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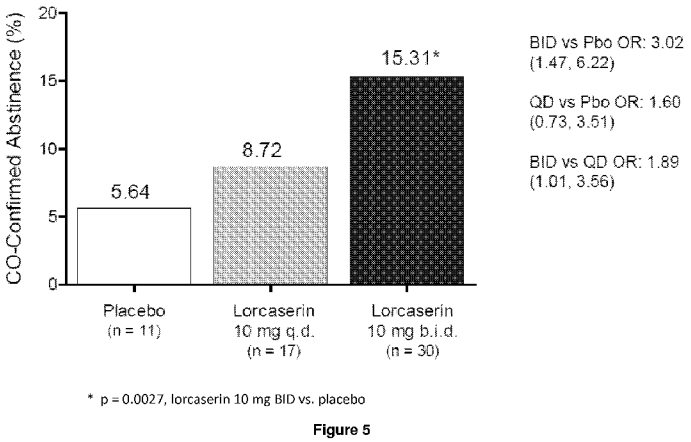

Figure 5

(57) Abstract: Provided are compositions comprising (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, optionally in combination with a supplemental agent, and methods for reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco; aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product; aiding in smoking cessation and preventing associated weight gain; controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use comprising administering (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, optionally in combination with a supplemental agent.

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COMPOSITIONS AND METHODS FOR CEASING TOBACCO SMOKING

Tobacco use is the leading cause of preventable illness and early death across the globe. According to the World Health Organization Fact Sheet (July 2013), 50% of all tobacco users die from a tobacco-related illness — this amounts to approximately six million people each year. It is estimated that greater than five million deaths per year result from direct tobacco use, with the remaining deaths resulting from exposure to second-hand smoke (*World Health Organization website. Fact Sheet No 339: Tobacco. www.who.int/mediacentre/factsheets/fs339/en/index.html. Updated July 2013. Accessed September 10, 2013*). According to the Centers for Disease Control and Prevention (CDC), approximately 43.8 million adults in the United States (U.S.) are cigarette smokers. In the U.S., tobacco use is responsible for one in five deaths each year (*World Health Organization website. Fact Sheet No 339: Tobacco. www.who.int/mediacentre/factsheets/fs339/en/index.html. Updated July 2013. Accessed September 10, 2013*). Tobacco use is directly related to cardiovascular disease, lung and other cancers, and chronic lower respiratory diseases (chronic bronchitis, emphysema, asthma, and other chronic lower respiratory diseases) (*Health Effects of Cigarette Smoking. Centers for Disease Prevention website. www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/ Accessed September 10, 2013*). These have held position as the top three leading causes of death in the U.S. since 2008, when chronic lower respiratory disease replaced cerebrovascular disease, which is also directly associated with tobacco use (*Molgaard CA, Bartok A, Peddecord KM, Rothrock J. The association between cerebrovascular disease and smoking: a case-control study. Neuroepidemiology. 1986;5(2):88-94*).

A study which surveyed the smoking behavior of 2138 US smokers over 8 years beginning in 2002 found that approximately one-third of subjects reported making a quit attempt over the previous year, approximately 85% of the original cohort made at least one quit attempt over the survey period, and the average quit rate was 3.8% for the retained cohort. Therefore the vast majority of smokers make quit attempts, but continued abstinence remains difficult to achieve (*Cummings KM, Cornelius ME, Carpenter MJ, et al. Abstract: How Many Smokers Have Tried to Quit? Society for Research on Nicotine and Tobacco. Poster Session 2. March 2013. POS2-65*).

Existing smoking cessation treatments include CHANTIX (varenicline) and ZYBAN (bupropion SR). However, the prescribing information for both CHANTIX and ZYBAN include black box warnings. The CHANTIX prescribing information carries a warning for

serious neuropsychiatric events, to include symptoms of agitation, hostility, depressed mood changes, behavior or thinking that are not typical for the patient, and suicidal ideation or suicidal behavior (*CHANTIX (varenicline) (package insert), New York, NY: Pfizer Labs, Division of Pfizer, Inc.; 2012*). In addition, the warning notes that a meta-analysis found cardiovascular events were infrequent, but some were reported more frequently in individuals treated with CHANTIX; the difference was not statistically significant (*CHANTIX (varenicline) (package insert), New York, NY: Pfizer Labs, Division of Pfizer, Inc.; 2012*). The ZYBAN prescribing information includes a similar black box warning for serious neuropsychiatric events during treatment as well as after discontinuation of treatment (*ZYBAN (bupropion hydrochloride) (package insert), Research Triangle Park, NC: GlaxoSmithKline; 2012*). Additional warnings include monitoring of individuals using antidepressants as there is an increased risk of suicidal thinking and behavior in children, adolescents and young adults, and other psychiatric disorders (*ZYBAN (bupropion hydrochloride) (package insert), Research Triangle Park, NC: GlaxoSmithKline; 2012*).

Further, weight gain is a well-recognized side effect of quitting smoking. Smoking cessation leads to weight gain in about 80% of smokers. The average weight gain in the first year after quitting is 4–5 kg, most of which is gained during the first 3 months. This amount of weight is typically viewed as a modest inconvenience compared with the health benefits of smoking cessation, but 10–20% of quitters gain more than 10 kg. Furthermore, a third of all subjects stated that they were unable to lose the excess weight after resuming smoking, lending support to the hypothesis that multiple quit attempts lead to cumulative weight gain (*Veldheer S, Yingst J, Foulds G, Hrabovsky S, Berg A, Sciamanna C, Foulds J. Once bitten, twice shy: concern about gaining weight after smoking cessation and its association with seeking treatment. Int J Clin Pract. (2014) 68:388-395*).

Given these statistics, it is perhaps not surprising that 50% of female smokers and 25% of male smokers cite fear of post-cessation weight gain (PCWG) as a major barrier to quitting, and approximately the same proportion cite weight gain as a cause of relapse in a previous quit attempt (*Meyers AW, Klesges RC, Winders SE, Ward KD, Peterson BA, Eck LH. Are weight concerns predictive of smoking cessation? A prospective analysis. J Consult Clin Psychol. (1997) 65: 448-452; Clark MM, Decker PA, Offord KP, Patten CA, Vickers KS, Croghan IT, Hays JT, Hurt RD, Dale LC. Weight concerns among male smokers. Addict Behav. (2004) 29:1637- 1641; Clark MM, Hurt RD, Croghan IT, Patten CA, Novotny P, Sloan JA, Dakhil SR, Croghan GA, Wos EJ, Rowland KM, Bernath A, Morton RF, Thomas SP, Tschetter LK, Garneau S, Stella PJ, Ebbert LP, Wender DB, Loprinzi CL. The prevalence of weight concerns in a smoking abstinence clinical trial. Addict Behav. (2006) 31:1144-1152.; Pomerleau CS,*

Kurth CL. Willingness of female smokers to tolerate postcessation weight gain. J Subst Abuse. (1996) 8:371-378; Pomerleau CS, Zucker AN, Stewart AJ. Characterizing concerns about post cessation weight gain: results from a national survey of women smokers. Nicotine Tob Res. (2001) 3:51-60). Women, in particular, are reluctant to gain weight while quitting; about 40% state they would resume smoking if they gained any weight at all (*Veldheer S, Yingst J, Foulds G, Hrabovsky S, Berg A, Sciamanna C, Foulds J. Once bitten, twice shy: concern about gaining weight after smoking cessation and its association with seeking treatment. Int J Clin Pract. (2014) 68:388-395; Pomerleau CS, Kurth CL. Willingness of female smokers to tolerate postcessation weight gain. J Subst Abuse (1996) 8:371-378; Pomerleau CS, Zucker AN, Stewart AJ. Characterizing concerns about post-cessation weight gain: results from a national survey of women smokers. Nicotine Tob Res. (2001) 3:51-60; Tønnesen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, Rijcken B, Sawe U. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. Eur Respir J. (1999) 13:238-246*).

Light and moderate smokers are generally considered to be more motivated to quit than heavy smokers, leaving an increasingly high proportion of 'hard-core' smokers who are less likely to stop smoking (*Hughes JR. The hardening hypothesis: is the ability to quit decreasing due to increasing nicotine dependence? A review and commentary. Drug Alcohol Depend. (2011) 117:111-117*). One of the factors commonly associated with weight-gain concern (WGC) is high nicotine dependence; thus, the prospect of quitting may be even more difficult for smokers who are both highly nicotine-dependent and weight concerned. In addition, somewhat paradoxically, heavy smokers tend to have higher body weights and a higher likelihood of obesity than lighter smokers, suggesting a more complex relationship between body weight and smoking (*Chiolero A, Jacot-Sadowski I, Faeh D, Paccaud F, Cornuz J. Association of cigarettes smoked daily with obesity in a general adult population. Obesity (Silver Spring) (2007) 15:1311-1318; John U, Hanke M, Rumpf HJ, Thyrian JR. Smoking status, cigarettes per day, and their relationship to overweight and obesity among former and current smokers in a national adult general population sample. Int J Obes (Lond). (2005) 29:1289-1294*). Several studies have found that overweight and obese smokers exhibit higher levels of smoking-related weight-gain concern than normal weight smokers (*Aubin H-J, Berlin I, Smadja E, West R. Factors associated with higher body mass index, weight concern, and weight gain in a multinational cohort study of smokers intending to quit. Int. J. Environ. Res. Public Health. (2009). 6:943-957; Levine MD, Bush T, Magnusson B, Cheng, Y, Chen X. Smoking-related weight concerns and obesity: differences among normal weight, overweight,*

and obese smokers using a telephone tobacco quitline. Nicotine Tob Res. (2013) 15:1136-1140). Given the convergence of high nicotine dependence and high weight-gain concern in obese smokers, smoking cessation interventions that address post-cessation weight gain could be especially beneficial for this subpopulation.

Despite the existence of several therapies for smoking cessation, long-term success rates are low and major barriers to quitting remain. There is a significant unmet need for safe and effective therapies that address these barriers. The present disclosure satisfies this need and provides related advantages as well.

SUMMARY

Prior to the present discovery, it was unclear whether a selective serotonin 2C receptor agonist would be able to drive clinically meaningful smoking cessation in humans—much less for particular individuals or in specific dosing regimens.

Provided is a method for reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for aiding in smoking cessation and preventing associated weight gain in an individual attempting to cease smoking and prevent weight gain comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of treatment for nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal comprising the step of: prescribing and/or administering to the individual an

effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

selecting an individual with an initial BMI ≥ 27 kg/m^2; and

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for at least one year.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or

withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for BMI during said administration; and

discontinuing said administration if the BMI of the individual becomes < 18.5 kg/m^2 during said administration.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual with an initial BMI ≤ 25 kg/m^2;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1% during said administration.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1 kg during said administration.

Also provided is a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent.

Also provided is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for use in combination with a supplemental agent.

Also provided is a supplemental agent chosen from nicotine replacement therapies, for use in combination with (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

DETAILED DESCRIPTION

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

INDIVIDUAL: As used herein, an "individual" is a human. An individual can be an adult or prepubertal (a child) and can be of any gender. The individual can be a patient or other individual seeking treatment. "Individual" is used herein interchangeably with "subject."

PLURALITY OF INDIVIDUALS: As used herein, a "plurality of individuals" means more than one individual.

ADMINISTERING: As used herein, "administering" means to provide a compound or other therapy, remedy or treatment. For example, a health care practitioner can directly provide a compound to an individual in the form of a sample, or can indirectly provide a compound to an individual by providing an oral or written prescription for the compound. Also, for example, an individual can obtain a compound by themselves without the involvement of a health care practitioner. Administration of the compound may or may not involve the individual actually internalizing the compound. In the case where an individual internalizes the compound, the body is transformed by the compound in some way.

PRESCRIBING: As used herein, "prescribing" means to order, authorize or recommend the use of a drug or other therapy, remedy or treatment. In some embodiments, a health care practitioner can orally advise, recommend or authorize the use of a compound, dosage regimen or other treatment to an individual. In this case the health care practitioner may or may not provide a prescription for the compound, dosage regimen or treatment. Further, the health care practitioner may or may not provide the recommended compound or

treatment. For example, the health care practitioner can advise the individual where to obtain the compound without providing the compound. In some embodiments, a health care practitioner can provide a prescription for the compound, dosage regimen or treatment to the individual. For example, a health care practitioner can give a written or oral prescription to an individual. A prescription can be written on paper or on electronic media such as a computer file, for example, on a handheld computer device. For example, a health care practitioner can transform a piece of paper or electronic media with a prescription for a compound, dosage regimen or treatment. In addition, a prescription can be called in (oral) or faxed in (written) to a pharmacy or a dispensary. In some embodiments, a sample of the compound or treatment can be given to the individual. As used herein, giving a sample of a compound constitutes an implicit prescription for the compound. Different health care systems around the world use different methods for prescribing and administering compounds or treatments and these methods are encompassed by the disclosure.

A prescription can include, for example, an individual's name and/or identifying information such as date of birth. In addition, for example, a prescription can include, the medication name, medication strength, dose, frequency of administration, route of administration, number or amount to be dispensed, number of refills, physician name, and/or physician signature. Further, for example, a prescription can include a DEA number or state number.

A healthcare practitioner can include, for example, a physician, nurse, nurse practitioner or other related health care professional who can prescribe or administer compounds (drugs) for weight management, smoking cessation, or nicotine dependence. In addition, a healthcare practitioner can include anyone who can recommend, prescribe, administer or prevent an individual from receiving a compound or drug including, for example, an insurance provider.

PREVENT, PREVENTING, OR PREVENTION: As used herein, the term "prevent," "preventing" or "prevention" such as prevention of weight gain associated with smoking cessation means prevention of the occurrence or onset of one or more symptoms associated with a particular disorder and does not necessarily mean the complete prevention of a disorder. For example, weight gain may be prevented even if the individual gains some amount of weight.

For example, the term "prevent," "preventing" and "prevention" refers to the administration of therapy on a prophylactic or preventative basis to an individual who may ultimately manifest at least one symptom of a disease or condition but who has not yet done so. Such individuals can be identified on the basis of risk factors that are known to correlate with the subsequent occurrence of the disease. Alternatively, prevention therapy can be administered

without prior identification of a risk factor, as a prophylactic measure. Delaying the onset of the at least one symptom can also be considered prevention or prophylaxis.

PHARMACEUTICALLY ACCEPTABLE SALTS, SOLVATES, AND HYDRATES: It is understood that when the phrase "pharmaceutically acceptable salts, solvates, and hydrates" or the phrase "pharmaceutically acceptable salt, solvate, or hydrate" is used when referring to a compound/compounds as described herein, it embraces pharmaceutically acceptable solvates and/or hydrates of the compound/compounds, pharmaceutically acceptable salts of the compound/compounds, as well as pharmaceutically acceptable solvates and/or hydrates of pharmaceutically acceptable salts of the compound/compounds. It is also understood that when the phrase "pharmaceutically acceptable solvates and hydrates" or the phrase "pharmaceutically acceptable solvate or hydrate" is used when referring to a compound/compounds as described herein that are salts, it embraces pharmaceutically acceptable solvates and/or hydrates of such salts. It is also understood by a person of ordinary skill in the art that hydrates are a subgenus of solvates.

TREAT, TREATING, OR TREATMENT: As used herein the term "treat," "treating" or "treatment" refers to the administration of therapy to an individual who already manifests, or who has previously manifested, at least one symptom of a disease, disorder, condition, dependence, or behavior. For example, "treating" can include any of the following with respect to a disease, disorder, condition, dependence, or behavior: alleviating, abating, ameliorating, inhibiting (*e.g.*, arresting the development), relieving, or causing regression. "Treating" can also include treating the symptoms, preventing additional symptoms, preventing the underlying physiological causes of the symptoms, or stopping the symptoms (either prophylactically and/or therapeutically) of a disease, disorder, condition, dependence, or behavior. For example, the term "treating" in reference to a disorder means a reduction in severity of one or more symptoms associated with a particular disorder. Therefore, treating a disorder does not necessarily mean a reduction in severity of all symptoms associated with a disorder and does not necessarily mean a complete reduction in the severity of one or more symptoms associated with a disorder. For example, a method for treatment of obesity can result in weight loss; however, the weight loss does not need to be enough such that the individual is no longer obese. It has been shown that even modest decreases in weight or related parameters such as BMI, waist circumference and percent body fat, can result in improvement of health, for example, lower blood pressure, improved blood lipid profiles, or a reduction in sleep apnea. Furthermore, it has been shown that smoking is an independent and major risk factor for cardiovascular disease. As such, lessening or ceasing tobacco use, *e.g.*, cigarette smoking, can result in improvement of health, particularly cardiovascular health.

WEIGHT MANAGEMENT: As used herein, the term "weight management" refers to controlling weight (also called weight control) and/or controlling parameters related to weight, for example, BMI, percent body fat and/or waist circumference. In the context of the present disclosure, weight management is directed toward preventing weight gain, controlling weight gain, reducing weight gain, maintaining weight, or inducing weight loss. In addition, weight management includes preventing an increase in BMI, reducing an increase in BMI, maintaining BMI, or reducing BMI; preventing an increase in percent body fat, reducing an increase in percent body fat, maintaining percent body fat, or reducing percent body fat; and preventing an increase in waist circumference, reducing an increase in waist circumference, maintaining waist circumference, or reducing waist circumference.

ADVERSE EVENT OR TOXIC EVENT: As used herein, an "adverse event" or "toxic event" is any untoward medical occurrence that may present itself during treatment. Adverse events associated with treatment may include, for example, headache, nausea, constipation, fatigue, dry mouth, dizziness, abnormal dreams, insomnia, nasopharyngitis, toothache, sinusitis, back pain, somnolence, viral gastroenteritis, seasonal allergy, or pain in an extremity. Additional possible adverse effects include, for example, gastrointestinal disorders (such as constipation, abdominal distension, and diarrhea), asthenia, chest pain, fatigue, drug hypersensitivity, fibromyalgia, temporomandibular joint syndrome, headache, dizziness, migraine, anxiety, depressed mood, irritability, suicidal ideation, bipolar disorder, depression, drug abuse, and dyspnea. In the methods disclosed herein, the term "adverse event" can be replaced by other more general terms such as "toxicity." The term "reducing the risk" of an adverse event means reducing the probability that an adverse event or toxic event could occur.

AGONIST: As used herein, the term "agonist" refers to a moiety that interacts with and activates a receptor, such as the 5-HT_{2C} serotonin receptor, and initiates a physiological or pharmacological response characteristic of that receptor.

IMMEDIATE-RELEASE DOSAGE FORM: The term "immediate-release dosage form" refers to a formulation which rapidly disintegrates upon oral administration to a human or other animal, releasing an active pharmaceutical ingredient (API) from the formulation. In some embodiments, the T80% of the immediate-release dosage form is less than 3 hours. In some embodiments, the T80% of the immediate-release dosage form is less than 1 hour. In some embodiments, the T80% of the immediate-release dosage form is less than 30 minutes. In some embodiments, the T80% of the immediate-release dosage form is less than 10 minutes.

T80%: The term "T80%" refers to the time needed to achieve 80% cumulative release of an API from a particular formulation comprising the API.

MODIFIED-RELEASE DOSAGE FORM: The term "modified-release dosage form" refers to any formulation that, upon oral administration to a human or other animal, releases an API after a given time (*i.e.*, delayed release) or for a prolonged period of time (extended release), *e.g.*, at a slower rate over an extended period of time when compared to an immediate-release dosage-form of the API (*e.g.*, sustained release). Exemplary modified-release dosage forms are described in WO2012/030927. In some embodiments, the modified-release dosage form comprises: a core comprising about 20.8 mg lorcaserin HCl hemihydrate, about 60 mg microcrystalline cellulose, about 65.5 mg mannitol, about 150 mg hydroxypropyl methylcellulose, about 0.75 mg colloidal silicon dioxide, and about 3 mg magnesium stearate; a functional coating comprising about 12.75 mg ethylcellulose dispersion type B, and about 2.25 mg OPADRY; and a film coating comprising about 13.5 mg OPADRY II.

NICOTINE REPLACEMENT THERAPY: As used herein, "nicotine replacement therapy" (commonly abbreviated to NRT) refers to the remedial administration of nicotine to the body by means other than a tobacco product. By way of example, nicotine replacement therapy may include transdermal nicotine delivery systems, including patches and other systems that are described in the art, for example, in U.S. Pat. Nos. 4,597,961, 5,004,610, 4,946,853, and 4,920,989. Inhaled nicotine (*e.g.*, delivery of the nicotine through pulmonary routes) is also known. Transmucosal administration (*e.g.*, delivery of nicotine to the systemic circulation through oral drug dosage forms) is also known. Oral drug dosage forms (*e.g.*, lozenge, capsule, gum, tablet, suppository, ointment, gel, pessary, membrane, and powder) are typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to allow immediate systemic absorption. It will be understood by those skilled in the art that a plurality of different treatments and means of administration can be used to treat a single individual. For example, an individual can be simultaneously treated with nicotine by transdermal administration and nicotine which is administered to the mucosa. In some embodiments, the nicotine replacement therapy is chosen from nicotine gum (*e.g.*, NICORETTE), nicotine transdermal systems such as nicotine patches (*e.g.*, HABITROL and NICODERM), nicotine lozenges (*e.g.*, COMMIT), nicotine microtabs (*e.g.*, NICORETTE Microtabs), nicotine sprays or inhalers (*e.g.*, NICOTROL), and other nicotine replacement therapies known in the art. In some embodiments, nicotine replacement therapy includes electronic cigarettes, personal vaporizers, and electronic nicotine delivery systems.

COMBINATION: As used herein, "combination" as used in reference to drug combinations and/or combinations of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof with at least one supplemental agent refers to (1) a product comprised of two or more components, *i.e.*,

drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, *e.g.*, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. Combinations include without limitation a fixed-dose combination product (FDC) in which two or more separate drug components are combined in a single dosage form; a co-packaged product comprising two or more separate drug products in their final dosage forms, packaged together with appropriate labeling to support the combination use; and an adjunctive therapy in which a patient is maintained on a second drug product that is used together with (*i.e.*, in adjunct to) the primary treatment, although the relative doses are not fixed, and drugs or biologics that are not necessarily given at the same time. Adjunctive therapy products may be co-packaged, and may or may not be labeled for concomitant use.

RESPONDER: As used herein, "responder" refers to an individual who experiences continuous abstinence from tobacco use during a specified period of administration of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In some embodiments, "responder" refers to an individual who reports no smoking or other nicotine use from Week 9 to Week 12 of administration of lorcaserin hydrochloride hemihydrate and exhibits an end-expiratory exhaled carbon monoxide-confirmed measurement of ≤ 10 ppm.

TOBACCO PRODUCT: As used herein, "tobacco product" refers to a product that incorporates tobacco, *i.e.*, the agricultural product of the leaves of plants in the genus *Nicotiana*. Tobacco products can generally be divided into two types: smoked tobacco including without limitation pipe tobacco, cigarettes (including electronic cigarettes) and cigars, as well as Mu'assel, Dokha, shisha tobacco, hookah tobacco, or simply shisha; and smokeless tobacco including without limitation chewing tobacco, dipping tobacco (also known as dip), moist snuff (or snuff), American moist snuff, snus, Iqmik, Naswar, Gutka,

Toombak, shammah, tobacco water, spit tobacco, creamy snuff or tobacco paste, dissolvable tobacco, and tobacco gum.

FAGERSTRÖM TEST: As used herein, "Fagerström test" refers to a standard test for nicotine dependence which is a test for assessing the intensity of nicotine addiction. *See Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., Fagerström, K. O. The Fagerström test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991; 86:1119-27.* The test consists of a brief, self-report survey that measures nicotine dependence on a scale of 0-10, with 10 being the highest level of dependence. A score of 0-2 corresponds to very low dependence. A score of 3-4 corresponds to low dependence. A score of 5 corresponds to moderate dependence. A score of 6-7 corresponds to high dependence. A score of 8-10 corresponds to very high dependence.

Other methods may be utilized to assess the craving for nicotine, including but not limited to, the nicotine craving test specified by the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R).

MOOD AND PHYSICAL SYMPTOMS SCALE: As used herein, "Mood and Physical Symptoms Scale" (MPSS) refers to a scale used to assess cigarette withdrawal symptoms (*West R, Hajek P: Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology 2004, 177(1-2):195-199*). The core elements of MPSS involve a 5-point rating of depressed mood, irritability, restlessness, difficulty concentrating and hunger and a 6-point rating of strength of urges to smoke and time spent with these urges.

LORCASERIN: As used herein, lorcaserin refers to (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine. Similarly, lorcaserin hydrochloride refers to the hydrochloric acid salt of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*see Statement on Nonproprietary Name Adopted by the USAN Council for Lorcaserin Hydrochloride*).

As used herein, the term "greater than" is used interchangeably with the symbol > and the term "less than" is used interchangeably with the symbol <. Likewise the term less than or equal to is used interchangeably with the symbol ≤ and the term greater than or equal to is used interchangeably with the symbol ≥.

When an integer is used in a method disclosed herein, the term "about" can be inserted before the integer. For example, the term "greater than 29 kg/m^2" can be substituted with "greater than about 29 kg/m^2".

As used in the present specification, the following abbreviations are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

°C	Degrees Celsius
A1C	Glycated hemoglobin
BID	Twice a day
BL	Baseline
BMI	Body Mass Index
BP	Blood pressure
BPM/bpm	Beats per minute
CAR	Continuous abstinence rate
CI	Confidence interval
cm	Centimeter
CO	Carbon monoxide
DOI	2,5-Dimethoxy-4-iodoamphetamine
DBP	Diastolic blood pressure
DEA	Drug Enforcement Administration
dL	Deciliter
E_{max}	Maximum possible effect
FDA	Food and Drug Administration
g	Gram
h	Hour
HDL	High-density lipoprotein
Kg/kg	Kilogram
lbs	Pounds
LDL	Low-density lipoprotein
M	Molar
m^2	Square Meter
mg	Milligram
min	Minute
MITT	Modified intention to treat
mmHg	Millimeters of Mercury
N/n	Number
NDA	New Drug Application
PP	Point prevalence
ppm	parts per million

QD	Once a day
SAE	Serious Adverse Events
SE	Standard Error
SBP	Systolic blood pressure
TGA	Thermogravimetric Analysis
wt	Weight
PXRD	X-ray powder diffraction

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers but not the exclusion of any other step or element or integer or group of elements or integers.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (*i.e.*, one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

Each embodiment described herein is to be applied *mutatis mutandis* to each and every other embodiment unless specifically stated otherwise.

Those skilled in the art will appreciate that the invention(s) described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention(s) includes all such variations and modifications. The invention(s) also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features unless specifically stated otherwise.

The present invention(s) is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the present invention.

It is appreciated that certain features of the invention(s), which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention(s), which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. For example, a method that recites prescribing or administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine can be separated into two methods—

one reciting prescribing (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and the other reciting administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine. In addition, for example, a method that recites prescribing (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and a separate method of the invention reciting administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine can be combined into a single method reciting prescribing and/or administering (*R*)-8-chloro-1-methyl-2,3,4,5- tetrahydro-1*H*-3-benzazepine.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows a schematic of the study design used in the Phase 2 clinical trial described in Example 3.

Figures 2 and 3 show the baseline characteristics of subjects in the Phase 2 clinical trial.

Figure 4 shows the disposition of subjects from the Phase 2 clinical trial.

Figure 5 shows CO-confirmed 4-week CARs for Weeks 9 to 12 in the MITT population from the Phase 2 clinical trial. "n" in Figures 5-8 is the number of subjects that reported not smoking (not even a puff or other nicotine use) and exhibited an end-expiratory CO level of ≤ 10 ppm.

Figure 6 shows CO-confirmed 4-week CARs for Weeks 5 to 8 in the MITT population.

Figure 7 shows CO-confirmed 4-week CARs for Weeks 5 to 12 in the MITT population.

Figure 8 shows CO-confirmed 4-week CARs for Weeks 3 to 12 in the MITT population.

Figure 9 shows the 7-day point prevalence smoking abstinence at Week 12 in the MITT population. "n" in Figure 9 is the number of subjects who were continuously abstinent for the 7-day period preceding a clinical visit and exhibited an end-expiratory CO level of ≤ 10 ppm.

Figure 10 shows the change from baseline in number of cigarettes smoked at Week 12 in the MITT population.

Figure 11 shows the change from baseline in body weight (in kg) at Week 12 in the MITT population.

Figure 12 shows the change from baseline in body weight (in kg) at Week 12 for responders in the MITT population. "Responders" in Figure 12 are subjects who had 4 weeks of continuous abstinence from Week 9 to Week 12 and exhibited an end-expiratory CO level of ≤ 10 ppm.

Figure 13 shows the change from baseline in body weight (in kg) at Week 12 by responder status in the MITT population. "Responders" in Figure 13 are subjects who had 4

weeks of continuous abstinence from Week 9 to Week 12 and exhibited an end-expiratory CO level of ≤ 10 ppm.

Figure 14 shows the change from baseline in body weight (in kg) at Week 12 by baseline BMI in the MITT population.

Figure 15 shows the change from baseline in body weight (in kg) at Week 12 by baseline BMI in the MITT population.

Figure 16 shows the change from baseline in body weight (in kg) at Week 12 by baseline BMI and responder status in the MITT population. "Responders" in Figure 16 are subjects who had 4 weeks of continuous abstinence from Week 9 to Week 12 and exhibited an end-expiratory CO level of ≤ 10 ppm.

Figure 17 shows a summary of treatment-emergent adverse events in the Phase 2 clinical trial.

Figure 18 shows potency and efficacy of lorcaserin in human, rat, and monkey 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors.

Figure 19 shows differences in exposure and 5-HT_2 receptor selectivity in humans and rats.

DETAILED DESCRIPTION

Provided is a method for aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In some embodiments, aiding in the cessation of use of a tobacco product is aiding smoking cessation, and the individual attempting to cease use of the tobacco product is an individual attempting to cease smoking.

Also provided is a method for aiding in the cessation of use of a tobacco product and the prevention of associated weight gain comprising the step of: prescribing and/or administering an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual attempting to cease use of the tobacco product. In some embodiments, aiding in the cessation of use of a tobacco product is aiding smoking cessation, and the individual attempting to cease use of the tobacco product is an individual attempting to cease smoking.

Also provided is a method for reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-

methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method for reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of treatment for nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal comprising the step of: prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use comprising the step of:
prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

selecting an individual with an initial BMI ≥ 27 kg/m^2; and

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for at least one year.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for BMI during said administration; and

discontinuing said administration if the BMI of the individual becomes < 18.5 kg/m^2 during said administration.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual with an initial BMI ≤ 25 kg/m^2;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1% during said administration.

In some embodiments, administration is discontinued if the body weight of the individual decreases by more than about 2% during said administration. In some embodiments, administration is discontinued if the body weight of the individual decreases by more than about 3% during said administration. In some embodiments, administration is discontinued if the body weight of the individual decreases by more than about 4% during said administration. In some embodiments, administration is discontinued if the body weight of the individual decreases by more than about 5% during said administration.

Also provided is a method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1 kg during said administration.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is for use as an aid to smoking cessation treatment. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is for use as an aid for cessation of cigarette smoking. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is for use as an aid to smoking cessation treatment and the prevention of associated weight gain. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is for use as a weight-neutral intervention for smoking cessation. In some embodiments, the weight gain occurs during smoking cessation. In some embodiments, the weight gain occurs post-smoking cessation.

Any embodiment of the invention directed to smoking cessation or the cessation or lessening of use of a tobacco product can be adapted to the cessation or lessening of use of nicotine administration from any and all sources or any individual source, including tobacco products (or specific examples thereof), tobacco replacement therapy (or specific examples thereof), and/or any electronic nicotine delivery system (*e.g.*, electronic cigarettes or personal vaporizers). The present invention specifically embraces all such embodiments.

"Selectivity" as disclosed herein refers to a relative comparison of the effects of an agonist on two or more receptors. In some embodiments, selectivity refers to the relative *in vitro* potency of an agonist for two receptors. In some embodiments, *in vitro* potency is quantified using a second messenger assay. In some embodiments, *in vitro* potency is quantified by EC_{50}. In some embodiments, selectivity refers to the relative binding affinity of an agonist for two receptors. In some embodiments, binding affinity is quantified by Ki. In some embodiments, selectivity is measured by comparing data generated from an IP accumulation assay. In some embodiments, selectivity is measured by comparing data generated from a calcium assay. In some embodiments, selectivity is measured by comparing data generated from a DOI assay. In some embodiments, selectivity values are determined using *in vitro* potency values generated in assays according to Example 2. For methodologies of ensuring the accuracy of *in vitro* potency values, see pages 155-157 of Cavero *et al.* (*Cavero I and Guillon J-M. Safety Pharmacology assessment of drugs with biased 5-HT_{2B} receptor agonism mediating cardiac valvulopathy. J Pharmacological and Toxicological Methods 69 (2014); 150-161*).

In some embodiments, (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, and pharmaceutically acceptable salts, solvates, and hydrates thereof encompass any one of the following salts, or a Markush group comprising any combination of the following salts as disclosed in WO2006/069363, WO2012/030927, WO2012/030938, WO2012/030951, and WO2012/030957:

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydroiodide salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine fumarate salt; and

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemifumarate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-acetamidobenzoate salt-cocrystal;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine *trans*-cinnamate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (±)-mandelate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemipamoate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1*S*)-(+)-10-camsylate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-L-malate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine L-glutamate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine L-aspartate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemimucate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine pyroglutamate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine glucuronate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-camphorate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine bisulfate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemisulfate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine mesylate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine nitrate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine sesqui-oxalate salt-cocrystal;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine adipate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine malonate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemimalonate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine glycolate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-edisylate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine phosphate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine citrate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-oxalate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine succinate salt; and
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine oxoglutarate salt; and
pharmaceutically acceptable solvates and hydrates thereof.

In some embodiments, (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and pharmaceutically acceptable salts, solvates, and hydrates thereof encompass any one of the following salts, or a Markush group comprising any combination of the following salts as disclosed in WO2006/069363, WO2012/030927, WO2012/030938, WO2012/030951, and WO2012/030957:

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydroiodide salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine fumarate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemifumarate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt hydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-4-acetamidobenzoate salt-cocrystal methyl ethyl ketone solvate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine *trans*-cinnamate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt solvate 1;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt solvate 2;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (±)-mandelate salt hydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemipamoate salt hydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1*S*)-(+)-10-camsylate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-L-malate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine L-glutamate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine L-aspartate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemimucate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine pyroglutamate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine glucuronate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-camphorate salt solvate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine bisulfate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemisulfate salt hydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine mesylate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide salt hemihydrate;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine nitrate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine sesqui-oxalate salt-cocrystal;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine adipate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine malonate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemimalonate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine glycolate salt;
(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-edisylate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine phosphate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine citrate salt hemihydrate;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemi-oxalate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine succinate salt;

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine oxoglutarate salt; and

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine oxoglutarate salt solvate.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is selected from an HCl salt of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and solvates or hydrates thereof.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is selected from a hydrate of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and pharmaceutically acceptable salts thereof.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is a hydrate of an HCl salt of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof.

It will be apparent to those skilled in the art that the dosage forms described herein may comprise, as the active component, either a compound described herein, a pharmaceutically acceptable salt of a compound described herein, a solvate or hydrate of a compound described herein, or a solvate or hydrate of a pharmaceutically acceptable salt of a compound described herein. Moreover, various hydrates and solvates of the compounds described herein and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of *K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999.* Accordingly, one aspect of the present disclosure pertains to methods of administering hydrates and solvates of compounds described herein and/or their pharmaceutical acceptable salts, that can be isolated and characterized by methods known in the art, such as,

thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (PXRD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

The present disclosure includes all isotopes of atoms occurring in the present salts and crystalline forms thereof. Isotopes include those atoms having the same atomic number but different mass numbers. One aspect of the present invention includes every combination of one or more atoms in the present salts and crystalline forms thereof that is replaced with an atom having the same atomic number but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^{1}H or ^{12}C, found in one the present salts and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as ^{2}H or ^{3}H (replacing ^{1}H), or ^{11}C, ^{13}C, or ^{14}C (replacing ^{12}C). A salt wherein such a replacement has taken place is commonly referred to as being isotopically-labeled. Isotopic-labeling of the present salts and crystalline forms thereof can be accomplished using any one of a variety of different synthetic methods known to those of ordinary skill in the art and they are readily credited with understanding the synthetic methods and available reagents needed to conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^{2}H (deuterium) and ^{3}H (tritium). Isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C. Isotopes of nitrogen include ^{13}N and ^{15}N. Isotopes of oxygen include ^{15}O, ^{17}O, and ^{18}C. An isotope of fluorine includes ^{18}F. An isotope of sulfur includes ^{35}S. An isotope of chlorine includes ^{36}Cl. Isotopes of bromine include ^{75}Br, ^{76}Br, ^{77}Br, and ^{82}Br. Isotopes of iodine include ^{123}I, ^{124}I, ^{125}I, and ^{131}I. Another aspect of the present invention includes compositions, such as those prepared during synthesis, preformulation, and the like, and pharmaceutical compositions, such as those prepared with the intent of using in a mammal for the treatment of one or more of the disorders described herein, comprising one or more of the present salts and crystalline forms thereof, wherein the naturally occurring distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and pharmaceutical compositions comprising salts and crystalline forms thereof as described herein wherein the salt is enriched at one or more positions with an isotope other than the most naturally abundant isotope. Methods are readily available to measure such isotope perturbations or enrichments, such as mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as radio-detectors used in connection with HPLC or GC.

In some embodiments, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual smokes ≥ 10 cigarettes per day. In some embodiments, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual smokes 11-20 cigarettes per day. In some embodiments, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual smokes 21-30 cigarettes per day. In some embodiments, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual smokes ≥ 31 cigarettes per day.

In some embodiments, the individual has an initial BMI selected from one of the following: ≥ 24 kg/m^2, ≥ 23 kg/m^2, ≥ 22.5 kg/m^2, ≥ 22 kg/m^2, ≥ 21 kg/m^2, ≥ 20 kg/m^2, ≥ 19 kg/m^2, or ≥ 18.5 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 23 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 22.5 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 22 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 18.5 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 18 kg/m^2. In some embodiments, prior to administration, the individual has an initial BMI ≥ 17.5 kg/m^2. In some embodiments, prior to administration, the individual has an initial body mass index ≥ 25 kg/m^2 and at least one weight-related comorbid condition.

In some embodiments, prior to administration, the individual has an initial body mass index ≥ 27 kg/m^2. In some embodiments, prior to administration, the individual has an initial body mass index ≥ 27 kg/m^2 and at least one weight-related comorbid condition.

In some embodiments, the weight-related comorbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance and sleep apnea. In some embodiments, the weight-related comorbid condition is selected from: hypertension, dyslipidemia, and type 2 diabetes.

In some embodiments, prior to administration, the individual has an initial body mass index ≥ 30 kg/m^2.

In some embodiments, the initial BMI of the individual prior to administration is 18.5 to 25 kg/m^2.

In some embodiments, the individual is suffering from depression prior to being administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the individual is suffering from a preexisting psychiatric disease prior to being administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the preexisting psychiatric disease is chosen from schizophrenia, bipolar disorder, or major depressive disorder.

In some embodiments, individuals are assessed for nicotine dependence based on the Fagerström test. In some embodiments, the individual has a score of 0, 1, or 2. In some embodiments, the individual has a score of 3 or 4. In some embodiments, the individual has a score of 5. In some embodiments, the individual has a score of 6 or 7. In some embodiments, the individual has a score of 8, 9, or 10. In some embodiments, the individual has a score ≥ 3. In some embodiments, the individual has a score ≥ 5. In some embodiments, the individual has a score ≥ 6. In some embodiments, the individual has a score ≥ 8.

In some embodiments, the individual has a Fagerström score of 0, 1, or 2 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of 0, 1, or 2 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of 0, 1, or 2 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of 3 or 4 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of 3 or 4 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of 3 or 4 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of 5 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of 5 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of 5 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of 6 or 7 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of 6 or 7 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of 6 or 7 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of 8, 9, or 10 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of 8, 9, or 10 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of 8, 9, or 10 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of ≥ 3 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 3 and a BMI ≥ 25

kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 3 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of ≥ 5 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 5 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 5 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of ≥ 6 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 6 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 6 and a BMI ≥ 30 kg/m^2.

In some embodiments, the individual has a Fagerström score of ≥ 8 and a BMI < 25 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 8 and a BMI ≥ 25 kg/m^2 and < 30 kg/m^2. In some embodiments, the individual has a Fagerström score of ≥ 8 and a BMI ≥ 30 kg/m^2.

In some embodiments, a questionnaire is used to evaluate symptoms experienced during quit, such as the urge to smoke, withdrawal, or reinforcing effects. In some embodiments, the questionnaire is selected from: the Minnesota Nicotine Withdrawal Score (MNWS), Brief Questionnaire of Smoking Urges (QSU-Brief), McNett Coping Effectiveness Questionnaire (mCEQ), Three-Factor Eating Questionnaire (TFEQ), and Food Craving Inventory (FCI).

In some embodiments, the nicotine dependency, addiction and/or withdrawal results from the use of tobacco products. In some embodiments, the nicotine dependency, addiction, and/or withdrawal results from cigarette smoking.

In some embodiments, the nicotine dependency, addiction and/or withdrawal results from the use of nicotine replacement therapies.

In some embodiments, the individual is first administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof on the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof at least 7 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a

pharmaceutically acceptable salt, solvate, or hydrate thereof about 7 to about 35 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof 7 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof at least 14 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof about 14 to about 35 days prior to the target quit day. In some embodiments, the individual is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof 14 days prior to the target quit day.

In some embodiments, the individual quits smoking between days 8 and 35 of treatment. In some embodiments, the individual quits smoking between days 15 and 35 of treatment. In some embodiments, the individual quits smoking between days 22 and 35 of treatment. In some embodiments, the individual quits smoking on day 8 of treatment. In some embodiments, the individual quits smoking on day 15 of treatment. In some embodiments, the individual quits smoking on day 22 of treatment.

In some embodiments, prior to administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the method further comprises the step of: instructing the individual to set a date to cease smoking tobacco. In some embodiments, administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof is initiated about 7 days prior to the date set to cease smoking tobacco.

In some embodiments, after administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, the method further comprises the step of: instructing the individual to set a date to cease smoking tobacco. In some embodiments, the date set to cease smoking tobacco occurs after at least 7 days of administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In some embodiments, the date set to cease smoking tobacco occurs prior to 36 days of administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the individual previously attempted to cease smoking tobacco but did not succeed in ceasing smoking tobacco. In some embodiments, the individual

previously attempted to cease smoking tobacco but subsequently relapsed and resumed smoking tobacco.

In some embodiments, the administration leads to a statistically significant improvement in the ability to tolerate the cessation of smoking as measured by analysis of data from the MPSS test.

In some embodiments, the individual has abstained from nicotine use for 12 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the individual has abstained from nicotine use for 24 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the individual has abstained from nicotine use for 9 months prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, the individual has abstained from nicotine use for 52 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In some embodiments, abstinence is self-reported. In some embodiments, the self-reporting is based on response to a questionnaire. In some embodiments, the questionnaire is a Nicotine Use Inventory. In some embodiments, an individual self-reports as not having smoking any cigarettes (even a puff). In some embodiments, the individual self-reports as not having used any other nicotine-containing products. In some embodiments, the individual self-reports as not having smoking any cigarettes (even a puff) and not having used any other nicotine-containing products.

In some embodiments, the duration of treatment is selected from: 12 weeks, 6 months, 9 months, 1 year, 18 months, 2 years, 3 years, 4 years, and 5 years.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 2 weeks. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 4 weeks. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 8 weeks. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 12 weeks. In some embodiments, the (*R*)-8-chloro-1-

methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 6 months. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 1 year. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 2 years. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for between about 7 weeks to about 12 weeks. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for between about 12 weeks to about 52 weeks. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for between about 6 months to about 1 year.

In some embodiments, the individual receives treatment for a first treatment period. In some embodiments, the individual receives treatment for an additional treatment period, *e.g.*, to increase the likelihood of long-term abstinence. In some embodiments, an individual who fails in a first treatment period is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof optionally in combination with a supplemental agent for a second treatment period. In some embodiments, an individual who relapses during a first treatment is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof optionally in combination with a supplemental agent for a second treatment period. In some embodiments, an individual who relapses following a first treatment is administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof optionally in combination with a supplemental agent for a second treatment period. In some embodiments, the first treatment period is 12 weeks. In some embodiments, the second treatment period is 12 weeks or less. In some embodiments, the second treatment period is 12 weeks. In some embodiments, the second treatment period is more than 12 weeks. In some embodiments, the first treatment period is one year. In some embodiments, the second treatment period is one year or less. In some embodiments, the second treatment period is one year. In some embodiments, the first treatment period is longer than the second treatment period. In some embodiments, the first treatment period is shorter than the second treatment period. In some embodiments, the first treatment period and the second period are of the same length of time.

In some embodiments, the prevention or reduction of weight gain, or inducement of weight loss, is measured relative to the amount of weight gain or loss typically experienced when an individual attempts smoking cessation. In some embodiments, the prevention or reduction of weight gain, or inducement of weight loss, is measured relative the amount of weight gain or loss typically experienced when an individual attempts smoking cessation with another drug.

In some embodiments, controlling weight gain comprises preventing weight gain. In some embodiments, controlling weight gain comprises inducing weight loss. In some embodiments, controlling weight gain comprises inducing weight loss of at least about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%. In some embodiments, the weight loss is at least 1%. In some embodiments, the weight loss is at least 1.5%. In some embodiments, the weight loss is at least 2%. In some embodiments, the weight loss is at least about 3%. In some embodiments, the weight loss is at least 4%. In some embodiments, the weight loss is at least 5%. In some embodiments, controlling weight gain comprises decreasing BMI. In some embodiments, controlling weight gain comprises decreasing percent body fat. In some embodiments, controlling weight gain comprises decreasing waist circumference. In some embodiments, controlling weight gain comprises decreasing BMI by at least about 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 kg/m^2. In some embodiments, BMI is decreased by at least 1 kg/m^2. In some embodiments, BMI is decreased by at least 1.5 kg/m^2. In some embodiments, BMI is decreased by at least 2 kg/m^2. In some embodiments, BMI is decreased by at least 2.5 kg/m^2. In some embodiments, BMI is decreased by at least 5 kg/m^2. In some embodiments, BMI is decreased by at least 10 kg/m^2. In some embodiments, controlling weight gain comprises decreasing percent body fat by at least about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%. In some embodiments, the decrease in percent body fat is at least 1%. In some embodiments, the decrease in percent body fat is at least 2.5%. In some embodiments, the decrease in percent body fat is at least 5%. In some embodiments, controlling weight gain comprises decreasing waist circumference by at least about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, or 10 cm. In some embodiments, the decrease in waist circumference is at least 1 cm. In some embodiments, the decrease in waist circumference is at least 2.5 cm. In some embodiments, the decrease in waist circumference is at least 5 cm. In some embodiments, controlling weight gain comprises decreasing body weight by at least about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, or 10 kg. In some embodiments, the decrease in body weight is at least 1 kg. In some embodiments, the decrease

in body weight is at least 2.5 kg. In some embodiments, the decrease in body weight is at least 5 kg.

In some embodiments, an individual is monitored for low BMI. In some embodiments, the BMI of the individual becomes a BMI selected from one of the following during administration: ≥ 18 kg/m^2, ≥ 17.5 kg/m^2, ≥ 17 kg/m^2, ≥ 16 kg/m^2, and ≥ 15 kg/m^2.

In some embodiments, the decrease in body weight is selected from one of the following: more than about 1.5%, more than about 2%, more than about 2.5%, more than about 3%, more than about 3.5%, more than about 4%, more than about 4.5%, and more than about 5%.

In some embodiments, the decrease in body weight is selected from one of the following: more than about 1.5 kg, more than about 2 kg, more than about 2.5 kg, more than about 3 kg, more than about 3.5 kg, more than about 4 kg, more than about 4.5 kg, and more than about 5 kg.

In some embodiments, the individual in need of treatment has a BMI selected from: ≥ 25 kg/m^2, ≥ 24 kg/m^2, ≥ 23 kg/m^2, ≥ 22 kg/m^2, ≥ 21 kg/m^2, ≥ 20 kg/m^2, ≥ 19 kg/m^2, and ≥ 18.5 kg/m^2. In some embodiments, BMI is not decreased by more than about 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,15, 16, 17, 18, 19, or 20 kg/m^2. In some embodiments, BMI is not decreased by more than 1 kg/m^2. In some embodiments, BMI is not decreased by more than 1.5 kg/m^2. In some embodiments, BMI is not decreased by more than 2 kg/m^2. In some embodiments, BMI is not decreased by more than 2.5 kg/m^2. In some embodiments, BMI is not decreased by more than 5 kg/m^2. In some embodiments, BMI is not decreased by more than 10 kg/m^2. In some embodiments, percent body fat is not decreased by more than about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%. In some embodiments, percent body fat is not decreased by more than 1%. In some embodiments, percent body fat is not decreased by more than 2.5%. In some embodiments, percent body fat is not decreased by more than 5%. In some embodiments, waist circumference is not decreased by more than about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, or 10 cm. In some embodiments, waist circumference is not decreased by more than 1 cm. In some embodiments, waist circumference is not decreased by more than 2.5 cm. In some embodiments, waist circumference is not decreased by more than 5 cm. In some embodiments, body weight is not decreased by more than about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, or 10 kg. In some embodiments, the decrease in body weight is not more than 1 kg. In some embodiments, the decrease in body weight is not more than 2.5 kg. In some embodiments, the decrease in body weight is not more than 5 kg.

In some embodiments, controlling weight gain comprises maintaining at least some weight loss for at least about 12 weeks, at least about 6 months, at least about 9 months, at least about one year, at least about 18 months, or at least about two years. For example, in some embodiments, an individual loses 5 kg during a first treatment and maintains at least 1 kg of that weight loss during a second treatment. In some embodiments, an individual loses 3 kg during the first 12 weeks of a treatment, and loses a total of 5 kg after one year of the treatment.

In some embodiments, use of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof is discontinued. For example, in some embodiments, use of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof is discontinued if the BMI of an individual becomes ≤ about 15 kg/m^2, ≤ about 15.5 kg/m^2, ≤ about 16 kg/m^2, ≤ about 16.5 kg/m^2, ≤ about 17 kg/m^2, ≤ about 17.5 kg/m^2, ≤ about 18 kg/m^2, ≤ about 18.5 kg/m^2, ≤ about 19 kg/m^2, ≤ about 19.5 kg/m^2 ≤ about 20 kg/m^2, ≤ about 20.5 kg/m^2, ≤ about 21 kg/m^2, ≤ about 21.5 kg/m^2, ≤ about 22 kg/m^2, ≤ about 22.5 kg/m^2, or ≤ about 23 kg/m^2.

In some embodiments, the individual experiences one or more additional beneficial effects as a result of the administration of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, optionally in combination with at least one supplemental agent, as described herein.

In some embodiments, the one or more additional beneficial effects are chosen from a decrease in an assessment of weight, an improvement in cardiovascular indications, and/or an improved glycemia. In some embodiments, the one or more additional beneficial effects are chosen from a decrease in an assessment of weight, an improvement in cardiovascular indications, and/or an improved lipidemia.

In some embodiments, the one or more additional beneficial effects comprise a decrease in an assessment of weight. In some embodiments, the decrease in an assessment of weight comprises weight loss. In some embodiments, the one or more beneficial effects comprises a decrease in hunger, a decrease in food cravings, or an increase in intermeal interval.

In some embodiments, the one or more additional beneficial effects comprise an improvement in one or more cardiovascular indications. In some embodiments, the improvement in one or more cardiovascular indications comprises one or more of a reduction in systolic and diastolic blood pressure (SBP and DBP, respectively), a decrease in heart rate, a

decrease in total cholesterol, a decrease in LDL cholesterol, a decrease in HDL cholesterol, and/or a decrease in triglyceride levels.

In some embodiments, the one or more additional beneficial effects comprise a reduction in SBP. In some embodiments, the reduction in SBP in an individual without type 2 diabetes is at least about 2 mmHg. In some embodiments, the reduction in SBP in an individual without type 2 diabetes is between 2 and 5 mmHg. In some embodiments, the reduction in SBP in an individual with type 2 diabetes is at least about 2 mmHg. In some embodiments, the reduction in SBP in an individual with type 2 diabetes is between about 2 and 5 mmHg. In some embodiments, the reduction in SBP in an individual with baseline impaired fasting glucose is at least about 1 mmHg. In some embodiments, the reduction in SBP in an individual with baseline impaired fasting glucose is between about 1 and 5 mmHg.

In some embodiments, the one or more additional beneficial effects comprise a reduction in DBP. In some embodiments, the reduction in DBP in an individual without type 2 diabetes is at least about 1 mmHg. In some embodiments, the reduction in DBP in an individual without type 2 diabetes is at least between about 1 and 5 mmHg. In some embodiments, the reduction in DBP in an individual with type 2 diabetes is at least about 1 mmHg. In some embodiments, the reduction in DBP in an individual with type 2 diabetes is between about 1 and 5 mmHg. In some embodiments, the reduction in DBP in an individual with baseline impaired fasting glucose is at least about 1 mmHg. In some embodiments, the reduction in DBP in an individual with baseline impaired fasting glucose is between about 1 and 5 mmHg.

In some embodiments, the one or more additional beneficial effects comprise a reduction in heart rate. In some embodiments, the reduction in heart rate in an individual without type 2 diabetes is at least about 2 BPM. In some embodiments, the reduction in heart rate in an individual without type 2 diabetes is between about 2 and 5 BPM. In some embodiments, the reduction in heart rate in an individual with type 2 diabetes is at least about 2 BPM. In some embodiments, the reduction in heart rate in an individual with type 2 diabetes is between about 2 and 5 BPM. In some embodiments, the reduction in heart rate in an individual with baseline impaired fasting glucose is at least about 2 BPM. In some embodiments, the reduction in heart rate in an individual with baseline impaired fasting glucose is between about 2 and 5 BPM.

In some embodiments, the improvement in lipidemia comprises a decrease in total cholesterol level. In some embodiments, the decrease in total cholesterol level in individuals without type 2 diabetes is at least about 1 mg/dL. In some embodiments, the decrease in total cholesterol level in individuals without type 2 diabetes is between about 1.5 and 2 mg/dL. In some embodiments, the decrease in total cholesterol level in individuals with type 2 diabetes is at least about 0.5 mg/dL. In some embodiments, the decrease in total cholesterol level in

individuals with type 2 diabetes is between about 0.5 and 1 mg/dL. In some embodiments, the decrease in total cholesterol level in individuals with baseline impaired fasting glucose is at least about 2 mg/dL. In some embodiments, the decrease in total cholesterol level in individuals with baseline impaired fasting glucose is between about 2 and 3 mg/dL.

In some embodiments, the improvement in lipidemia comprises a decrease in LDL cholesterol level. In some embodiments, the decrease in LDL cholesterol level in individuals without type 2 diabetes is at least about 1 mg/dL. In some embodiments, the decrease in LDL cholesterol level in individuals without type 2 diabetes is between about 1 and 2 mg/dL. In some embodiments, the decrease in LDL cholesterol level in individuals with type 2 diabetes is at least about 1 mg/dL. In some embodiments, the decrease in LDL cholesterol level in individuals with type 2 diabetes is between about 1 and 1.5 mg/dL. In some embodiments, the decrease in LDL cholesterol level in individuals with baseline impaired fasting glucose is at least about 2 mg/dL. In some embodiments, the decrease in LDL cholesterol level in individuals with baseline impaired fasting glucose is between about 2 and 3 mg/dL.

In some embodiments, the improvement in lipidemia comprises a decrease in HDL cholesterol level. In some embodiments, the decrease in HDL cholesterol level in individuals without type 2 diabetes is at least about 4 mg/dL. In some embodiments, the decrease in HDL cholesterol level in individuals without type 2 diabetes is between about 3 and 6 mg/dL. In some embodiments, the decrease in HDL cholesterol level in individuals with type 2 diabetes is at least about 5 mg/dL. In some embodiments, the decrease in HDL cholesterol level in individuals with type 2 diabetes is between about 7 and 10 mg/dL. In some embodiments, the decrease in HDL cholesterol level in individuals with baseline impaired fasting glucose is at least about 2 mg/dL. In some embodiments, the decrease in HDL cholesterol level in individuals with baseline impaired fasting glucose is between about 2 and 3 mg/dL.

In some embodiments, the one or more additional beneficial effects comprise an improvement in glycemia. In some embodiments, the improvement in glycemia comprises a reduction in fasting plasma glucose and/or a reduction in glycated hemoglobin (A1C) levels. In some embodiments, the improvement in glycemia comprises a reduction in fasting plasma glucose. In some embodiments, the improvement in glycemia comprises a reduction in glycated hemoglobin (A1C) levels. In some embodiments, the improvement in glycemia comprises a decrease in triglyceride levels.

The compounds provided herein can be administered in a wide variety of dosage forms. It will be obvious to those skilled in the art that the dosage forms may comprise, as the active component, either a compound provided herein or a pharmaceutically acceptable salt, solvate, or hydrate of a compound provided herein.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered in a tablet suitable for oral administration.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants and disintegrants can be used in tablets and capsules for oral administration. Liquid preparations for oral administration can be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations can be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives and flavorings and colorants can be added to the liquid preparations. Parenteral dosage forms can be prepared by dissolving the compound in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see *Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro et al.).*

While it is possible that, for use in the prophylaxis or treatment, a compound can, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with minimal degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds provided herein, together with a conventional adjuvant, carrier, or diluent, can thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile

injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof can comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

In some embodiments, the active ingredient is formulated as an immediate-release dosage form using, *e.g.*, techniques known in the art. In some embodiments, the active ingredient is formulated as a modified-release dosage form using, *e.g.*, techniques known in the art. In some embodiments, the active ingredient is formulated as a sustained-release dosage form using, *e.g.*, techniques known in the art. In some embodiments, the active ingredient is formulated as a delayed-release dosage form using, *e.g.*, techniques known in the art.

In some embodiments, the method comprises a plurality of administrations of the modified-release dosage form, with a frequency wherein the average interval between any two sequential administrations is: at least about 24 hours, or about 24 hours.

In some embodiments, the method comprises a plurality of administrations of the modified-release dosage form, and the modified-release dosage form is administered once a day.

In some embodiments, the plurality of administrations is: at least about 30, at least about 180; at least about 365, or at least about 730.

In some embodiments, the plasma concentration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof in the individual administered a modified-release dosage form, as described herein, has a C_{max} of: less than about 60 ng/mL; less than about 40 ng/mL; less than about 20 ng/mL; or less than about 10 ng/mL. In some embodiments, the C_{max} divided by the therapeutically effective amount is equal to: less than about 1×10^{-5} mL^{-1}; less than about 5×10^{-6} mL^{-1}; less than about 1×10^{-6} mL^{-1}; or less than about 5×10^{-7} mL^{-1}. In some embodiments, the C_{max} occurs: more than 30 minutes after administration; more than 1 hour after administration; or more than 2 hours after administration. In some embodiments, the C_{max} occurs: more than 3 hours after administration, more than 6 hours after administration, or more than 12 hours after administration.

In some embodiments, the average peak to trough ratio of the plasma concentration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof in the individual administered a modified-release dosage form as described herein, is: less than about 3:1, less than about 2:1, less than about 1.5:1, or less than about 1.1:1.

In some embodiments, the modified-release dosage form further comprises (hydroxypropyl)methyl cellulose.

In some embodiments, the modified-release dosage form further comprises one or more ingredients selected from: microcrystalline cellulose, mannitol, and magnesium stearate.

In some embodiments, the modified-release dosage form further comprises a film coating.

In some embodiments, the film coating comprises a water-soluble film coating.

In some embodiments, the film coating comprises ethyl cellulose.

In some embodiments, the film coating further comprises (hydroxypropyl)methyl cellulose.

In some embodiments, the ratio of the ethyl cellulose to the (hydroxypropyl)methyl cellulose is: about 75:25, about 80:20, or about 85:15.

In some embodiments, the modified-release dosage form comprises a core tablet and a film coating; wherein the core tablet comprises: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate, Form III; mannitol; (hydroxypropyl)methyl cellulose; microcrystalline cellulose; and magnesium stearate; and the film coating comprises a water-soluble film coating.

In some embodiments, the modified-release dosage form comprises a core tablet and a film coating, wherein the weight to weight ratio of the core tablet to the coating is about 20:1; and wherein the core tablet comprises: about 7% (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate, Form III; about 22.5% mannitol; about 50% (hydroxypropyl)methyl cellulose; about 20% microcrystalline cellulose; and about 0.5% magnesium stearate; and the film coating comprises a water-soluble film coating.

In some embodiments, the modified-release dosage form comprises a core tablet and a film coating; wherein the core tablet comprises: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate, Form III; mannitol; (hydroxypropyl)methyl cellulose; microcrystalline cellulose; and magnesium stearate; and the film coating comprises: ethyl cellulose; and (hydroxypropyl)methyl cellulose.

In some embodiments, the modified-release dosage form comprises a core tablet and a film coating, wherein the weight to weight ratio of the core tablet to the coating is about 20:1; and wherein the core tablet comprises: about 7% (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-

3-benzazepine hydrochloride salt hemihydrate, Form III; about 22.5% mannitol; about 50% (hydroxypropyl)methyl cellulose; about 20% microcrystalline cellulose; and about 0.5% magnesium stearate; and the film coating comprises: about 85% ethyl cellulose; and about 15% (hydroxypropyl)methyl cellulose; or about 75% ethyl cellulose; and about 25% (hydroxypropyl)methyl cellulose.

For oral administration, the pharmaceutical composition can be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

The dose when using the compounds provided herein can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the individual, on the compound employed, on whether an acute or chronic disease state is treated or prophylaxis conducted or on whether further active compounds are administered in addition to the compounds provided herein. Representative doses include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, about 0.001 mg to about 500 mg, about 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate from the healthcare provider it may be necessary to deviate upward or downward from the doses described herein.

All dosage amounts disclosed herein are calculated with respect to the active moiety, *i.e.*, the molecule or ion that gives the intended pharmacologic or physiologic action. Further, all dosage amounts of lorcaserin disclosed herein are for lorcaserin in the anhydrous hydrochloride form. One of skill in the art will recognize that dosage amounts for other salt or crystalline forms of lorcaserin can be adjusted to equate lorcaserin in the anhydrous hydrochloride form. For example, 10 mg of lorcaserin as disclosed herein encompasses a

dosage form containing 10 mg of anhydrous lorcaserin hydrochloride and 10.4 mg of crystalline lorcaserin hydrochloride hemihydrate. In addition, 10 mg of lorcaserin as disclosed herein includes any salt or crystalline form with the same amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine as found in 10 mg of the anhydrous lorcaserin hydrochloride.

Alternatively, the dosage amounts of lorcaserin disclosed herein can be replaced with dosage amounts for other salt or crystalline forms, formulations, and dosage regimens that exhibit bioequivalence to the specified amount of anhydrous lorcaserin hydrochloride, including forms with 80-125% of the AUC and/or C_{max} for the specified amount of anhydrous lorcaserin hydrochloride as measured by method disclosed in the FDA's Guidance for Industry for Bioavailability and Bioequivalence (*Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2003, Revision 1, www.fda.gov/cder/guidance/index.htm*). For example, the dosage amounts of lorcaserin disclosed herein can be replaced with dosage amounts for other salt or crystalline forms, formulations, and dosage regimens that exhibit bioequivalence to 10 mg of anhydrous lorcaserin hydrochloride in an immediate-release orally administered tablet as described in the FDA package insert for BELVIQ® (*BELVIQ (lorcaserin HCl) (package insert), revised August 2012*).

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the individual and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the individual, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, whether an acute or chronic disease state is being treated or prophylaxis conducted or whether further active compounds are administered in addition to the compounds provided herein such as part of a drug combination. The dosage

regimen for treating a disease condition with the compounds and/or compositions provided herein is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods disclosed herein.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose greater than or equal to 20 mg per day, greater than or equal to 25 mg per day, greater than or equal to 30 mg per day, greater than or equal to 35 mg per day, or greater than or equal to 40 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to or less than 20 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose of at least 20 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 20 mg per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to at least 12.5 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to between 12.5 mg and 20 per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 12.5 mg per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the

individual in a dose equal to at least 15 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to between 15 and 20 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 15 mg per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to at least 17.5 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to between 17.5 and 20 mg per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 17.5 mg per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to or less than 10 mg twice per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 10 mg twice per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to at least 5 mg twice per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 5 mg twice per day.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to at least 7.5 mg twice per day. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 7.5 mg twice per day.

In some embodiments, the individual is also being prescribed and/or administered a supplemental agent.

Also provided is a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent.

As used herein, "supplemental agent" refers to an additional therapeutic agent which complements the activity of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof described herein as it relates to methods for reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco; aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product; aiding in smoking cessation and preventing associated weight gain; controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use. In some embodiments, the "supplemental agent" is not phentermine.

Supplemental agents include nicotine replacement therapies, antidepressants and anxiolytics such as selective serotonin reuptake inhibitors, *e.g.*, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and the like. Serotonin and norepinephrine reuptake inhibitors, such as duloxetine, venlafaxine, and the like may also be used. Norepinephrine and dopamine reuptake inhibitors such as bupropion may also be used. Tetracyclic antidepressants such as mirtazapine; combined reuptake inhibitors and receptor blockers such as trazodone, nefazodone, maprotiline; tricyclic antidepressants, such as amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine; monoamine oxidase inhibitors, such as phenelzine, tranylcypromine, isocarboxazid, selegiline; benzodiazepines such as lorazepam, clonazepam, alprazolam, and diazepam; serotonin 1A receptor agonists such as buspirone, aripiprazole, quetiapine, tandospirone and bifeprunox; and beta-adrenergic receptor blockers, such as propranolol may also be used. Other supplemental agents include other pharmacologic agents such as UTP, amiloride, antibiotics, bronchodilators, anti-inflammatory agents, and mucolytics (*e.g.*, n-acetyl-cysteine).

In some embodiments, the supplemental agent is chosen from nicotine replacement therapies. In some embodiments, the nicotine replacement therapy is chosen from nicotine gum, nicotine transdermal systems, nicotine lozenges, nicotine microtabs, and nicotine sprays or inhalers. In some embodiments, the supplemental agent is an electronic cigarette.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and nicotine gum.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and a nicotine transdermal system.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and a nicotine lozenge.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and a nicotine microtab.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and a nicotine spray or inhaler.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and an electronic cigarette.

In some embodiments, the supplemental agent is chosen from antidepressants.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and an antidepressant. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the antidepressant are formulated as a fixed dose combination product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the antidepressant are formulated as a co-packaged product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the antidepressant are formulated for adjunctive therapy.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and nortriptyline. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the nortriptyline are formulated as a fixed dose combination product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable

salt, solvate, or hydrate thereof and the nortriptyline are formulated as a co-packaged product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the nortriptyline are formulated for adjunctive therapy.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and bupropion. In some embodiments, (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine\ or pharmaceutically acceptable salt, solvate, or hydrate thereof and the bupropion are formulated as a fixed dose combination product. In some embodiments, the (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the bupropion are formulated as a co-packaged product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the bupropion are formulated for adjunctive therapy.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and clonidine or a pharmaceutically acceptable salt thereof. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the clonidine are formulated as a fixed dose combination product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the clonidine are formulated as a co-packaged product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the clonidine are formulated for adjunctive therapy.

In some embodiments, the composition comprises (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and varenicline or a pharmaceutically acceptable salt thereof. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the varenicline or a pharmaceutically acceptable salt thereof are formulated as a fixed dose combination product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof and the varenicline or a pharmaceutically acceptable salt thereof are formulated as a co-packaged product. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof

and the varenicline or a pharmaceutically acceptable salt thereof are formulated for adjunctive therapy.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is an HCl salt of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or solvate or hydrate thereof.

In some embodiments, the individual has previously undergone treatment with a supplemental agent. In some embodiments, the individual was refractory to the previous treatment with the supplemental agent.

In some embodiments, the individual has previously undergone treatment with a nicotine replacement therapy. In some embodiments, the individual was refractory to the previous treatment with the nicotine replacement therapy.

Also provided is a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

Also provided is a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent for use as a medicament for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

Also provided is a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent in the manufacture of a medicament for: reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco; aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product; aiding in smoking cessation and preventing associated weight gain; controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

Also provided is a unit dosage form of a composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent.

Also provided is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for use in combination with a supplemental agent.

Also provided is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for use in combination with a supplemental agent, for: reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco; aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product; aiding in smoking cessation and preventing associated weight gain; controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; treating nicotine dependency, addiction and/or withdrawal in an individual

attempting to treat nicotine dependency, addiction and/or withdrawal; or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

Also provided is a supplemental agent chosen from nicotine replacement therapies, for use in combination with (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Also provided is a supplemental agent for use in combination with (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for: reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco; aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product; aiding in smoking cessation and preventing associated weight gain; controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco; treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is formulated as an immediate-release dosage form and the supplemental agent is also formulated as an immediate-release dosage form. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is formulated as an immediate-release dosage form and the supplemental agent is formulated as a modified-release dosage form. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is formulated as a modified-release dosage form and the supplemental agent is formulated as an immediate-release dosage form. In some embodiments, the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is formulated as a modified-release dosage form and the supplemental agent is also formulated as a modified-release dosage form.

The (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof may be administered sequentially or concurrently with the one or more other supplemental agents identified herein. The amounts of formulation and pharmacologic agent depend, for example, on what type of pharmacologic agent(s) are used, and the scheduling and routes of administration.

Supplemental agents may be delivered concomitantly with (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof, or may be administered independently. Supplemental agent delivery may be via any suitable method known in the art including orally, inhalation, injection, etc.

In some embodiments, the methods described herein further comprise the step of: providing the individual with educational materials and/or counseling. In some embodiments, the counseling relates to smoking cessation. In some embodiments, the counseling relates to weight management, including without limitation counseling regarding diet and exercise. In some embodiments, the counseling relates to both smoking cessation and weight management, including without limitation counseling regarding diet and exercise.

In some embodiments, the methods described herein further comprise the step of: providing the individual with biochemical feedback; acupuncture; hypnosis; behavioral intervention; support services; and/or psychosocial treatment.

EXAMPLES

Example 1 – Generation of Stable Cell Lines

Plasmid DNA coding for a receptor of interest is produced using standard molecular biology tools. The plasmid typically contains a multi-cloning site where the coding sequence for the receptor of interest is inserted, a promoter to drive expression of the receptor when introduced into a host cell, and a resistance gene sequence that causes the host cell to produce a protein that confers antibiotic resistance. A commonly used promoter is the cytomegalovirus promoter (CMV), and a commonly used resistance gene is the *neo* gene that confers resistance to neomycin. The plasmid DNA is introduced into parental cells (commonly used cell lines include CHO-K1 and HEK293) using methods such as lipofection or electroporation. Cells are then allowed to recover in culture for 1-2 days. At this point, a selection agent (*e.g.*, neomycin if the expression plasmid contained the *neo* gene) is added to the cell culture media at a concentration sufficient to kill any cells that did not uptake the plasmid DNA and therefore have not become neomycin resistant.

Since transient transfection is an efficient method to introduce plasmid DNA into cells, many cells in the culture will initially display neomycin resistance. Over the course of a few cell divisions, expression of proteins encoded by the plasmid is typically lost and most cells will eventually be killed by the antibiotic. However, in a small number of cells, the plasmid DNA may become randomly integrated into the chromosomal DNA. If the plasmid DNA becomes integrated in a way that allows continued expression of the *neo* gene, these cells become permanently resistant to neomycin. Typically, after culturing the transfected cells for

two weeks, most of the remaining cells are those that have integrated the plasmid in this manner.

The resulting stable pool of cells is highly heterogeneous, and may express vastly different levels of receptor (or no receptor at all). While these types of cell populations may provide functional responses when stimulated with appropriate agonists to the receptor of interest, they are typically not suitable for careful pharmacological studies in view of receptor reserve effects caused by high expression levels.

Clonal cell lines are therefore derived from this cell population. The cells are plated in multi-well plates at a density of one cell per well. After cell plating, the plates are inspected and wells containing more than one cell are rejected. The cells are then cultured for a period of time and those that continue to divide in the presence of neomycin are eventually expanded into larger culture vessels until there are sufficient cells for evaluation.

Evaluation of Cells

Numerous methods can be used to evaluate the cells. Characterization in functional assays may reveal that some cells exaggerate the potencies and efficacies of agonists, likely indicating the presence of a receptor reserve. The preparation of cell membranes for evaluation in radioligand binding assays allows for quantitative determination of membrane receptor densities. Evaluation of cell surface receptor density may also be performed by flow cytometry using antibodies to the receptor or an epitope tag that can be engineered into the receptor, typically at the N-terminus for GPCRs. The flow cytometry method allows one to determine if the clonal cell population expresses the receptor in a homogenous manner (which would be expected) and quantitate relative expression levels between each clonal cell population. However, it does not provide absolute receptor expression levels.

If the cell line is intended to be free of receptor reserve effects, receptor expression should be low (relative to other clones evaluated) and homogeneous (if flow cytometry evaluation is possible). In functional assays, a suitable clone will produce agonist potencies that are lower than other clones (*i.e.*, higher EC_{50} values). If partial agonists are available, the absence of receptor reserve will be reflected in low efficacies relative to full agonists, whereas cells with higher receptor expression levels will exaggerate partial agonist efficacies. In cells expressing high receptor levels, partial agonists may no longer display efficacies lower than full agonists.

If agents that irreversibly bind to or covalently interact with the receptor of interest are available, treatment of cell lines that contain no receptor reserve should reduce the available receptor density measured by radioligand binding and may reduce the magnitude of functional

responses to agonists. However, the reduction of receptor density should occur without producing reductions in agonist potencies or partial agonist efficacies.

Example 2 – Potency and Efficacy of Lorcaserin on 5-HT_2 Receptors

Lorcaserin potency and efficacy were evaluated for rat, monkey, and human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Lorcaserin-mediated signaling was observed in stable clonal cell lines expressing low receptor densities. Phenoxybenzamine (PBZ) was used as an irreversible 5-HT_2 receptor antagonist to allow for progressive reductions of receptor binding sites in each cell line in order to observe potency and efficacy in the absence of receptor reserve effects (which may have generated inconsistent results in previous studies).

Cell Lines

HEK293 cell lines were generated to stably express human, rat, and monkey 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors using standard procedures.

IP Accumulation Assay

HEK293 cells expressing recombinant 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors were added to sterile poly-D-lysine-coated 96-well microtiter plates (35,000 cells/well) and labeled with 0.6 μCi/well of [^{3}H]inositol in myo-inositol-free DMEM for 18 hours. PBZ prepared in myo-inositol-free DMEM was then added to a final specified concentration and incubation was conducted for 1 hour at room temperature. Unincorporated [^{3}H]inositol and PBZ were removed by aspiration and replaced with fresh myo-inositol free DMEM supplemented with LiCl (10 mM final) and pargyline (10 μM final). Serially diluted test compounds were then added and incubation was conducted for 2 hours at 37°C. Incubations were then terminated by lysing cells with the addition of ice-cold 0.1 M formic acid followed by freezing at -80°C. After thawing, total [^{3}H]inositol phosphates were resolved from [^{3}H]inositol using AG1-X8 ion exchange resin (Biorad) and [^{3}H]inositol phosphates were measured by scintillation counting using a Perkin Elmer TopCount scintillation counter. EC_{50} determinations were performed at a minimum total of 8 or 10 different concentrations, and triplicate determinations were made at each test concentration.

Raw counts from the scintillation counter were exported to GraphPad Prism for further analysis. Data were fit to a three parameter sigmoid dose response function using a nonlinear regression to obtain EC_{50} values and curve height. Compound efficacies were calculated as a percentage of the serotonin efficacy, which was defined as 100% in each experiment. Since IP accumulation experiments typically involved multiple assay plates with serotonin dose-responsed on only 1 plate, the magnitude of the serotonin response on each plate was determined from the positive and negative control wells, which contained serotonin (typically

at 1 or 10 μM) and assay buffer, respectively. Each compound efficacy was calculated as a percentage of the serotonin positive control response on its assay plate.

Stable, clonal cell lines expressing recombinant human, rat, and monkey 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors were established and used to profile lorcaserin and a panel of reference compounds in IP accumulation and calcium assays. Cell surface receptor densities, as assessed by radioligand binding, were very high in the human and monkey cell lines and were lower in the rat cell line. Receptor densities in all three cell lines were modulated by PBZ.

Calcium Assay

Cells were harvested, counted, resuspended in assay buffer [1X HBSS (with calcium and magnesium) containing 20 mM HEPES at pH 7.4], and plated at 20,000 cells per well (25 μL per well) into standard tissue culture grade black plates with clear bottoms. One vial of Molecular Devices Calcium 4 dye was diluted with 10 mL of assay buffer. A 1 mL aliquot was then diluted 10-fold with assay buffer supplemented with 2.5 mM probenecid. This dye stock was added to the assay plates at 25 μL per well and incubated for 1 hour at 37 °C. Test compounds were serially diluted in DMSO before being further diluted in assay buffer. Controls and test compounds (in 25 μL assay buffer) were then added to assay plates using a Molecular Devices FLIPR instrument. Plates were read every two seconds for 1.5 minutes and the peak height was determined for each well. Dose response curves included ten compound concentrations in which triplicate determinations were made at each test concentration.

Raw counts were exported to GraphPad Prism (v.5) for further analysis. Data were fit to a three parameter sigmoid dose response function using a nonlinear regression to obtain EC_{50} values and curve height. Compound efficacies were calculated as a percentage of the serotonin efficacy, which was defined as 100% in each experiment.

Radioligand Binding Assay

HEK293 cells expressing the recombinant 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors were harvested, suspended in ice-cold phosphate buffered saline, pH 7.4 (PBS), and then centrifuged at 48,000 g for 20 min at 4°C. The resulting cell pellet was then re-suspended in wash buffer containing 20 mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized on ice using a Brinkman Polytron, and centrifuged (48,000 g for 20 min at 4°C). The pellet was then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice, and centrifuged (48,000 g for 20 min at 4°C). Crude membrane pellets were stored at –80°C until used for radioligand binding assays.

Radioligand binding assays were performed using the commercially available 5-HT_2 receptor agonist [^{125}I]DOI as the radioligand and nonspecific binding was determined in the presence of unlabeled DOI at a saturating concentration of 10 μM. Competition experiments consisted of addition of 95 μL of Assay Buffer (20 mM HEPES, pH 7.4, 10 mM MgCl2), 50

μL of membranes, 50 μL of radioligand stock, and 5 μL of test compound diluted in assay buffer to 96-well microtiter plates, which were then incubated for one hour at room temperature. Assay incubations were terminated by rapid filtration through Perkin Elmer F/C filtration plates under vacuum pressure using a 96-well Packard filtration apparatus, followed by washing filter plates several times with ice-cold Assay Buffer. Plates were then dried at 45°C for a minimum of two hours. Finally, 25 μL of BetaScint scintillation cocktail was added to each well and the plates were counted in a Packard TopCount scintillation counter. In each competition study, test compounds were dosed at eight to ten concentrations with triplicate determinations at each test concentration. A reference compound, typically DOI, was included in every runset for quality control purposes.

Raw data sets from scintillation counters were uploaded for processing. Competition curves were fit to a nonlinear least squares curve fitting program to obtain IC_{50} values. Ki values were determined from IC_{50} values using the Cheng-Prusoff equation and the Kd value for each radioligand-receptor pair. Mean Ki values were calculated from the mean of the logKi values.

Results

Figure 18 shows potency and efficacy data generated using the IP accumulation assay for each combination of the human, rat, and monkey 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Lorcaserin demonstrated high selectivity for the human 5-HT_{2C} receptor, with an EC_{50} (39.2 nM) approximately 14 times lower than the EC_{50} for the 5-HT_{2A} receptor (553 nM) and approximately 60 times lower than the EC_{50} for the 5-HT_{2B} receptor (2380 nM). Lorcaserin also demonstrated high efficacy (81%) at the human 5-HT_{2C} receptor relative to serotonin. In contrast, lorcaserin demonstrated mixed potency for the rat 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, with greatest selectivity for the 5-HT_{2B} receptor (195 nM, compared to 545 nM and 1110 nM for the 5-HT_{2C} and 5-HT_{2A} receptors, respectively). Lorcaserin also demonstrated high efficacy (94%) at the rat 5-HT_{2B} receptor relative to serotonin.

Figure 19 (left side) shows a comparison of drug concentration in humans to the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor activation data. EC_{50} values (as measured by the IP accumulation assay) are shown as horizontal lines plotted against observed lorcaserin concentrations (expressed as plasma free fractions) for subjects treated with lorcaserin 10 mg BID in a previous study. Figure 19 (right side) shows a comparison of drug concentration in rats to the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor activation data. EC_{50} values for receptor activation (as measured by the IP accumulation assay) are shown as horizontal lines plotted against the observed lorcaserin concentrations (expressed as plasma free fractions) for rats treated with 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day of lorcaserin. In humans, the

plasma drug concentration following the administration of lorcaserin was approximately equal to the EC_{50} value from the IP accumulation assay for the 5-HT_{2C} receptor, and did not approach the EC_{50} value for the 5-HT_{2A} or 5-HT_{2B} receptors. However, in rats, the plasma drug concentration for the lowest dose of lorcaserin administered (*i.e.*, 10 mg/kg/day) was greater than or equal to the EC_{50} values from the IP accumulation assays for each of the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Providing higher doses of lorcaserin to rats increased the plasma drug concentration, but would be unlikely to improve efficacy given that full receptor activation is expected to be achieved at a low dose. A low dose of lorcaserin is therefore likely to be sufficient for efficacy observed in rats.

Example 3 – Phase 2 Study

A 12-week, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of lorcaserin as a potential aid to smoking cessation. In the trial, 603 active smokers were randomized to receive lorcaserin 10 mg BID, 10 mg QD, or placebo in a 1:1:1 ratio (*BELVIQ (lorcaserin HCl) (package insert), revised August 2012*). Patients at baseline were dependent on nicotine and averaged 18 cigarettes per day. Patients were dosed for two weeks before attempting to quit around day 15 of the trial, and received smoking cessation counseling during the trial. The primary objective of the study was to assess smoking cessation efficacy, as measured by the carbon monoxide-confirmed continuous abstinence rate (CAR) during the last four weeks of the trial (Weeks 9 to 12). The carbon monoxide-confirmed CAR is defined as no reported smoking or other nicotine use and an end-expiratory exhaled carbon monoxide measurement of less than or equal to ten parts per million. Secondary objectives for the study included assessment of body weight change, safety, and tolerability. Additional outcome measures included CAR for Weeks 5 to 8 of treatment, CAR for Weeks 5 to 12 of treatment, CAR for Weeks 3 to 12 of treatment, 7-day point prevalence (PP) smoking abstinence, and questionnaires regarding the urge to smoke, withdrawal, reinforcing effects, and eating behavior. Endpoints of interest also included the number of cigarettes smoked per day, abstinence with occasional slips (< 5 cigarettes per day), time to abstinence (in weeks), and time to relapse (if abstinent).

A schematic of the study design is provided in Figure 1. Baseline characteristics for the study subjects are provided in Figures 2 and 3. A summary of the disposition of subjects from the study is provided in Figure 4. Data for end-expiratory carbon monoxide (CO)-confirmed CARs for Weeks 5-8, 5-12, and 3-12 is provided in Figures 5-8.

Subjects treated with lorcaserin 10 mg BID had statistically significantly greater end-expiratory CO-confirmed CARs for Weeks 9 to 12 than subjects treated with lorcaserin 10 mg

QD or placebo. The primary endpoint was achieved by 5.64%, 8.72%, and 15.31% of subjects in the placebo, lorcaserin 10 mg QD, and lorcaserin 10 mg BID groups, respectively (p-value = 0.0027 and odds ratio = 3.02 for lorcaserin 10 mg BID versus placebo). End-expiratory CO-confirmed CARs for Weeks 9 to 12 were not significantly different for subjects treated with lorcaserin 10 mg QD versus subjects treated with placebo (Figure 5).

A statistically significantly greater percentage of subjects treated with lorcaserin 10 mg BID exhibited continuous abstinence during the 7-day period preceding a clinical visit (as verified by end-expiratory CO levels ≤10 ppm) for time points past 6 weeks of treatment compared to subjects treated with placebo (Figure 9). Further, subjects treated with lorcaserin 10 mg BID had a numerically greater reduction in the number of cigarettes smoked at Week 12 (as measured by the Nicotine Use Inventory) compared to subjects treated with placebo (Figure 10).

Subjects treated with lorcaserin 10 mg BID had significantly greater weight loss at Week 12 than subjects treated with lorcaserin 10 mg QD or placebo (p values = and 0.0217 and 0.0004, respectively). Weight loss was not significantly different for subjects treated with lorcaserin 10 mg QD versus subjects treated with placebo (Figures 11 and 13). Comparable weight loss was observed at Week 12 for subjects treated with lorcaserin 10 mg BID across the entire BMI range studied, and for subjects treated with lorcaserin 10 mg QD across the entire BMI range studied (Figures 14 and 15).

Responders (defined as subjects with 4 weeks of continuous CO-confirmed abstinence from Weeks 9 to 12) who were treated with lorcaserin 10 mg BID lost 0.41 kg (SE 0.58 kg) at Week 12 relative to baseline, while those treated with lorcaserin 10 mg QD or placebo gained 0.76 kg (SE 0.47 kg) and 0.73 kg (SE 1.14 kg), respectively, at Week 12 relative to baseline (Figures 12 and 13).

Subjects treated with lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo who did not quit smoking (*i.e.*, non-responders) had greater weight loss than responders for each respective treatment at Week 12 (Figure 13). Non-responders who were treated with lorcaserin 10 mg BID lost 1.02 kg (SE 0.21 kg) at Week 12 relative to baseline, while those treated with lorcaserin 10 mg QD or placebo lost 0.50 kg (SE 0.21 kg) and 0.01 kg (SE 0.23 kg), respectively, at Week 12 relative to baseline (Figure 13).

A summary of treatment-emergent adverse events is shown in Figure 17. Overall, treatment with lorcaserin was well-tolerated. Adverse events were similar to those most frequently associated with lorcaserin in previous clinical trials (*e.g.*, headache, nausea, constipation, dizziness, and dry mouth). Serious Adverse Events (SAEs) were infrequent and none were considered related to study treatment.

Example 4 - Salts

Various synthetic routes to (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, its related salts, enantiomers, crystalline forms, and intermediates, have been reported in WO2003/086306, WO2005/019179, WO2006/069363, WO2007/120517, WO2008/070111, and WO2009/111004, WO2010/148207, WO2011/153206, WO2012/030939, WO2012/030938, WO2012/030951, WO2012/030953, and WO2012/030957, each of which is incorporated herein by reference in its entirety.

Example 5 – Dosage Forms

Various modified-release dosage forms comprising (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine salts and crystalline forms thereof have been reported in WO2012/030927, which is incorporated herein by reference in its entirety.

Example 6 – Modified-Release Tablets Comprising (*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride Salt Hemihydrate, Form III

Modified-release tablet formulations of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride salt hemihydrate, Form III (Compound 1) were prepared. The upper limit of the desired release profile as established by pharmacokinetics simulation was defined as a C_{max} not more than the C_{max} observed when dosing 10 mg immediate-release tablets BID.

Reagents and Materials

(*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate, Form III

Hydroxypropyl methyl cellulose K4M, Colorcon

Microcrystalline cellulose (Avicel PH102), FMC

Mannitol, Pearlitol 200SD, Roquette

Mannitol, Mannogem EZ, SPI Pharma

Mannitol, Mannogem 2080, SPI Pharma

Magnesium stearate, vegetable grade, Mallinckrodt

Surelease® (ethyl cellulose dispersion), Colorcon

Opadry® (YS-1-7472), Colorcon

Opadry® II Blue (89F90951), Colorcon

Manufacturing

The following batches were manufactured:

Ingredient	Batch										
	1	2	3	4	5	6	7	8	9	10	11
	Core Tablet (mg)										
Compound 1 Hydrochloride Salt Hemihydrate, Form III	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8	31.2	31.2
Mannitol	67.7	67.7	67.7	67.7	67.7	97.7	97.7	67.7	67.7	57.3	57.3
HPMC K4M	150	150	150	150	150	120	120	150	150	150	150
Avicel PH102	60	60	60	60	60	60	60	60	60	60	60
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Coating (mg)										
Opadry® II Blue	15.1	0	0	0	0	0	0	0	0	0	0
Surelease®/Opadry® 85/15	0	7.8	13.7	0	0	8.7	15.5	0	0	8.7	15.4
Surelease®/Opadry® 80/20	0	0	0	0	14.9	0	0	0	0	0	0
Surelease®/Opadry® 75/25	0	0	0	16.2	0	0	0	7.5	29.7	0	0

All modified-release tablets were manufactured with a direct compression process at a batch size of 300 g to 500 g as follows. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate, HPMC, mannitol and MCC were blended in a 2-quart V blender (Globe Pharma MaxiBlend®) for 12 min. The mixture was screened through a sieve (#20). The sieved mixture was blended for a further 5-10 min, magnesium stearate was added and blending was continued for a further 5 min. The mixture was compressed into tablets using a Piccola PLC rotary tablet press (10-20 rpm; 10 kp) and the tablets were coated using a Vector LDCS Hi-Coater® with an 11.5"-diameter pan.

Dissolution Testing

Dissolution testing was performed using USP apparatus I (basket method) in 900 mL 0.1 N HCl solution at 37 °C and 100 rpm. The concentration of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine was analyzed using an HPLC method. The time needed to achieve 80% cumulative release (T80%) was estimated from the dissolution profiles.

Establishment of the Upper Limit of the Release Profile

The GastroPlus™ software (Simulations Plus, Inc., Lancaster, CA) was used to simulate the pharmacokinetics of Compound 1 from immediate-release and modified-release tablets. The release profile follows first order release kinetics and T80% is approximately 8 hours. The lower limit was not defined. Pharmacokinetics parameters of Compound 1 were obtained from an open-label, single-dose, cross-over clinical study in the fed and fasted state. Input variables and default values for GastroPlus™ simulation were as follows

Compound 1 Parameters

LogP:	2.56
pKa:	9.53
Dosage form:	a) controlled release tablet with 20-mg QD dosing or b) immediate-release tablet of 10-mg BID dosing
Solubility:	400 mg/mL
Particle density:	1.2 g/mL
Effective permeability:	3.54×10^{-6} cm/s

Physiological Parameters (Default Values)

Stomach retention time:	0.25 h
Dose volume:	250 mL
Small intestine transit time:	3.3 h
Small intestine radius:	1.2 cm
Small intestine length:	300 cm
Colon volume:	1200 mL

Pharmacokinetics Parameters

Body weight:	94 kg
Blood to plasma concentration ratio:	1.3

Clearance:	19.56 L/h
Apparent volume of distribution:	307.36 L

Effect of Surelease®/Opadry® Coating

A Surelease®/Opadry® ratio of 85/15 was evaluated. Application of Surelease®/Opadry® (85/15) coating decreases the release rate of Compound 1 hydrochloride salt hemihydrate, Form III substantially. At a coating weight gain of 2.6% (Batch 2), the percentage of release was reduced by 20% to 30% after a 1-h lag time, compared to the release from Batch 1. Release was further delayed at a higher coating weight gain (4.6%) (Batch 2). T80% of Batch 2 was 9 h and T80% of Batch 3 was 12 h. A lag time of 2 hours was observed for Batch 3. It can be also observed that the release kinetics shifted away from first order towards more constant release, especially at a coating weight gain of 4.6%.

Effect of Surelease®/Opadry® Ratio

The release profiles of tablets coated with different Surelease®/Opadry® ratios at the coating weight gain of approximately 5% were compared. Batch 1 tablets coated with Opadry® II Blue, were included as control. The formulation of core tablets is identical for all batches. As the ratio of Surelease®/Opadry® increases from 75/25 to 85/15, the release rate of Compound 1 is progressively reduced.

Effect of HPMC K4M Level in the Core Tablet

To evaluate the effect of reducing the level HPMC K4M in the core tablet on the release profile, core tablets were prepared containing 40% HPMC K4M. The amount of mannitol was increased to maintain the 300 mg tablet weight. The tablets were coated with Surelease®/Opadry® (85/15) at a coating weight gain of approximately 3% (Batch 6) and 5% (Batch 7).

Release of the API was faster by 10% to 15% in Batches 6 and 7 containing 40% HPMC K4M when compared to similarly coated tablets from Batches 2 and 3 containing 50% HPMC K4M.

Effect of the Surelease®/Opadry® Coating Level

Batches 8, 4 and 9 were coated with Surelease®/Opadry® (75/25) at different coating weight gains to assess the effect of coating weight on the release-rate of Compound 1 hydrochloride salt hemihydrate, Form III.

A higher coating weight gain reduced the rate of release. T80% is 7 hours, 8 hours, and 10 hours corresponding to a coating weight gain of 2.5%, 5.4%, and 9.9%, respectively.

Effect of API Loading

Batches 10 and 11 were developed to assess the impact of API loading level in the tablet on the release rate. The increase of API was compensated by decreasing the quantity of mannitol by the same amount.

Increasing the API loading in the core tablets from 6.93% to 10.4% showed a limited impact on the release profile. Accelerated API release from Batch 10 occurred in the first 6 hours and accelerated API release from Batch 11 occurred in the first 8 hours during dissolution. After that, the release profiles are essentially converged with the tablets with 6.63% loading (Batches 2 and 3). The impact of higher Compound 1 hydrochloride salt hemihydrate, Form III loading on its release is less pronounced at a coating weight gain of 3% than at a coating weight gain of 5%.

In summary, a flexible and robust modified-release formulation of Compound 1 hydrochloride salt hemihydrate, Form III was developed using two controlling mechanisms: HPMC swelling and ethyl cellulose coating. The Surelease®/Opadry® ratio, coating weight gain, and HPMC level were identified as the critical formulation parameters.

Other uses of the disclosed methods will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

What is claimed is:

1. A method for aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

2. A method for aiding in the cessation of use of a tobacco product and the prevention of associated weight gain comprising the step of:

prescribing and/or administering an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual attempting to cease use of the tobacco product.

3. The method of claim 1 or 2, wherein aiding in the cessation of use of a tobacco product is aiding smoking cessation, and wherein the individual attempting to cease use of the tobacco product is an individual attempting to cease smoking.

4. A method for reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

5. A method for controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

6. The method of claim 5, wherein controlling weight gain comprises preventing weight gain.

7. The method of claim 6, wherein controlling weight gain comprises inducing weight loss.

8. The method of claim 7, wherein controlling weight gain comprises inducing weight loss of at least about 1% after 12 weeks of administration.

9. The method of claim 7, wherein controlling weight gain comprises inducing weight loss of at least about 1.5% after 12 weeks of administration.

10. The method of claim 7, wherein controlling weight gain comprises inducing weight loss of at least about 2% after 12 weeks of administration.

11. The method of claim 7, wherein controlling weight gain comprises decreasing BMI.

12. The method of claim 7, wherein controlling weight gain comprises decreasing percent body fat.

13. The method of claim 7, wherein controlling weight gain comprises decreasing waist circumference.

14. A method for reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

15. The method of any one of claims 1 to 14, wherein prior to administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof, the method further comprises the step of:

instructing the individual to set a date to cease smoking tobacco.

16. The method of claim 15, wherein administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is initiated about 7 days prior to the date set to cease smoking tobacco.

17. The method of any one of claims 1 to 14, wherein after administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof, the method further comprises the step of:

instructing the individual to set a date to cease smoking tobacco.

18. The method of claim 17, wherein the date set to cease smoking tobacco occurs after at least 7 days of administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

19. The method of claim 17 or 18, wherein the date set to cease smoking tobacco occurs prior to 36 days of administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

20. The method of any one of claims 1 to 19, wherein the individual previously attempted to cease smoking tobacco but did not succeed in ceasing smoking tobacco.

21. The method of any one of claims 1 to 19, wherein the individual previously attempted to cease smoking tobacco but subsequently relapsed and resumed smoking tobacco.

22. The method of any one of claims 1 to 21, wherein the administration leads to a statistically significant improvement in the ability to tolerate the cessation of smoking as measured by analysis of data from the MPSS test.

23. A method of treatment for nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

24. A method of reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use comprising the step of:

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

25. The method of claim 23 or 24, wherein the individual has abstained from nicotine use for 12 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

26. The method of claim 23 or 24, wherein the individual has abstained from nicotine use for 24 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

27. The method of claim 23 or 24, wherein the individual has abstained from nicotine use for 9 months prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

28. The method of claim 23 or 24, wherein the individual has abstained from nicotine use for 52 weeks prior to prescribing and/or administering the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

29. The method of any one of claims 1 to 28, wherein, prior to administration, the individual has an initial body mass index < 25 kg/m^2.

30. The method of any one of claims 1 to 28, wherein, prior to administration, the individual has an initial body mass index ≥ 25 kg/m^2.

31. The method of any one of claims 1 to 28, wherein, prior to administration, the individual has an initial body mass index ≥ 27 kg/m^2.

32. The method of claim 30 or 31, wherein, prior to administration, the individual has at least one weight-related comorbid condition.

33. The method of claim 32, wherein the weight-related comorbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance and sleep apnea.

34. The method of claim 32, wherein the weight-related comorbid condition is selected from: hypertension, dyslipidemia, and type 2 diabetes.

35. The method of any one of claims 1 to 28, wherein, prior to administration, the individual has an initial body mass index ≥ 30 kg/m^2.

36. A method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

selecting an individual with an initial BMI ≥ 27 kg/m^2; and

prescribing and/or administering to the individual an effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for at least one year.

37. The method of claim 36, wherein the individual is prescribed and/or administered the effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof for one year.

38. The method of claim 36 or 37, wherein, prior to administration, the individual has at least one weight-related comorbid condition.

39. The method of claim 38, wherein the weight-related comorbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance and sleep apnea.

40. The method of claim 38, wherein the weight-related comorbid condition is selected from: hypertension, dyslipidemia, and type 2 diabetes.

41. The method of any one of claims 36 to 40, wherein, prior to administration, the individual has an initial body mass index ≥ 30 kg/m^2.

42. A method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco

product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for BMI during said administration; and

discontinuing said administration if the BMI of the individual becomes < 18.5 kg/m^2 during said administration.

43. The method of claim 42, wherein the initial BMI of the individual prior to administration is about 18.5 to about 25 kg/m^2.

44. The method of claim 43, wherein the individual has an initial BMI selected from one of the following: ≥ 24 kg/m^2, ≥ 23 kg/m^2, ≥ 22.5 kg/m^2, ≥ 22 kg/m^2, ≥ 21 kg/m^2, ≥ 20 kg/m^2, ≥ 19 kg/m^2, and ≥ 18.5 kg/m^2.

45. The method of claim 43 or 44, wherein the BMI of the individual becomes a BMI selected from one of the following: ≤ 18 kg/m^2, ≤ 17.5 kg/m^2, ≤ 17 kg/m^2, ≤ 16 kg/m^2, and ≤ 15 kg/m^2.

46. A method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual with an initial BMI ≤ 25 kg/m^2;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1% during said administration.

47. The method of claim 46, wherein the initial BMI of the individual prior to administration is about 18.5 to about 25 kg/m^2.

48. The method of claim 47, wherein the individual has an initial BMI selected from one of the following: ≥ 24 kg/m^2, ≥ 23 kg/m^2, ≥ 22.5 kg/m^2, ≥ 22 kg/m^2, ≥ 21 kg/m^2, ≥ 20 kg/m^2, ≥ 19 kg/m^2, and ≥ 18.5 kg/m^2.

49. The method of any one of claims 46 to 48, wherein the decrease in body weight is selected from one of the following: more than about 1.5%, more than about 2%, more than about 2.5%, more than about 3%, more than about 3.5%, more than about 4%, more than about 4.5%, and more than about 5%.

50. A method of reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco, aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product, aiding in smoking cessation and preventing associated weight gain, controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco, treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal, or reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use, comprising:

administering (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof to an individual;

monitoring the individual for body weight during said administration; and

discontinuing said administration if the body weight of the individual decreases by more than about 1 kg during said administration.

51. The method of claim 50, wherein the initial BMI of the individual prior to administration is about 18.5 to about 25 kg/m^2.

52. The method of claim 51, wherein the individual has an initial BMI selected from one of the following: ≥ 24 kg/m^2, ≥ 23 kg/m^2, ≥ 22.5 kg/m^2, ≥ 22 kg/m^2, ≥ 21 kg/m^2, ≥ 20 kg/m^2, ≥ 19 kg/m^2, and ≥ 18.5 kg/m^2.

53. The method of claim 51 or 52, wherein the decrease in body weight is selected from one of the following: more than about 1.5 kg, more than about 2 kg, more than about 2.5 kg, more than about 3 kg, more than about 3.5 kg, more than about 4 kg, more than about 4.5 kg, and more than about 5 kg.

54. The method of any one of claims 1 to 53, wherein the administration leads to a statistically significant improvement in the ability to tolerate the cessation of smoking as measured by analysis of data from the MPSS test.

55. The method of any one of claims 1 to 54, wherein the individual is suffering from depression prior to being administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

56. The method of any one of claims 1 to 55, wherein the individual is suffering from a preexisting psychiatric disease prior to being administered the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof.

57. The method of claim 56, wherein the preexisting psychiatric disease is chosen from schizophrenia, bipolar disorder, and major depressive disorder.

58. The method of any one of claims 1 to 57, wherein the individual is also being prescribed and/or administered a supplemental agent.

59. The method of claim 58, wherein the supplemental agent is varenicline or a pharmaceutically acceptable salt thereof.

60. The method of claim 58, wherein the supplemental agent is clonidine.

61. The method of claim 58, wherein the supplemental agent is a nicotine replacement therapy.

62. The method of claim 61, wherein the nicotine replacement therapy is chosen from nicotine gum, nicotine transdermal systems, nicotine lozenges, nicotine microtabs, and nicotine sprays or inhalers.

63. The method of claim 58, wherein the supplemental agent is an antidepressant.

64. The method of claim 63, wherein the antidepressant is chosen from nortriptyline and bupropion.

65. The method of any one of claims 1 to 64, wherein the individual has previously undergone treatment with a supplemental agent.

66. The method of claim 65, wherein the individual was refractory to said treatment with said supplemental agent.

67. The method of any one of claims 1 to 64, wherein the individual has previously undergone treatment with a nicotine replacement therapy.

68. The method of claim 67, wherein the individual was refractory to said treatment with said nicotine replacement therapy.

69. The method of any one of claims 1 to 68, wherein, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual smokes ≥10 cigarettes per day.

70. The method of any one of claims 1 to 69, wherein, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual has a moderate nicotine addiction as measured by the Fagerström Test for nicotine dependence.

71. The method of any one of claims 1 to 69, wherein, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt,

solvate, or hydrate thereof, the individual has a high nicotine addiction as measured by the Fagerström Test for nicotine dependence score.

72. The method of any one of claims 1 to 69, wherein, prior to administration of the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof, the individual has a very high nicotine addiction as measured by the Fagerström Test for nicotine dependence score.

73. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 2 weeks.

74. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 4 weeks.

75. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 8 weeks.

76. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 12 weeks.

77. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 6 months.

78. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 1 year.

79. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for at least about 2 years.

80. The method of any one of claims 1 to 72, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered for between about 12 weeks to about 52 weeks.

81. The method of any one of claims 1 to 80, further comprising the step of:
providing the individual with educational materials and/or counseling.

82. The method of any one of claims 1 to 81, further comprising the step of:
providing the individual with biochemical feedback; acupuncture; hypnosis; behavioral intervention; support services; and/or psychosocial treatment.

83. The method of any one of claims 1 to 82, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride, or a solvate or hydrate thereof.

84. The method of any one of claims 1 to 83, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate.

85. The method of claim 83, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 20 mg per day.

86. The method of claim 83, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or solvate or hydrate thereof is prescribed and/or administered to the individual in a dose equal to 10 mg twice per day.

87. The method of any one of claims 1 to 86, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is administered in a tablet suitable for oral administration.

88. A composition comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof and at least one supplemental agent.

89. The composition of claim 88, wherein the supplemental agent is chosen from nicotine replacement therapies.

90. The composition of claim 88, wherein the supplemental agent is chosen from antidepressants.

91. The composition of claim 88, wherein the supplemental agent is chosen from clonidine or a pharmaceutically acceptable salt thereof.

92. The composition of claim 88, wherein the supplemental agent is chosen from varenicline or a pharmaceutically acceptable salt thereof.

93. The composition of any one of claims 88 to 92, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is selected from an HCl salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and solvates or hydrates thereof.

94. The composition of any one of claims 88 to 92, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is selected from a hydrate of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and pharmaceutically acceptable salts thereof.

95. The composition of any one of claims 88 to 92, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is a hydrate of an HCl salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

96. The composition of any one of claims 88 to 92, wherein the (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or pharmaceutically acceptable salt, solvate, or hydrate thereof is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate.

97. A composition as claimed in any one of claims 88 to 96 for use in a method of:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

98. A composition according to any one of claims 88 to 96 for use as a medicament for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

99. The composition according to any one of claims 88 to 96 in the manufacture of a medicament for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

100. A unit dosage form of a composition according to any one of claims 88 to 96.

101. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for use in a method of:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

102. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof for use as a medicament for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

103. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof in the manufacture of a medicament for:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

104. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof having at least one of the attributes described herein for use in combination with a supplemental agent.

105. (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof according to claim 104, for use in a method of:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

106. A supplemental agent chosen from nicotine replacement therapies, for use in combination with (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof having at least one of the attributes described herein.

107. A supplemental agent according to claim 106 for use in a method of:

reducing the frequency of smoking tobacco in an individual attempting to reduce frequency of smoking tobacco;

aiding in the cessation or lessening of use of a tobacco product in an individual attempting to cease or lessen use of a tobacco product;

aiding in smoking cessation and preventing associated weight gain;

controlling weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

reducing weight gain associated with smoking cessation by an individual attempting to cease smoking tobacco;

treating nicotine dependency, addiction and/or withdrawal in an individual attempting to treat nicotine dependency, addiction and/or withdrawal; or

reducing the likelihood of relapse use of nicotine by an individual attempting to cease nicotine use.

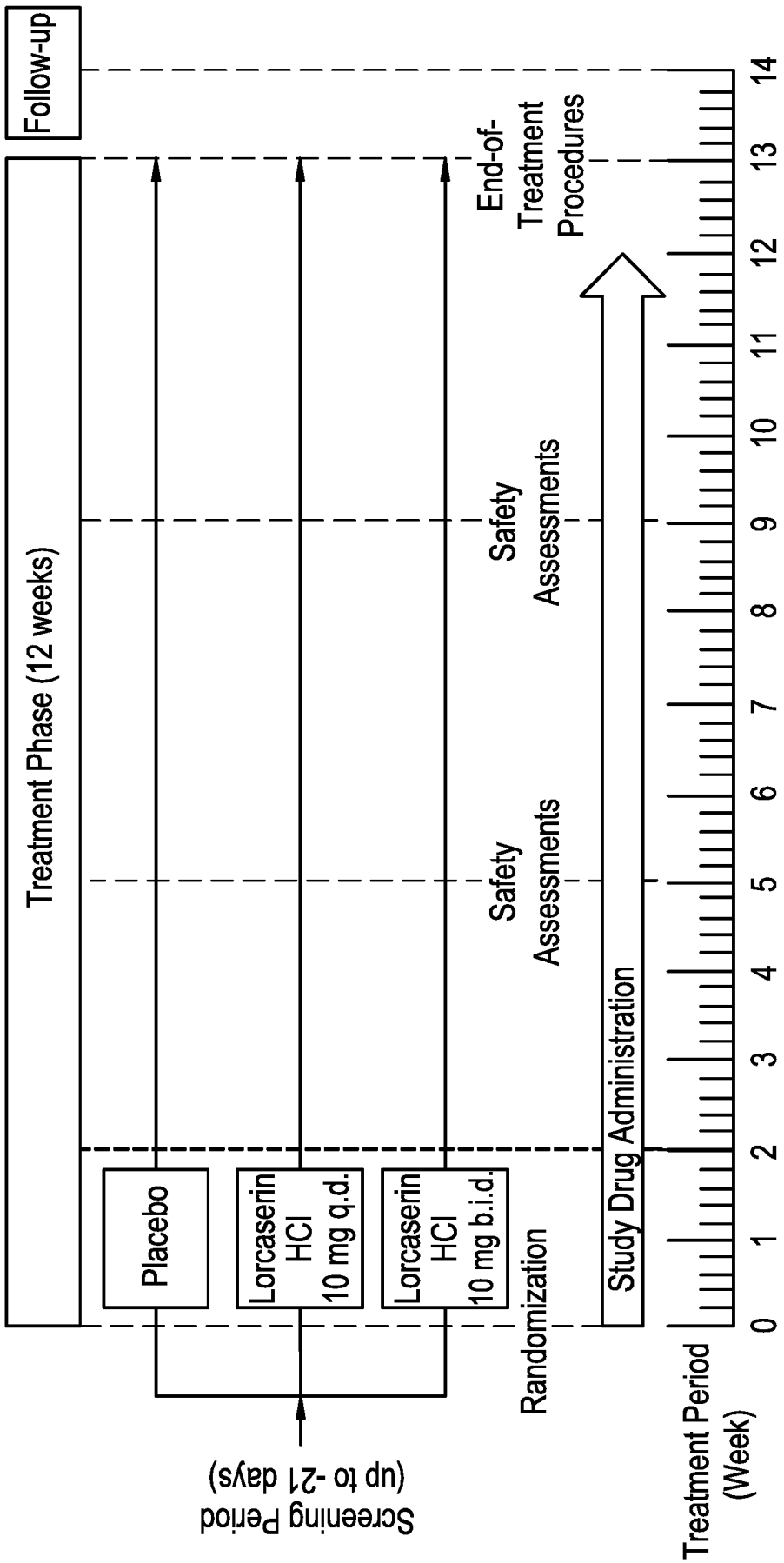

Follow-up
Treatment Phase (12 weeks)
End-of-Treatment Procedures
Safety Assessments
Safety Assessments
Placebo
Lorcaserin HCl 10 mg q.d.
Lorcaserin HCl 10 mg b.i.d.
Study Drug Administration
Randomization
Day 15 Target Quit Day
Screening Period (up to -21 days)
Treatment Period (Week)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Figure 1

Demographic	Placebo (N=200)	Lorcaserin 10 mg q.d. (N=202)	Lorcaserin 10 mg b.i.d. (N=201)
Sex			
Male	82 (41.0%)	102 (50.5%)	91 (45.3%)
Female	118 (59.0%)	100 (49.5%)	110 (54.7%)
Age (years)			
Mean (SD)	46.3 (11.7)	45.0 (11.3)	45.6 (11.3)
Min - Max	19 - 65	19 - 65	19 - 65
Race			
White	154 (77.0%)	154 (76.2%)	156 (77.6%)
Black or African American	42 (21.0%)	43 (21.3%)	37 (18.4%)
Asian	1 (0.5%)	3 (1.5%)	1 (0.5%)
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	1 (0.5%)
Native Hawaiian or Other Pacific Islander	1 (0.5%)	0 (0.0%)	2 (1.0%)
Other	1 (0.5%)	1 (0.5%)	4 (2.0%)
Ethnicity			
Hispanic or Latino	10 (5.0%)	26 (12.9%)	16 (8.0%)
Not Hispanic or Latino	190 (95.0%)	176 (87.1%)	185 (92.0%)

Figure 2

Demographic	Placebo (N=200)	Lorcaserin 10 mg q.d. (N=202)	Lorcaserin 10 mg b.i.d. (N=201)
Weight (kg)			
Mean (SD)	80.1 (16.1)	81.6 (14.6)	79.6 (17.1)
Height (cm)			
Mean (SD)	169.7 (8.9)	170.6 (9.0)	169.8 (9.9)
BMI (kg/m^2)			
Mean (SD)	27.8 (5.1)	28.0 (4.5)	27.5 (4.9)
BMI Group (kg/m^2)			
< 25	59 (29.5%)	52 (25.7%)	67 (33.3%)
≥ 25 and < 30	76 (38.0%)	88 (43.6%)	73 (36.3%)
≥ 30	65 (32.5%)	62 (30.7%)	61 (30.3%)
Baseline FTND* Score			
Mean (SD)	5.7 (1.8)	5.5 (2.0)	5.6 (2.0)

Figure 3

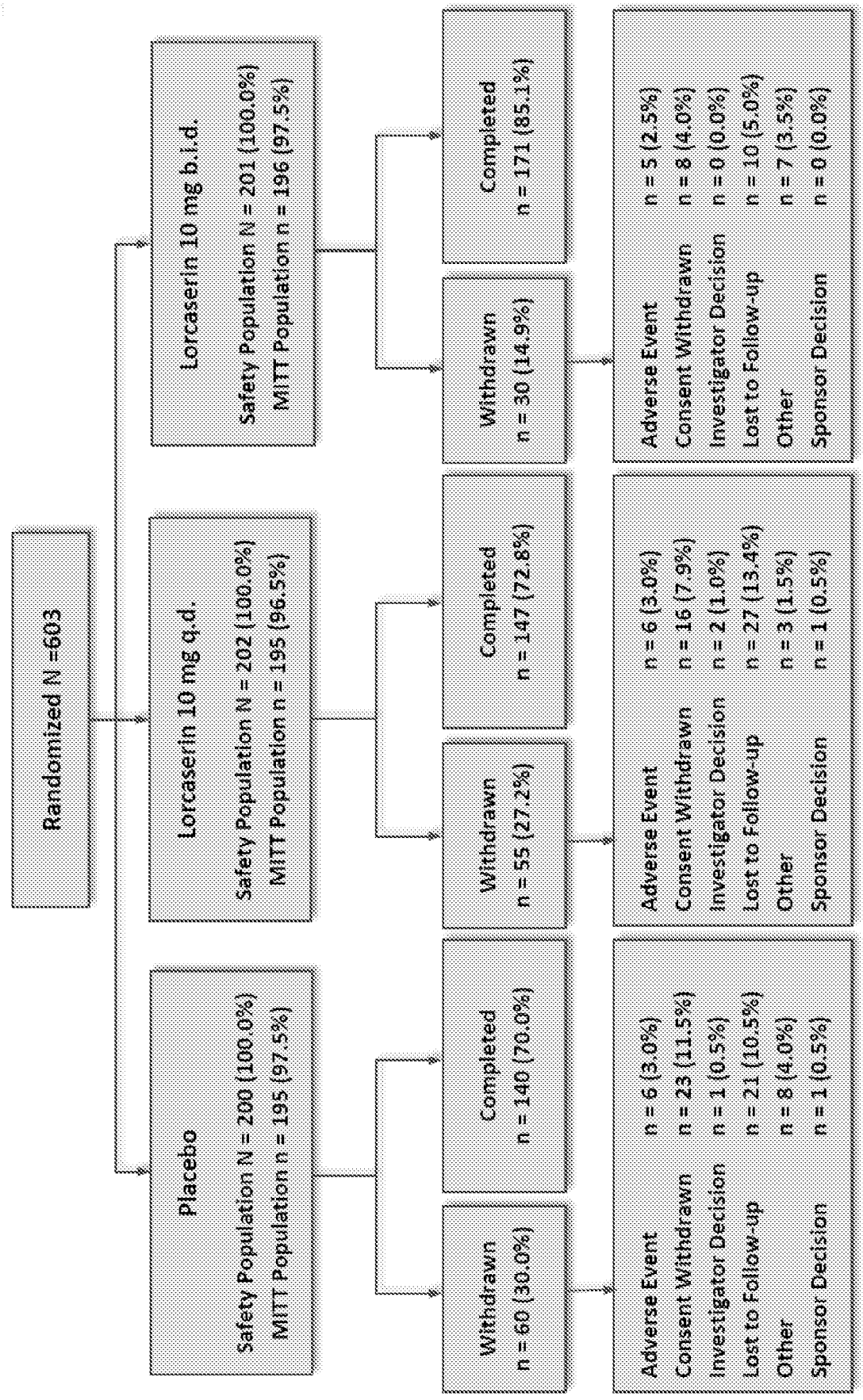
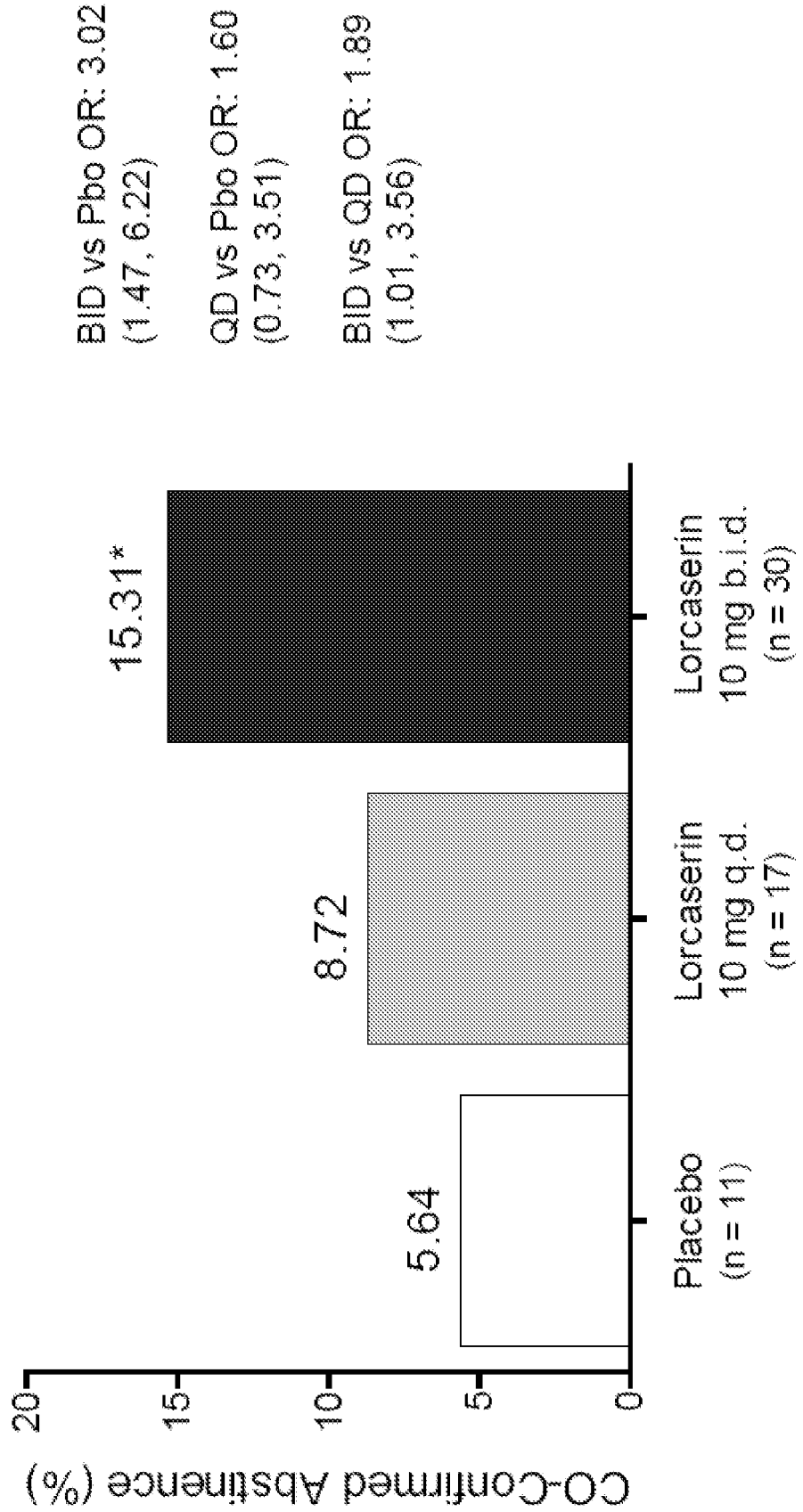

Randomized N =603
Placebo
Safety Population N = 200 (100.0%)
MITT Population n = 195 (97.5%)
Lorcaserin 10 mg q.d.
Safety Population N = 202 (100.0%)
MITT Population n = 195 (96.5%)
Lorcaserin 10 mg b.i.d.
Safety Population N = 201 (100.0%)
MITT Population n = 196 (97.5%)
Completed
n = 140 (70.0%)
Withdrawn
n = 60 (30.0%)
Completed
n = 147 (72.8%)
Withdrawn
n = 55 (27.2%)
Completed
n = 171 (85.1%)
Withdrawn
n = 30 (14.9%)
Adverse Event n = 6 (3.0%)
Consent Withdrawn n = 23 (11.5%)
Investigator Decision n = 1 (0.5%)
Lost to Follow-up n = 21 (10.5%)
Other n = 8 (4.0%)
Sponsor Decision n = 1 (0.5%)
Adverse Event n = 6 (3.0%)
Consent Withdrawn n = 16 (7.9%)
Investigator Decision n = 2 (1.0%)
Lost to Follow-up n = 27 (13.4%)
Other n = 3 (1.5%)
Sponsor Decision n = 1 (0.5%)
Adverse Event n = 5 (2.5%)
Consent Withdrawn n = 8 (4.0%)
Investigator Decision n = 0 (0.0%)
Lost to Follow-up n = 10 (5.0%)
Other n = 7 (3.5%)
Sponsor Decision n = 0 (0.0%)

Figure 4



* p = 0.0027, lorcaserin 10 mg BID vs. placebo

Figure 5

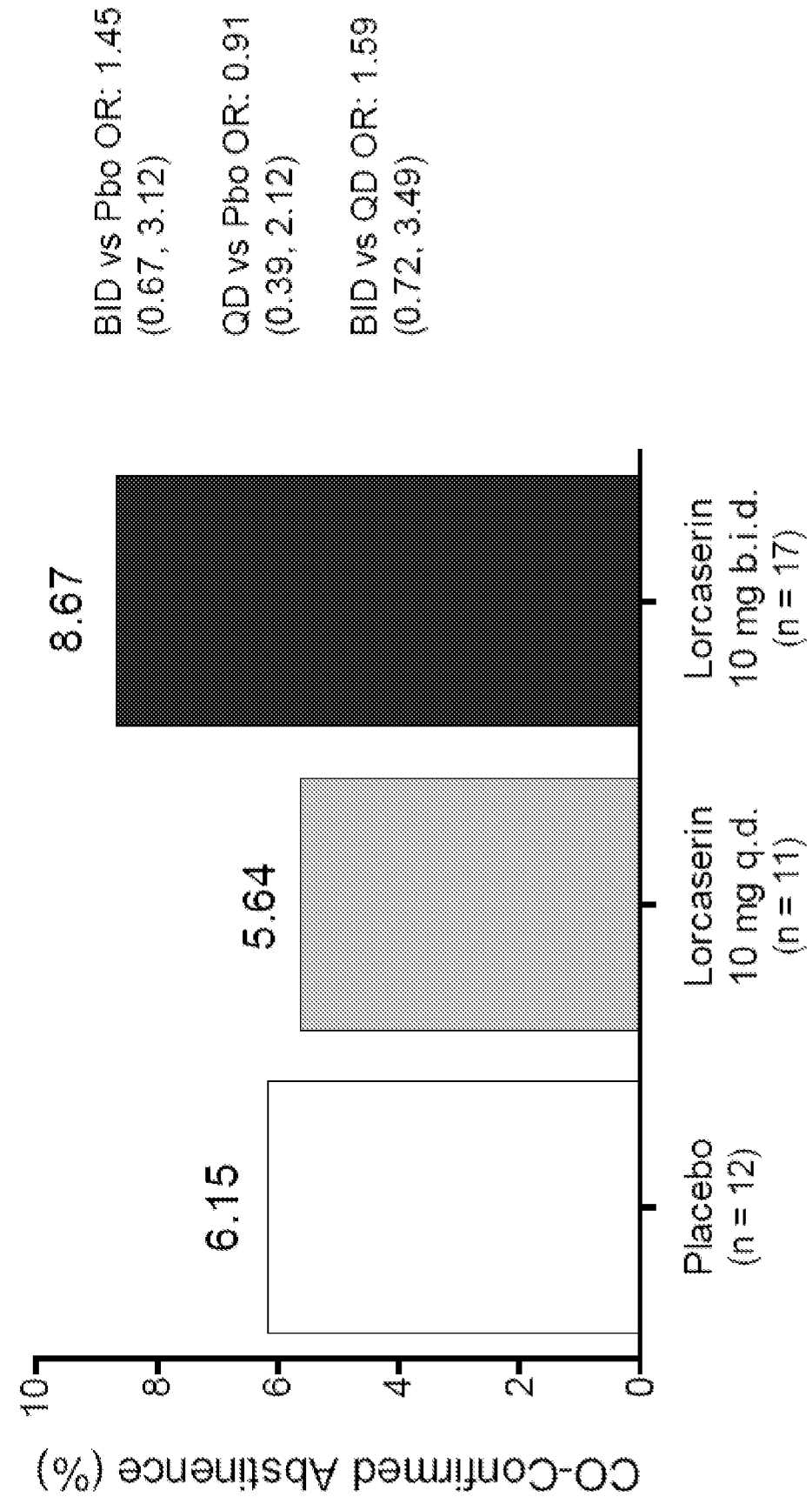

BID vs Pbo OR: 1.45
(0.67, 3.12)
QD vs Pbo OR: 0.91
(0.39, 2.12)
BID vs QD OR: 1.59
(0.72, 3.49)
CO-Confirmed Abstinence (%)
0
2
4
6
8
10
6.15
5.64
8.67
Placebo
(n = 12)
Lorcaserin
10 mg q.d.
(n = 11)
Lorcaserin
10 mg b.i.d.
(n = 17)

Figure 6

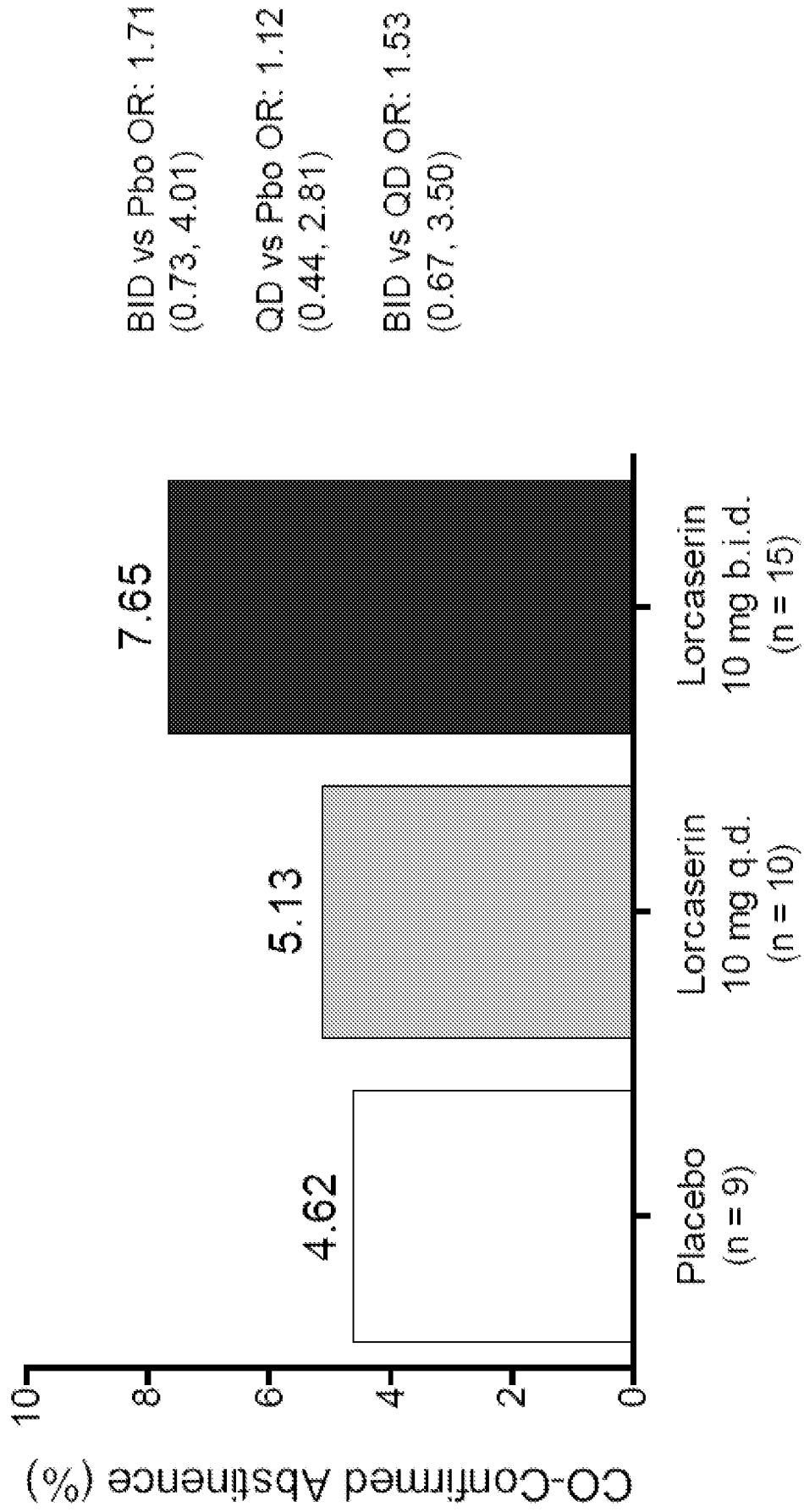

BID vs Pbo OR: 1.71
(0.73, 4.01)
QD vs Pbo OR: 1.12
(0.44, 2.81)
BID vs QD OR: 1.53
(0.67, 3.50)
7.65
5.13
4.62
CO-Confirmed Abstinence (%)
0
2
4
6
8
10
Placebo
(n = 9)
Lorcaserin
10 mg q.d.
(n = 10)
Lorcaserin
10 mg b.i.d.
(n = 15)

Figure 7

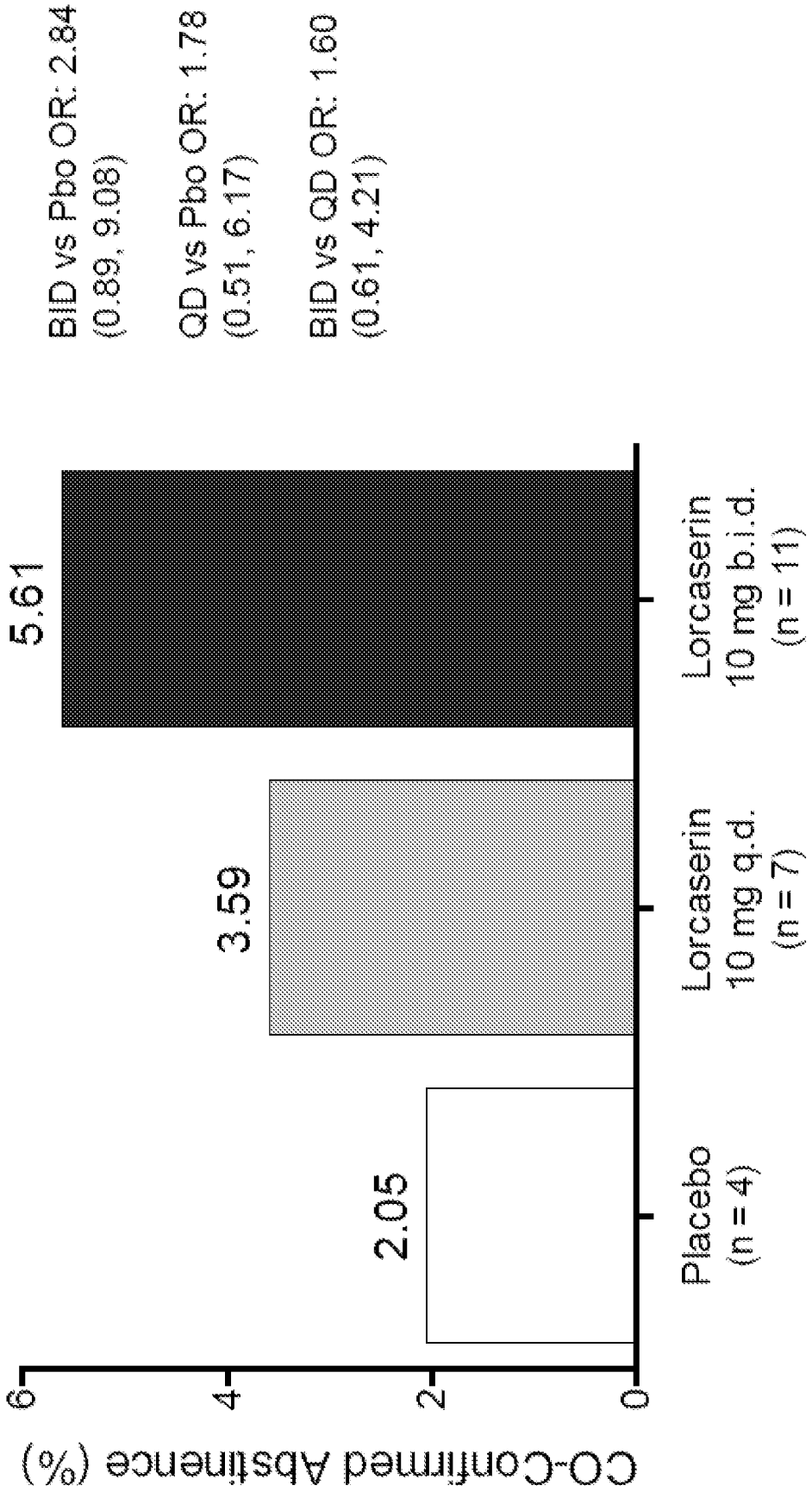

BID vs Pbo OR: 2.84
(0.89, 9.08)
QD vs Pbo OR: 1.78
(0.51, 6.17)
BID vs QD OR: 1.60
(0.61, 4.21)
CO-Confirmed Abstinence (%)
0
2
4
6
2.05
3.59
5.61
Placebo
(n = 4)
Lorcaserin
10 mg q.d.
(n = 7)
Lorcaserin
10 mg b.i.d.
(n = 11)

Figure 8

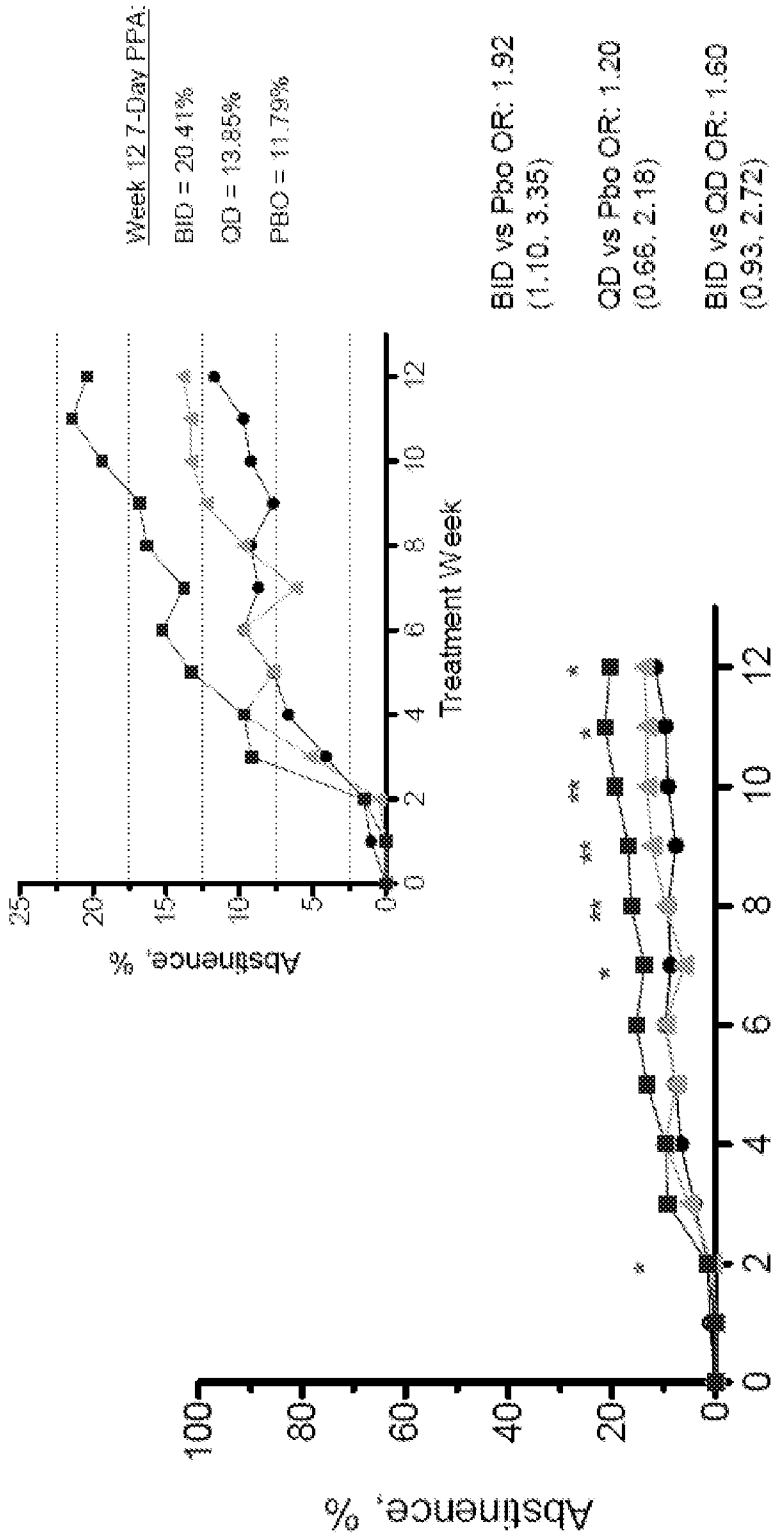

Week 12 7-Day PPA:
BID = 20.41%
QD = 13.85%
PBO = 11.79%
BID vs Pbo OR: 1.92
(1.10, 3.35)
QD vs Pbo OR: 1.20
(0.66, 2.18)
BID vs QD OR: 1.60
(0.93, 2.72)
Abstinence, %
Treatment Week
Placebo
(N = 141)
Lorcaserin 10 mg q.d.
(N = 170)
Lorcaserin 10 mg b.i.d.
(N = 170)
* p < 0.05; ** p < 0.01, lorcaserin 10 mg BID vs. placebo

Figure 9

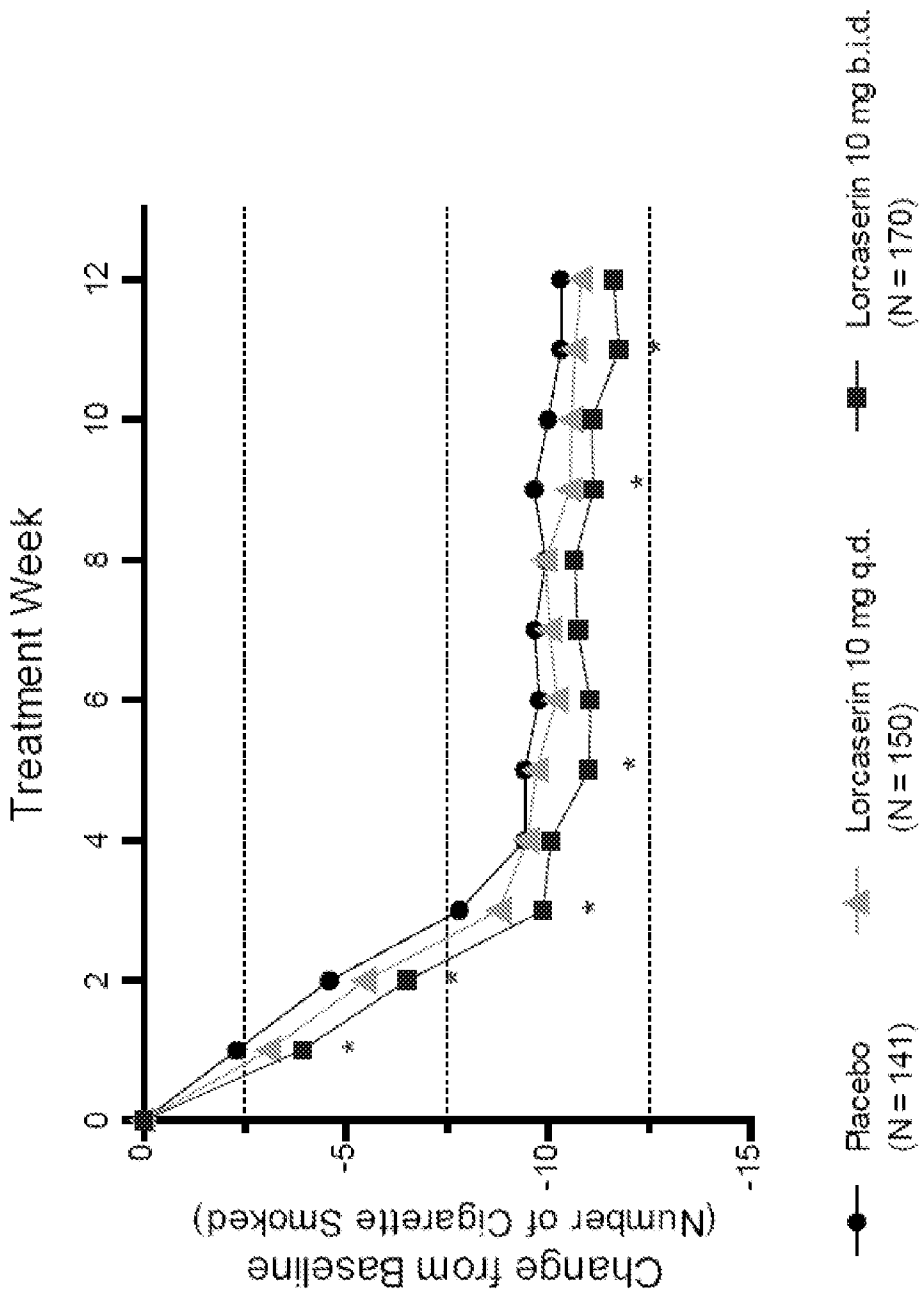


Figure 10

* $p < 0.05$; lorcaserin 10 mg BID vs. placebo

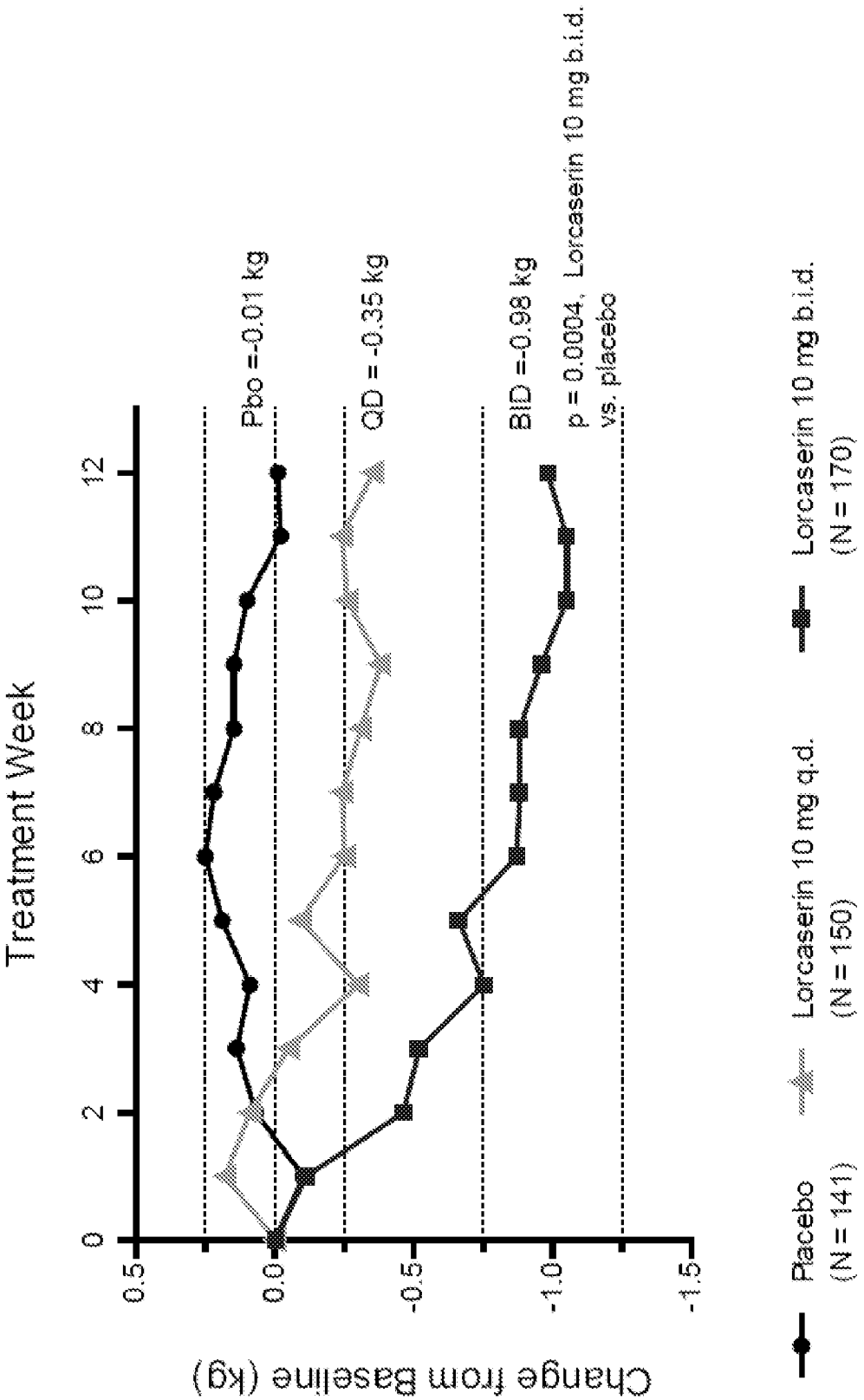

Change from Baseline (kg)
0.5
0.0
-0.5
-1.0
-1.5
Treatment Week
0
2
4
6
8
10
12
Pbo =-0.01 kg
QD = -0.35 kg
BID =-0.98 kg
p = 0.0004, Lorcaserin 10 mg b.i.d. vs. placebo
Placebo (N = 141)
Lorcaserin 10 mg q.d. (N = 150)
Lorcaserin 10 mg b.i.d. (N = 170)

Figure 11

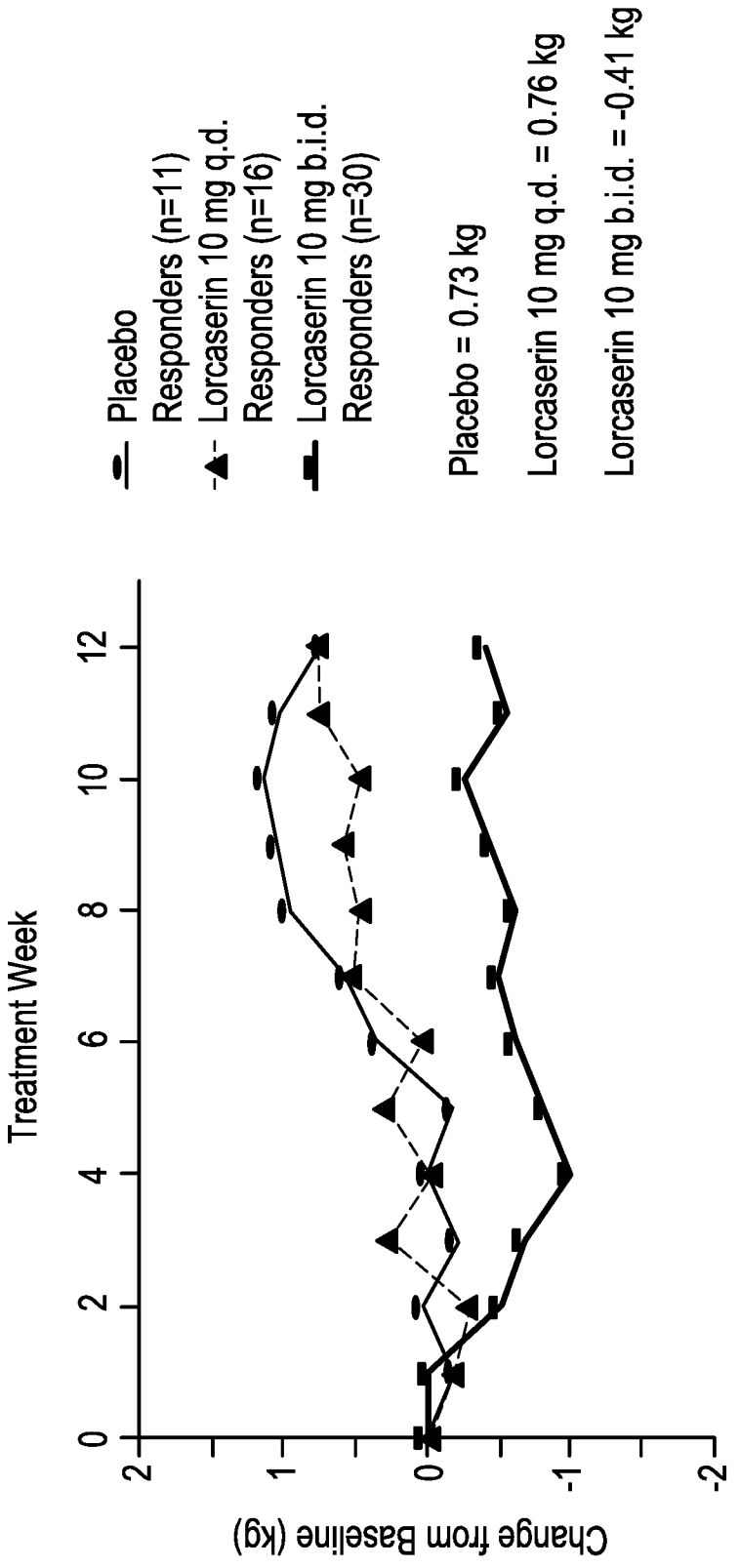

Placebo
Responders (n=11)
Lorcaserin 10 mg q.d.
Responders (n=16)
Lorcaserin 10 mg b.i.d.
Responders (n=30)
Placebo = 0.73 kg
Lorcaserin 10 mg q.d. = 0.76 kg
Lorcaserin 10 mg b.i.d. = -0.41 kg
Change from Baseline (kg)
2
1
0
-1
-2
Treatment Week
0
2
4
6
8
10
12

Figure 12

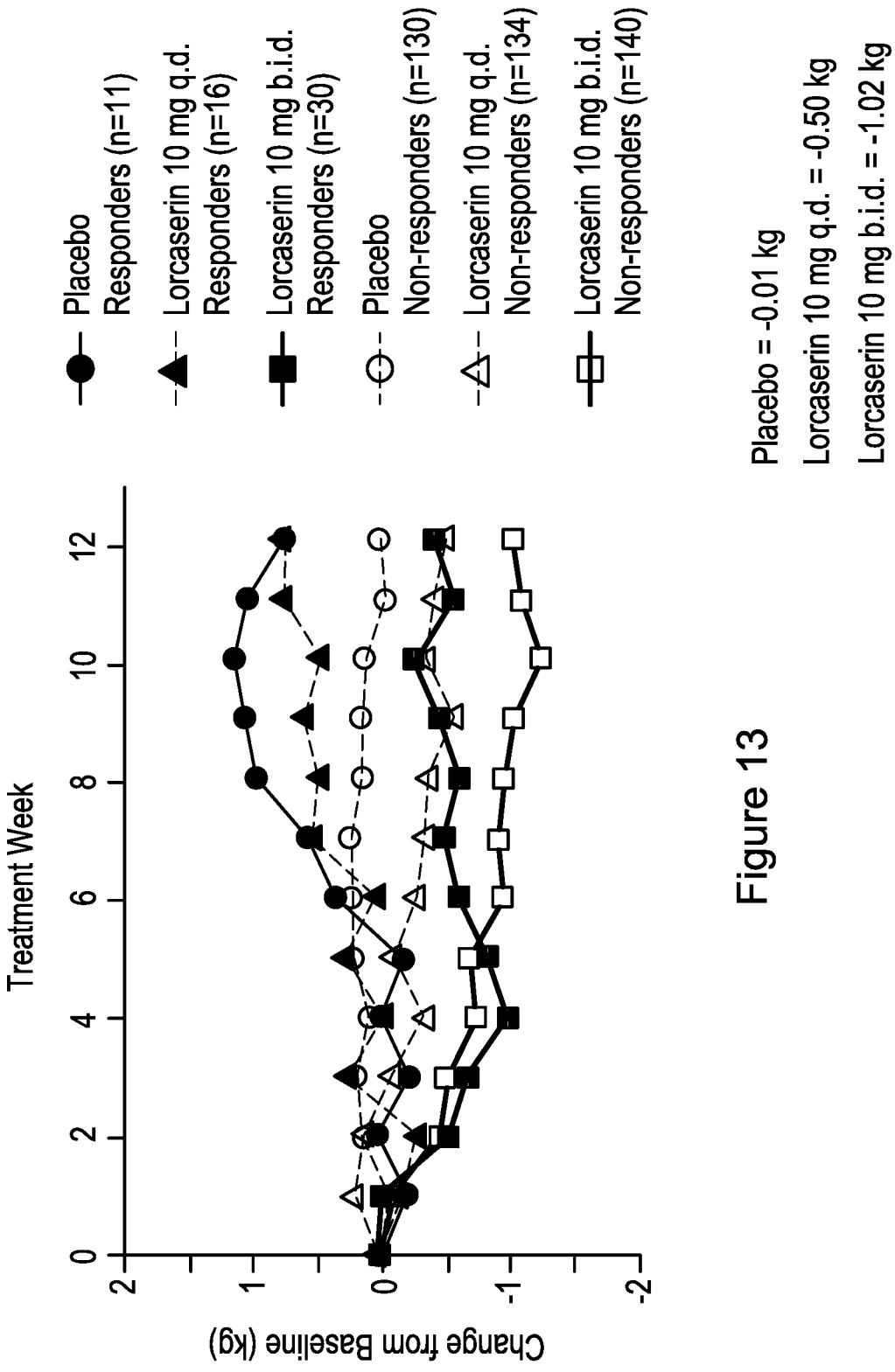

Placebo
Responders (n=11)
Lorcaserin 10 mg q.d.
Responders (n=16)
Lorcaserin 10 mg b.i.d.
Responders (n=30)
Placebo
Non-responders (n=130)
Lorcaserin 10 mg q.d.
Non-responders (n=134)
Lorcaserin 10 mg b.i.d.
Non-responders (n=140)
Change from Baseline (kg)
2
1
0
-1
-2
Treatment Week
0
2
4
6
8
10
12
Placebo = -0.01 kg
Lorcaserin 10 mg q.d. = -0.50 kg
Lorcaserin 10 mg b.i.d. = -1.02 kg

Figure 13

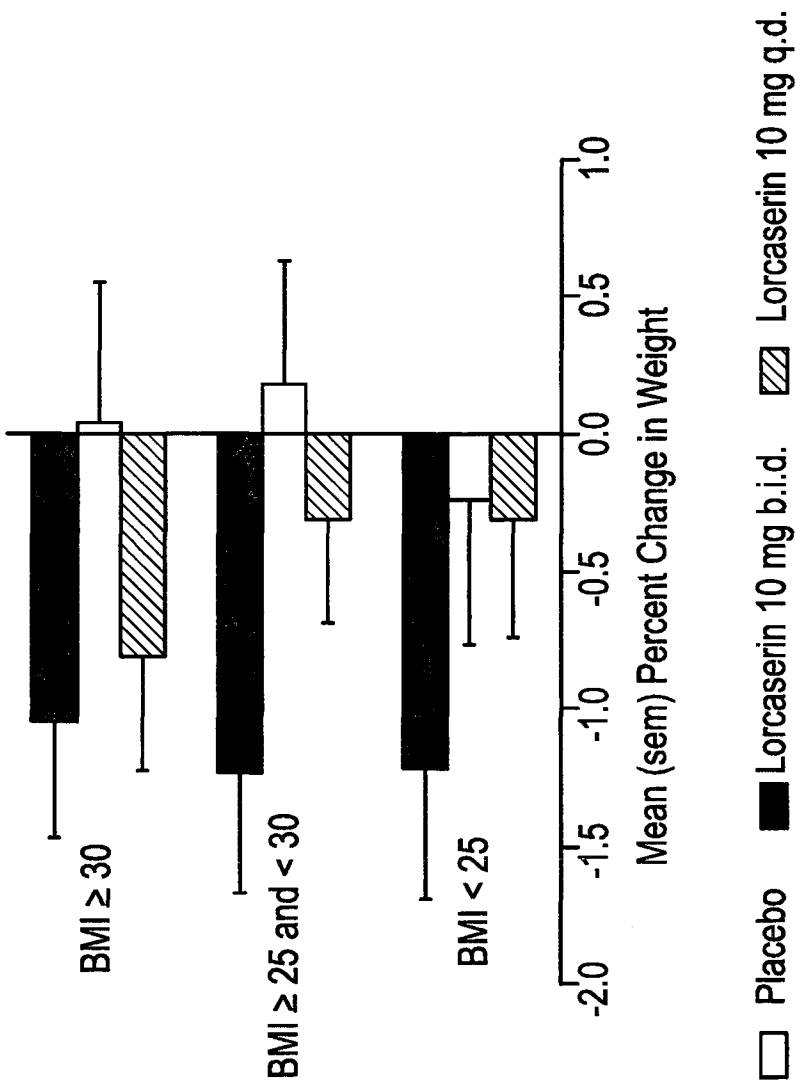

Placebo
Lorcaserin 10 mg b.i.d.
Lorcaserin 10 mg q.d.
Mean (sem) Percent Change in Weight
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
BMI ≥ 30
BMI ≥ 25 and < 30
BMI < 25

Figure 14

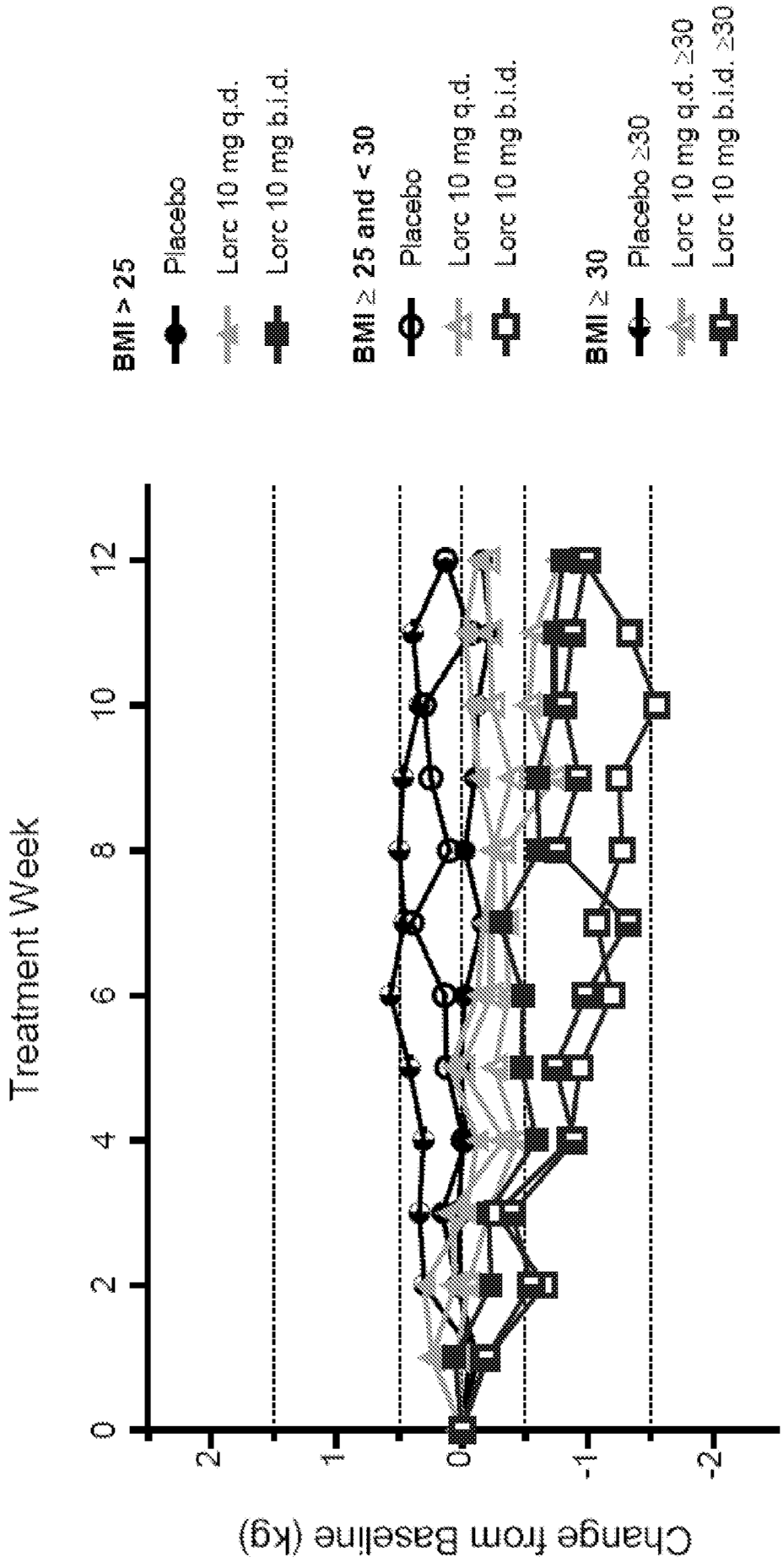

BMI > 25
Placebo
Lorc 10 mg q.d.
Lorc 10 mg b.i.d.
BMI ≥ 25 and < 30
Placebo
Lorc 10 mg q.d.
Lorc 10 mg b.i.d.
BMI ≥ 30
Placebo ≥30
Lorc 10 mg q.d. ≥30
Lorc 10 mg b.i.d. ≥30
Treatment Week
0
2
4
6
8
10
12
Change from Baseline (kg)
2
1
0
-1
-2

Figure 15

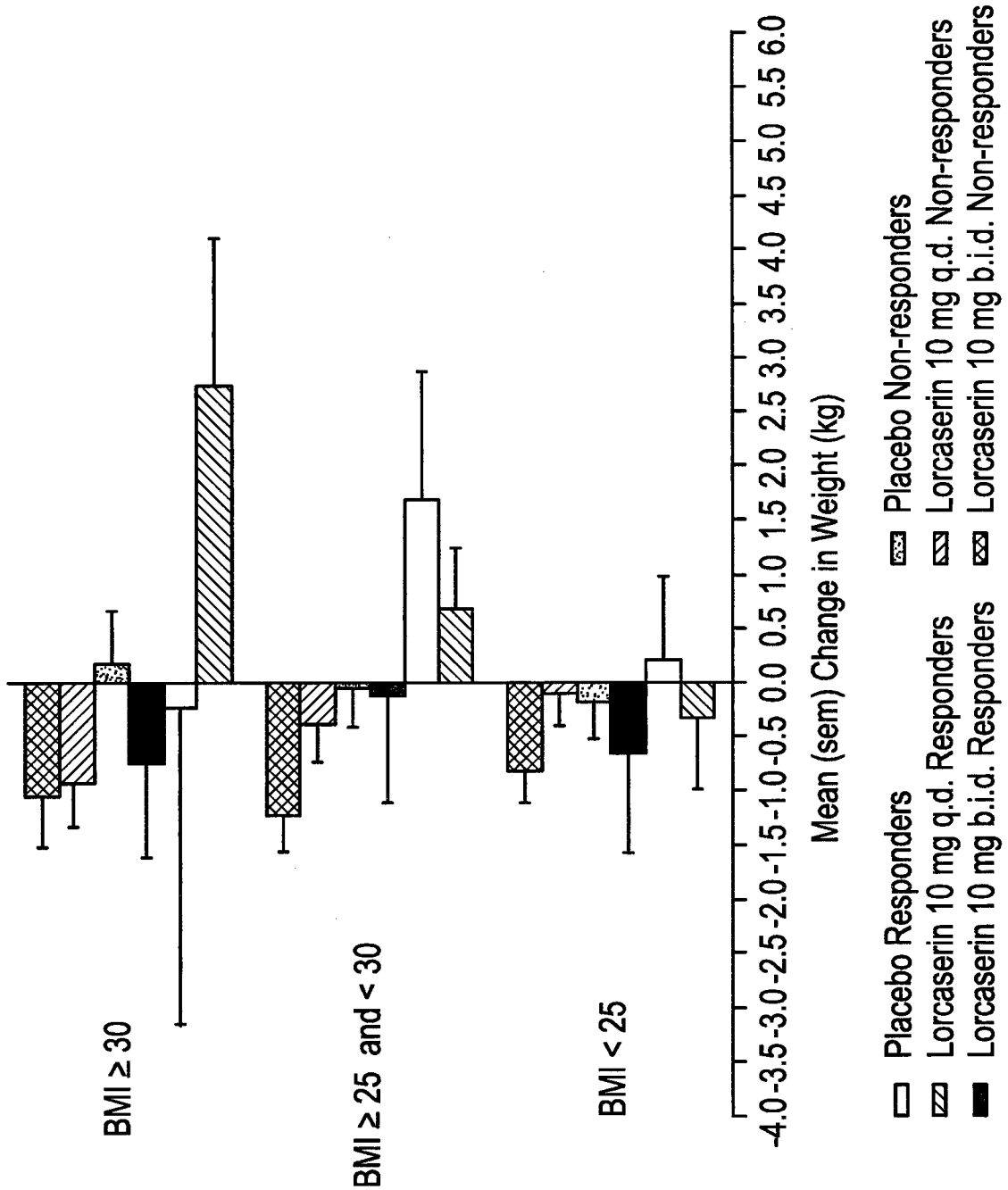

BMI ≥ 30
BMI ≥ 25 and < 30
BMI < 25
-4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Mean (sem) Change in Weight (kg)
Placebo Responders
Lorcaserin 10 mg q.d. Responders
Lorcaserin 10 mg b.i.d. Responders
Placebo Non-responders
Lorcaserin 10 mg q.d. Non-responders
Lorcaserin 10 mg b.i.d. Non-responders

Figure 16

Category	Placebo (N=200)	Lorcaserin 10 mg QD (N=202)	Lorcaserin 10 mg BID (N=201)	Any Lorcaserin Dose (N=403)
Number of Subjects reporting AE	**110 (55.0)**	**111 (55.0)**	**125 (62.2)**	**236 (58.6)**
Number of Subjects Reporting SAE	1 (0.5)	4 (2.0)	3 (1.5)	7 (1.7)
Number of Subjects with AE Causing Study Discontinuation or Study Drug Withdrawal	10 (5.0)	9 (4.5)	5 (2.5)	14 (3.5)
Number AEs Reported[a]	**246**	**266**	**319**	**585**
Number of Subjects Reporting AE by Severity[b]				
Grade 1: Mild	56 (28.0)	64 (31.7)	54 (26.9)	118 (29.3)
Grade 2: Moderate	49 (24.5)	40 (19.8)	63 (31.3)	103 (25.6)
Grade 3: Severe	5 (2.5)	7 (3.5)	8 (4.0)	15 (3.7)
Grade 4: Life-threatening	0	0	0	0
Grade 5: Death	0	0	0	0
Number of Subjects Reporting AE by Relationship to Study Drug[b]				
Not Related	56 (28.0)	55 (27.2)	58 (28.9)	113 (28.0)
Related	54 (27.0)	56 (27.7)	67 (33.3)	123 (30.5)

[a] in counting the number of adverse events reported, an adverse event was defined as an event with a unique subject identification number, preferred term and onset date

[b] subjects reporting more than one event are counted once at the maximum intensity or at the most direct relationship

Figure 17

	EC_{50} (nM)	Efficacy (% 5-HT)
Human 5-HT_{2A}	553	25
Human 5-HT_{2B}	2380	151
Human 5-HT_{2C}	39.2	81
Rat 5-HT_{2A}	1110	24
Rat 5-HT_{2B}	195	94
Rat 5-HT_{2C}	545	72
Monkey 5-HT_{2A}	499	19
Monkey 5-HT_{2B}	725	107
Monkey 5-HT_{2C}	51.4	85

Figure 18

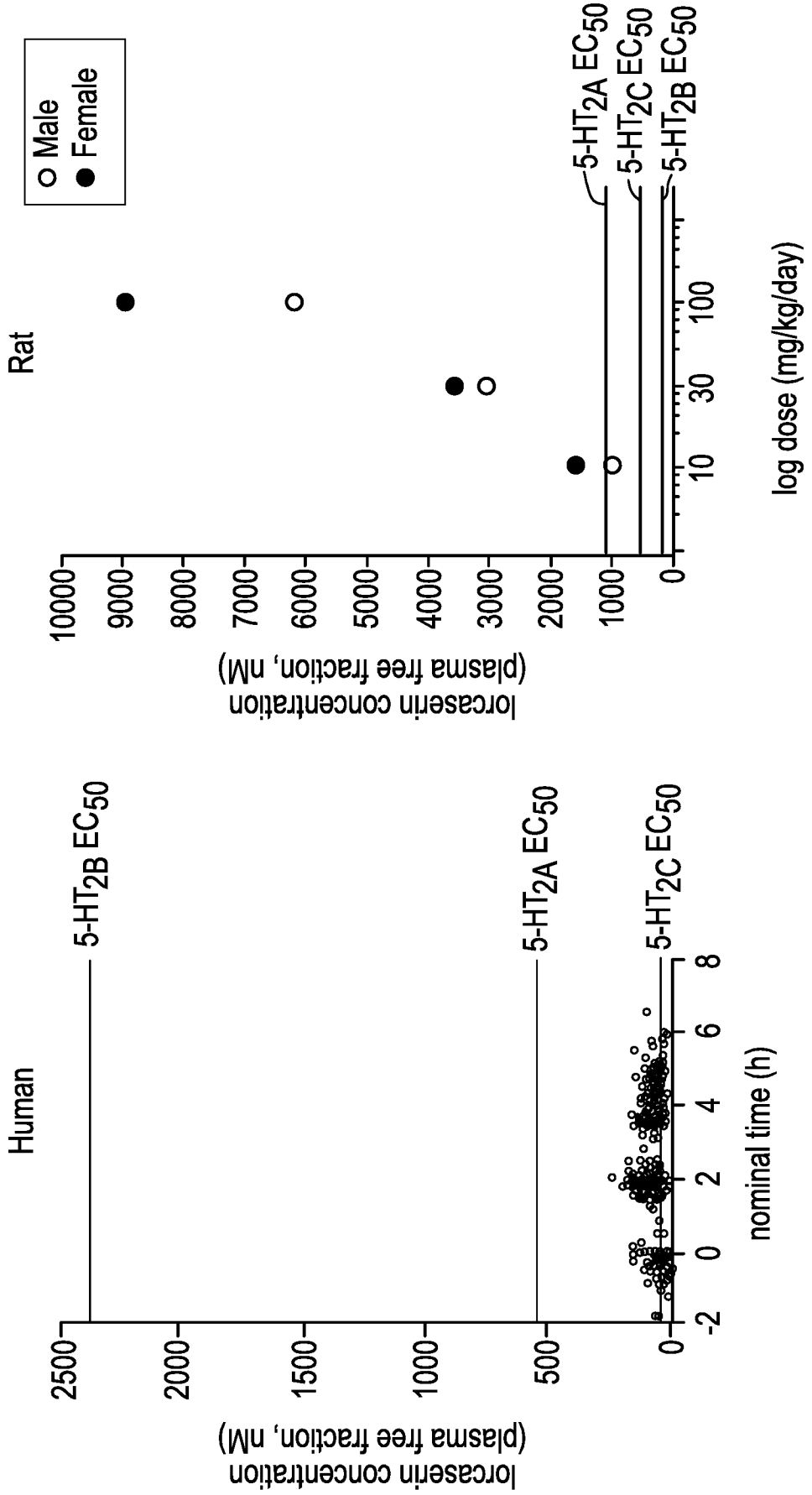

Rat
Male
Female
5-HT2A EC50
5-HT2C EC50
5-HT2B EC50
lorcaserin concentration (plasma free fraction, nM)
log dose (mg/kg/day)
Human
nominal time (h)

FIGURE 19

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/058016

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/55 A61P25/34 A61K31/135 A61K31/137
A61K31/4168 A61K9/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUY A. HIGGINS ET AL: "From obesity to substance abuse: therapeutic opportunities for 5-HT2C receptor agonists", TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 34, no. 10, 1 October 2013 (2013-10-01), pages 560-570, XP055162077, ISSN: 0165-6147, DOI: 10.1016/j.tips.2013.08.001	1-59, 65-88, 92-107
Y	page 566, right-hand column, paragraph 2 - page 567, left-hand column, paragraph 1; table 2	60-64, 89-91
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2016	15/01/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/058016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUY A HIGGINS ET AL: "The 5-HT2C Receptor Agonist Lorcaserin Reduces Nicotine Self-Administration, Discrimination, and Reinstatement: Relationship to Feeding Behavior and Impulse Control", NEUROPSYCHOPHARMACOLOGY, vol. 37, no. 5, 21 December 2011 (2011-12-21), pages 1177-1191, XP055141024, ISSN: 0893-133X, DOI: 10.1038/npp.2011.303	1-57, 65-87, 97-103
Y	page 1180, right-hand column, last paragraph - page 1186, left-hand column, paragraph 2 page 1187, left-hand column, paragraph 2	58-64, 88-96, 104-107

X	US 2011/014277 A1 (BIELEY HARLAN CLAYTON [US]) 20 January 2011 (2011-01-20)	1-58, 65-88, 93-107
Y	paragraphs [0013], [0020]; claims 1,6; figure 1	59-64, 89-92

X	US 2014/213579 A1 (SANCHEZ MATILDE [US] ET AL) 31 July 2014 (2014-07-31) paragraphs [0387], [0388], [0389]; examples 1-3	5-22, 29-35, 54-57, 65-87

Y	WILLIAM H FRISHMAN: "Smoking cessation pharmacotherapy - nicotine and non-nicotine preparation", PREVENTIVE CARDIOLOGY, vol. 10, no. 2 suppl 1, 30 April 2007 (2007-04-30), pages 10-22, XP055239402, US ISSN: 1520-037X the whole document	58-64, 88-96, 104-107

X,P	Woodcliff Lake ET AL: "Eisai and Arena Pharmaceuticals Report Results of an Investigational Phase 2 Trial of Lorcaserin HCl as an Aid for Smoking Cessation --Trial Met Primary Efficacy Endpoint with Statistical Significance After 12 Weeks of Treatment", , 3 November 2014 (2014-11-03), XP055161629, Retrieved from the Internet: URL:http://files.shareholder.com/downloads/ARNA/3832921258x0x790638/D8F6EDCD-1B75-4DCD-A98F-FF410D84B7AB/ARNA_News_2014_11_3_General.pdf [retrieved on 2015-01-13] the whole document	1-35, 42-57, 65-76, 81-87, 97-103

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/058016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2015/066344 A1 (ARENA PHARM INC [US]) 7 May 2015 (2015-05-07) claims; example 4	1-107
X,P	FR 3 017 297 A1 (GREENPHARMA SAS [FR]; KEY OBS SAS [FR]) 14 August 2015 (2015-08-14) example 3	1-4, 15-35, 42-58, 65-72, 81-88, 93-107

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/058016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011014277 A1	20-01-2011	CA 2776160 A1	07-04-2011
		CN 102573821 A	11-07-2012
		JP 2013506678 A	28-02-2013
		US 2011014277 A1	20-01-2011
		WO 2011041451 A2	07-04-2011
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		AU 2012392187 A1	23-04-2015
		CA 2886875 A1	17-04-2014
		JP 2015534563 A	03-12-2015
		KR 20150070249 A	24-06-2015
		PH 12015500733 A1	01-06-2015
		US 2014213579 A1	31-07-2014
		US 2015297610 A1	22-10-2015
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		WO 2014058441 A1	17-04-2014
WO 2015066344 A1	07-05-2015	NONE	
FR 3017297 A1	14-08-2015	FR 3017296 A1	14-08-2015
		FR 3017297 A1	14-08-2015