epidemiologic Studies-Depression (CES-D);
3. a lifetime history of psychosis, bipolar disorder or schizophrenia;
4. use of anti-psychotic medication within the past 30 days;
5. use of weight-loss medications within the past 30 days or current participation in a program specifically designed to help with weight loss;
6. weight fluctuations of 20 pounds or more in the past 6 months (self-report);
7. use of any treatments for tobacco dependence within the past 30 days;
8. use of an investigational drug within the past 30 days;
9. recent history (past 3 months) of abuse of or dependence on a substance other than tobacco. Including: heavy alcohol consumption (If male, drinking > 4 alcoholic beverages per day for past month and if female, drinking > 3 alcoholic beverages per day for past month); use of cocaine, heroin, club drugs (i.e., MDMA/"ecstasy"), methamphetamine, or hallucinogens (e.g., LSD) at any time during the past 3 months; and use of marijuana on a weekly basis for the past 3 months
10. current use of triptans, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), selective serotoninnorepinephrine reuptake inhibitors (SNRIs), dextromethorphan, tricyclic antidepressants (TCAs), bupropion, lithium, tramadol, tryptophan, and St. John's Wort, or any other medication known to involve the serotonergic neurotransmitter system (see human subjects section);
11. uncontrolled hypertension (systolic >160 mm Hg and/or diastolic >100 mm Hg) documented on 2 separate occasions;
12. current use of medications known to interact with varenicline or lorcaserin. These can include benzodiazepines, narcotics, anti-epileptics;
13. another household member or relative participating in the study;
14. insulin dependent diabetic or unstable type 2 diabetic on oral diabetic medications.
15. a known allergy to varenicline or lorcaserin.
16. Women who are pregnant or lactating, or who are of childbearing potential and are likely to become pregnant during the medication phase but are not willing to use a reliable form of contraception, will also be excluded. Reliable forms of contraception include oral contraception, diaphragm or condom (with spermicide), injections, intrauterine device, surgical sterilization, and abstinence.
17. Has an unstable medical condition as determined by the physician investigator
18. Subject describes having a medical history of: a) unstable angina; b) myocardial infarction within the past 3 months; c) coronary angioplasty or d) an untreated cardiac dysrhythmia.
19. Subject currently has cancer [excluding non-melanoma skin cancer] not in remission
20. Known history of seizures

Will a Certificate of Confidentiality (COC) be obtained from NIH? ☐ Yes ☒ No

Study Design

Methods:

This will be a randomized, placebo-controlled, parallel-group clinical trial. Overweight and obese adult smokers will be randomized to one of two arms:

- lorcaserin for 24 weeks in combination with varenicline for 12 weeks;
- placebo for 24 weeks in combination with varenicline for 12 weeks;

We will assess the following:

- changes in weight, WC, and BMI
- 7-day point-prevalence smoking abstinence weekly through week 24 and prolonged smoking abstinence at 24 and 52 weeks. Subjects will have a target quit date 8 days after starting medication.

Study Medications

- Varenicline: Varenicline is an oral medication with a recommended dosage of 0.5 mg once daily for 3 days, increasing to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 1 mg twice daily for the remaining 11 weeks of treatment. The target quit date (TQD) will be one day after the one-week dose-escalation treatment (day 8 of therapy). Varenicline will be continued for a total of 12 weeks.
- Lorcaserin: Lorcaserin is an oral medication with a recommended dosage of 10 mg twice daily. Subjects will be randomized to receive either (1) active lorcaserin for 24 weeks simultaneously with active varenicline, (2) placebo lorcaserin for 24 weeks simultaneously with active varenicline. Lorcaserin will be taken in a dose of 10 mg twice daily. The placebo for lorcaserin and will be encapsulated with the assistance of the Mayo Clinic inpatient pharmacy, which will also help with the distribution of study medication and instructions for its use.

Subject Retention: Participants will be remunerated up to $145, prorated to the number of completed visits.

Statistical Information

Statistical Considerations

Statistical Design/Randomization:

A randomization program will be generated using SASDMS to randomize patients using a ratio of 1:1 assignment to Placebo + varenicline or Lorcaserin + varenicline. The randomization will be stratified by sex (Male/Female) and BMI (27-34.9 and 35-39.9).

All study medication will be labeled and dispensed according to subject ID by the Mayo Clinic Pharmacy.

Definitions:

- Height, Body Weight, and Waist Circumference*:* The primary outcome will be weight gain at 24 weeks, and a secondary outcome will be WC at 24 weeks. Height will be measured in stocking feet using a vertical stadiometer. Body weight will be measured with a digital scale that will be calibrated on a regular basis using certified weights. Participants will be measured with their shoes and heavy outer garments removed and pockets emptied. BMI will be calculated (as kg/m^2) from measured weight and height. The WC measurement will be standardized in the following way: While the subject is standing

upright, a measuring tape will be held in the horizontal plane around the bare abdomen at the iliac crest, and measurements will be taken at the end of a normal expiration with the tape snug and not compressing the skin.

- Smoking Abstinence definitions: Smoking abstinence definitions are based upon published recommendations:[49]
    - *Point-prevalence smoking abstinence* will be adjudicated if both of the following criteria are met: (1) Self-reported smoking abstinence for the last 7 days defined as a negative response to the question, "Have you used any type of tobacco, even a puff, in the past 7 days;" and (2) Expired air CO <8 ppm.
    - *Prolonged smoking abstinence* will be adjudicated if the following criteria are met: 1) Self-reported smoking abstinence since 2 weeks after target quit date (TQD). Negative response to the question, "Have you used any type of tobacco, even a puff, for 7 consecutive days or at least once each week on two consecutive weeks since xx/xx/xxxx?", where xx/xx/xxxx corresponds to the date 2 weeks after the TQD; 2) Biochemically confirmed smoking abstinence at the visit for which prolonged smoking abstinence is being obtained.

Power Statement:
The primary aim of the current study is to obtain preliminary evidence of the efficacy of a 24-week course of lorcaserin (10 mg twice a day) in attenuating weight gain in weight-concerned adult smokers who use varenicline to stop smoking. With this aim in mind, we have designed a randomized phase II screening trial to decide whether a larger study of this experimental regimen is warranted and to provide preliminary data for designing a larger phase III trial to confirm efficacy.[50]

For this study, the primary endpoint will be weight change from baseline to week 24 among subjects receiving active varenicline who meet criteria for prolonged smoking abstinence at week 24. In a trial evaluating the potential efficacy of maintenance therapy with varenicline, the point-prevalence abstinence rate after 12 weeks of open-label varenicline treatment was 64.1%,[30] and in our pilot study of sibutramine and varenicline the prolonged smoking abstinence rate at week 12 was 60%.[17] In order to be conservative, for the present study we assume that 30% of the subjects enrolled in the current trial who receive active varenicline will meet criteria for prolonged smoking abstinence at 24 weeks. In two large randomized trials assessing the efficacy of 12 weeks of varenicline for initiating smoking abstinence, the mean ± SD weight change from baseline at week 12 among subjects assigned to varenicline who were abstinent from smoking for weeks 9-12 was 2.89 ± 2.95 kg and 2.37 ± 2.95 kg.[31,51] From these studies, we assume that the standard deviation of weight change from baseline at 24 weeks among subjects who meet criteria for prolonged smoking abstinence will be 3.0 kg. We believe that an intervention that reduces weight gain by 2.0 kg or more would warrant further investigation. Using these assumptions, we have determined that an effective sample size of n = 15 subjects per group who meet criteria for prolonged smoking abstinence will provide statistical power (one-tailed, alpha = 0.20) of 82% to provide preliminary evidence of the efficacy of lorcaserin in attenuating weight gain for smokers who stop smoking using varenicline. Under the assumption that the prolonged smoking abstinence rate will be 30%, we propose a sample-size of N=50 per group.

Data Analysis Plan:
We will use descriptive statistics to summarize baseline characteristics (e.g. age, ethnicity, education, and results of the WEL Questionnaire, WCS, Control of Eating Questionnaire, and CES -D) and tobacco use history (e.g., cigarettes per day, FTND). Summaries will be generated for the entire sample, as well as according to

treatment group both overall and for those who meet the criteria for prolonged smoking abstinence at 24 weeks. For the primary endpoint of weight change at week 24 among subjects receiving active varenicline who meet the criteria for prolonged smoking abstinence, values will be compared between treatment groups using a one-tailed test with a *P* value ≤ 0.20 used as evidence to suggest that a larger phase III study should be pursued.[50] For consistency, one-tailed *P* values will also be reported for the secondary endpoints of WC and blood pressure. For the prolonged abstinence endpoints we will also use one-tailed, alpha=0.20 level tests as evidence to suggest further studies are warranted. For all other analyses, two-tailed *P* values will be reported. In all cases, treatment effects will be presented using point estimates and 90% confidence intervals.

Endpoints

Primary: Lorcaserin will be associated with significantly less weight gain than placebo in weight-concerned adult smokers who are treated simultaneously with varenicline for 12 weeks and are meet criteria for prolonged abstinence at the end of the lorcaserin medication phase (24 weeks).

- *Secondary:* Lorcaserin will be associated with significantly decreased WC and BMI compared to placebo in weight-concerned adult smokers who meet criteria for prolonged abstinence at the end of the medication phase (24 weeks). Weight change from baseline to 24 weeks among subjects who meet criteria for prolonged smoking abstinence will be compared between groups using the two-sample t-test. For this analysis, a *P* value ≤ 0.20 will be used as evidence to suggest that a larger phase III study should be pursued.[50] Similar analyses will be performed for the secondary endpoints of WC and BMI. Subjects who discontinue study participation will not meet criteria for prolonged smoking abstinence. For this reason, there should not be any missing data for the primary analysis. We will also perform secondary analyses that include all randomized subjects. For these analyses, we will use multiple imputation to impute values for subjects who discontinue study participation prior to 24 weeks. In all cases, we will assess distributional assumptions and use transformations or non-parametric analyses as appropriate.

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