

Description

Title of Invention: USE OF CENTANAFADINE IN TREATMENT OF ADHD SYMPTOMS

Technical Field

[0001] Field of the Disclosure

The disclosure relates generally to methods of using centanafadine in treatment of ADHD symptoms.

Background Art

[0002] Brief Description of Related Technology

According to the Attention Deficit Disorder Association, an estimated 9.8 percent (six million) of children and adolescents in the U.S. have attention-deficit/hyperactivity disorder (ADHD). ADHD is a neurodevelopmental disorder defined by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity [DSM-5].

[0003] These brain operations include important functions such as attention, concentration, memory, motivation and effort, learning from mistakes, impulsivity, hyperactivity, organization, and social skills. ADHD has no known cure and the majority of people do not outgrow it. Approximately two-thirds or more of children with ADHD continue to have symptoms and challenges in adulthood.

[0004] Executive function refers to a set of mental skills that help individuals manage and regulate their thoughts, actions, and emotions to achieve goals. These skills are essential for tasks such as planning, organizing, problem-solving, initiating tasks, inhibiting inappropriate responses, shifting between tasks, and maintaining focus and attention. Executive function plays a crucial role in various aspects of daily life, including academic achievement, social interactions, and overall functioning.

[0005] In ADHD (Attention Deficit Hyperactivity Disorder), deficits in executive function are commonly observed and contribute to the characteristic symptoms of the disorder. Individuals with ADHD often struggle with a) inhibition - difficulty inhibiting impulsive behaviors or responses, leading to actions without considering consequences or social norms; b) working memory - challenges in holding and manipulating information in mind, affecting tasks such as following instructions, remembering information, or completing multi-step tasks; c) flexibility - trouble adapting to changes in plans or situations, resulting in difficulties with transitioning between tasks or activities; d) planning and organization - struggles with planning ahead, setting goals, breaking tasks into manageable steps, and organizing materials or information; e) initiation and persistence - difficulty starting tasks or projects and maintaining effort over time, often leading to procrastination or incomplete work; and f) self-regulation -

challenges in regulating emotions and behavior, leading to mood swings, irritability, and difficulties managing frustration or anger.

[0006] Executive function plays a crucial role in the lives of children with ADHD, as it influences their ability to regulate behavior, manage tasks, and achieve goals. The above-mentioned deficits can manifest themselves as challenges with inhibitory control, such as having difficulty in resisting immediate temptations, interrupting others, or waiting their turn in activities. This can lead to social challenges, such as conflicts with peers or difficulties following rules in group settings. Further, deficits in executive function in children can significantly impact academic performance, social relationships, and daily functioning in individuals with ADHD. They may experience academic difficulties due to challenges in organizing materials, completing assignments, and following through on tasks. In social situations, impulsivity and poor inhibition can lead to interpersonal problems, while difficulties with planning and organization may affect daily routines and activities.

[0007] Understanding and addressing executive function deficits are crucial aspects of managing ADHD. Interventions such as behavioral strategies, cognitive-behavioral therapy, organizational skills training, and medication management aim to improve executive function skills and help individuals with ADHD function more effectively in various domains of life. Executive function can be evaluated using several methods.

[0008] ADHD-RS-5

The ADHD-RS-5 (Attention Deficit Hyperactivity Disorder Rating Scale-5) is a widely used tool for assessing symptoms of ADHD (Attention Deficit Hyperactivity Disorder) in children and adolescents aged 5 to 17 years. It's designed to be completed by parents, teachers, or clinicians who observe the child in various settings.

[0009] The scale consists of 18 items that cover both inattentive and hyperactive-impulsive symptoms of ADHD, as outlined in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). Each item is rated on a scale from 0 to 3, with higher scores indicating more severe symptoms.

[0010] The items assess various aspects of behavior such as attention span, impulsivity, hyperactivity, and organizational skills. The scale helps in providing a quantitative measure of ADHD symptoms, aiding clinicians in diagnosis, treatment planning, and monitoring treatment progress over time.

[0011] The ADHD-RS-5 is considered a valuable tool in clinical practice and research for its standardized approach to assessing ADHD symptoms and its ability to track symptom severity over time. It's often used in conjunction with other assessment measures and clinical interviews to provide a comprehensive evaluation of ADHD.

[0012] CGI-S-5

The CGI-S-5 scale, also known as the Clinical Global Impression-Severity Scale, is a

widely used assessment tool in clinical psychiatry and psychology. It's designed to provide a clinician's overall impression of a patient's severity of illness, taking into account all available information including the patient's history, symptoms, behavior, and the clinician's observations.

[0013] The CGI-S-5 scale typically consists of a single item rated on a seven-point scale, with each point representing a different level of severity. The ratings usually range from:

1. Normal, not at all ill
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most extremely ill patients

[0014] Clinicians use the CGI-S-5 scale to assess a wide range of psychiatric conditions, including mood disorders, anxiety disorders, psychotic disorders, and other mental health conditions. It provides a quick and straightforward way to communicate the clinician's impression of the patient's overall level of functioning and severity of symptoms, which can be useful for treatment planning, monitoring progress over time, and evaluating the effectiveness of interventions.

[0015] Connors 3

The Connors 3 (Connors Third Edition) is a comprehensive assessment tool used to evaluate attention-deficit/hyperactivity disorder (ADHD) and related behavioral, emotional, and academic problems in children and adolescents aged 6 to 18 years. It's often used by clinicians, educators, and researchers to aid in diagnosis, treatment planning, and monitoring progress over time.

[0016] The Connors 3 is designed to assess various aspects of a child's behavior, including inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and emotional distress. It consists of parent, teacher, and self-report forms, each containing a series of questions or statements about the child's behavior. Respondents rate the frequency and severity of each behavior on a scale, typically ranging from 0 (not true at all) to 3 (very much true).

[0017] The assessment generates several scores and indices, including:

1. ADHD Index: Provides an overall measure of ADHD symptom severity.
2. Inattention/Hyperactivity Index: Assesses specific symptoms of inattention and hyperactivity/impulsivity.
3. Learning Problems Index: Evaluates difficulties related to academic performance and learning.

4. Executive Functioning Index: Measures difficulties with organization, planning, and problem-solving.

5. Aggression Scale: Assesses aggressive behaviors and conduct problems.

6. Emotional Distress Scale: Measures emotional problems such as anxiety and depression.

[0018] Additionally, the Conners 3 provides T-scores and percentile ranks based on normative data, allowing clinicians to compare a child's scores to those of a representative sample of children of the same age and gender.

[0019] Overall, the Conners 3 is a valuable tool for assessing ADHD and related behavioral issues, providing insights into a child's functioning across various domains and informing treatment decisions. It's important to use the Conners 3 as part of a comprehensive evaluation that includes clinical interviews, observations, and other assessment measures.

[0020] While all three evaluation tools are used in the assessment of mental health and behavioral issues, they differ in their specific focus, structure, and scoring methods. The choice of scale depends on the goals of the assessment and the specific aspects of behavior or symptoms being targeted.

Summary of Invention

[0021] Several aspects of the disclosure are summarized below:

[0022] A method of treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0023] A method of treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0024] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0025] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0026] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical ac-

ceptable salt thereof.

- [0027] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0028] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0029] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD.
- [0030] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0031] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0032] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0033] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0034] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0035] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

- [0036] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0037] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0038] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0039] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0040] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0041] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0042] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0043] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0044] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

- [0045] Centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0046] Centanafadine or a pharmaceutically acceptable salt thereof for use or in a method of use described herein.
- [0047] A method of treating ADHD comprising administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof, wherein symptoms of ADHD are reduced at 1 week after beginning treatment, as assessed by a method selected from the group consisting of ADHD-RS-5 total raw score, CGI-S-ADHD score, Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, and Conners-3 Parent Short t-score Peer Relations Content Scale.
- [0048] Use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD as assessed by a method selected from the group consisting of ADHD-RS-5 total raw score, CGI-S-ADHD score, Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, and Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof, wherein symptoms of ADHD are reduced at 1 week after beginning administration.
- [0049] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 assessment by administering to a patient having ADHD a daily dose of about 150 mg to about 600 mg of centanafadine or a pharmaceutical acceptable salt thereof, wherein the patient is 5 to 17 years of age.
- [0050] Use of centanafadine or a pharmaceutical acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 assessment by administering to a patient having ADHD a daily dose of about 150 mg to about 600 mg of centanafadine or a pharmaceutical acceptable salt thereof, wherein the patient is 5 to 17 years of age.
- [0051] For the methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, figures, and examples, and claims provided herein.

[0052] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the methods are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

Brief Description of Drawings

[0053] For further facilitating the understanding of the present invention, 51 drawing figures are appended hereto.

[0054] [Fig.1]Figure 1 shows a high level summary of the clinical trials.

[0055] [Fig.2]Figure 2 shows a summary of the clinical trial designs.

[0056] [Fig.3]Figure 3 shows the key inclusion/exclusion criteria.

[0057] [Fig.4]Figure 4 shows the endpoints of the clinical trials.

[0058] [Fig.5]Figure 5 shows the subject disposition in adolescents.

[0059] [Fig.6]Figure 6 shows the subject disposition in children.

[0060] [Fig.7]Figure 7 shows the baseline demographics in adolescents.

[0061] [Fig.8]Figure 8 shows the baseline demographics in children.

[0062] [Fig.9]Figure 9 shows the least squares mean (LSM) change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents.

[0063] [Fig.10]Figure 10 shows the least squares mean (LSM) change from baseline in ADHD-RS-5 total raw score (MMRM) in children.

[0064] [Fig.11]Figure 11 shows the least squares mean (LSM) change from baseline in CGI-S-ADHD Score (MMRM) in adolescents.

[0065] [Fig.12]Figure 12 shows the least squares mean (LSM) change from baseline in CGI-S-ADHD Score (MMRM) in adolescents.

[0066] [Fig.13]Figure 13 shows dosing guidance.

[0067] [Fig.14A]Figure 14 A shows mean change from baseline in ADHD-RS-5 total raw score (MMRM) in children by baseline weights (20-35 kg).

[0068] [Fig.14B]Figure 14B shows mean change from baseline in ADHD-RS-5 total raw score (MMRM) in children by baseline weights (35-50 kg).

[0069] [Fig.14C]Figure 14C shows mean change from baseline in ADHD-RS-5 total raw score (MMRM) in children by baseline weights (> 50 kg).

[0070] [Fig.15]Figure 15 shows efficacy conclusions ADHD-RS-5 and CGI-S in adolescents.

[0071] [Fig.16]Figure 16 shows efficacy conclusions ADHD-RS-5 and CGI-S in children.

[0072] [Fig.17]Figure 17 shows LSM change from baseline in Conners-3 parent short t-score hyperactive/impulsive content scale (MMRM) in adolescents.

[0073] [Fig.18]Figure 18 shows LSM change from baseline in Conners-3 parent short t-score

- hyperactive/impulsive content scale (MMRM) vs. self-report in adolescents.
- [0074] [Fig.19]Figure 19 shows LSM change from baseline in Conners-3 parent short t-score hyperactive/impulsive content scale (MMRM) in children.
- [0075] [Fig.20]Figure 20 shows LSM change from baseline in Conners-3 parent short t-score inattentive content scale (MMRM) in adolescents.
- [0076] [Fig.21]Figure 21 shows LSM change from baseline in Conners-3 parent short t-score inattentive content scale (MMRM) vs self-report in adolescents.
- [0077] [Fig.22]Figure 22 shows LSM change from baseline in Conners-3 parent short t-score inattentive content scale (MMRM) in children.
- [0078] [Fig.23]Figure 23 shows LSM change from baseline in Conners-3 parent short t-score defiance/aggression content scale (MMRM) in adolescents.
- [0079] [Fig.24]Figure 24 shows LSM change from baseline in Conners-3 parent short t-score defiance/aggression content scale (MMRM) vs. self-report in adolescents.
- [0080] [Fig.25]Figure 25 shows LSM change from baseline in Conners-3 parent short t-score defiance/aggression content scale (MMRM) in children.
- [0081] [Fig.26]Figure 26 shows LSM change from baseline in Conners-3 parent short t-score executive functioning content scale (MMRM) in adolescents.
- [0082] [Fig.27]Figure 27 shows LSM change from baseline in Conners-3 parent short t-score executive functioning content scale (MMRM) in children.
- [0083] [Fig.28]Figure 28 shows LSM change from baseline in Conners-3 parent short t-score learning problems content scale (MMRM) in adolescents.
- [0084] [Fig.29]Figure 29 shows LSM change from baseline in Conners-3 parent short t-score learning problems content scale (MMRM) vs self-report in adolescents.
- [0085] [Fig.30]Figure 30 shows LSM change from baseline in Conners-3 parent short t-score learning problems content scale (MMRM) in children.
- [0086] [Fig.31]Figure 31 shows LSM change from baseline in Conners-3 parent short t-score peer relations content scale (MMRM) in adolescents.
- [0087] [Fig.32]Figure 32 shows LSM change from baseline in Conners-3 parent short t-score peer relations content scale (MMRM) vs family relations self-report in adolescents.
- [0088] [Fig.33]Figure 33 shows LSM change from baseline in Conners-3 parent short t-score peer relations content scale (MMRM) in children.
- [0089] [Fig.34]Figure 34 shows subjects achieving a 30%, 40%, or 50% response or CGI-C-ADHD of 1 or 2 at week 6 in adolescents, last observation carried forward (LOCF).
- [0090] [Fig.35]Figure 35 shows subjects achieving a 30%, 40%, or 50% response or CGI-C-ADHD of 1 or 2 at week 6 in children, last observation carried forward (LOCF).
- [0091] [Fig.36A]Figure 36A shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents by sex assigned at birth (female).
- [0092] [Fig.36B]Figure 36B shows LSM Change from baseline in ADHD-RS-5 total raw

- score (MMRM) in adolescents by sex assigned at birth (male).
- [0093] [Fig.37A]Figure 37A shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in children by sex assigned at birth (female).
- [0094] [Fig.37B]Figure 37B shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in children by sex assigned at birth (male).
- [0095] [Fig.38A]Figure 38A shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents by race (black).
- [0096] [Fig.38B]Figure 38B shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents by race (white).
- [0097] [Fig.39A]Figure 39A shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in children by race (black).
- [0098] [Fig.39B]Figure 39B shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in children by race (white).
- [0099] [Fig.40A]Figure 40A shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents by ethnicity (Hispanic and Latino).
- [0100] [Fig.40B]Figure 40B shows LSM Change from baseline in ADHD-RS-5 total raw score (MMRM) in adolescents by ethnicity (non Hispanic/Latino).
- [0101] [Fig.41A]Figure 41A shows LSM change from baseline in ADHD-RS-5 total raw score (MMRM) in children by ethnicity (Hispanic and Latino).
- [0102] [Fig.41B]Figure 41B shows LSM change from baseline in ADHD-RS-5 total raw score (MMRM) in children by ethnicity (non Hispanic/Latino).
- [0103] [Fig.42]Figure 42 shows quality of life assessment at Week 6 - pediatric.
- [0104] [Fig.43]Figure 43 shows ADHD-RS-5 impairment subscale scores at week 6.
- [0105] [Fig.44]Figure 44 shows incidence of adverse events (AEs) - all causalities - adolescents.
- [0106] [Fig.45]Figure 45 shows incidence of adverse events (AEs) - all causalities - children.
- [0107] [Fig.46A]Figure 46A shows most common treatment emergent adverse events (TEAEs) (> 2%) in CTN and greater than placebo - adolescents.
- [0108] [Fig.46B]Figure 46B shows most common treatment emergent adverse events (TEAEs) (> 2%) in CTN and greater than placebo - children.
- [0109] [Fig.47]Figure 47 shows most common treatment emergent adverse events (TEAEs) (> 2%) in CTN and greater than placebo - adolescents.
- [0110] [Fig.48]Figure 48 shows most common treatment emergent adverse events (TEAEs) (> 2%) in CTN and greater than placebo - children.
- [0111] [Fig.49]Figure 49 shows adverse events related to suicidality.
- [0112] [Fig.50]Figure 50 shows incidence of treatment emergent adverse events (TEAEs) - abuse potential related.
- [0113] [Fig.51]Figure 51 shows adverse events (AEs) of special interest (rash) - children and

adolescents.

Description of Embodiments

[0114] **DETAILED DESCRIPTION**

(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0] hexane (centanafadine) is an unbalanced triple reuptake inhibitor with the most potency towards norepinephrine reuptake (NE), one-sixth as much towards dopamine reuptake (DA), and one-fourteenth as much towards serotonin reuptake (5-HT). The present disclosure provides methods of treating ADHD comprising administering centanafadine or a pharmaceutical acceptable salt thereof to a patient having ADHD.

[0115] Pharmaceutically acceptable salts are known in the art and include salts that are physiologically acceptable at the dosage amount and form to be administered, for example, hydrochloride salts. As used herein,

"(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane" is also to be understood as embracing the compound in crystalline and amorphous form including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" may be used interchangeably herein, and are meant to include all crystalline forms of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrides), and conformational polymorphs, as well as mixtures thereof, unless a particular crystalline form is referred to. In embodiments, CTN is provided as a CTN hydrochloride salt. In the description herein, the amounts of CTN, weight percentages of CTN, or ranges thereof in the pharmaceutical formulations, beads, core particles, etc., are applicable to centanafadine free base, as well as to pharmaceutically acceptable salts thereof, such that any description by weight should be viewed as both for CTN free base, and in addition in the alternative as description applicable to a pharmaceutically acceptable salt form, unless specified otherwise.

[0116] In some embodiments, the disclosed methods comprise administering centanafidine hydrochloride.

[0117] Patients

[0118] The disclosed methods comprise treating ADHD and reducing ADHD symptoms in a patient having ADHD. In some embodiments, the patient is a child or adolescent. As used herein, "child" or "children" refer to patients 4 to 12 years of age (e.g., 4, 5, 6, 7, 8, 9, 10, 11, or 12 years of age). In some embodiments, the child is 6 to 12 years of age (e.g., 4 to 5 years of age). As used herein, "adolescent" refers to patients 13 to 17 years

of age (e.g., 13, 14, 15, 16, or 17 years of age), for example, 15 to 17 years of age. In some embodiments, the patient is 5 to 17 years of age.

- [0119] In some embodiments, the patient having ADHD does not have a comorbid diagnosis of Tourette's Disorder, severe generalized anxiety disorder (GAD), panic disorder, conduct disorder, psychosis, post-traumatic stress disorder (PTSD), bipolar disorder, autistic spectrum disorders (ASD), severe oppositional defiant disorder (ODD), severe obsessive-compulsive disorder (OCD), or major depressive disorder (MDD) with current major depressive episode (MDE).
- [0120] In some embodiments, the patient has not derived a therapeutic benefit from adequate courses of two classes of therapy for ADHD during the patient's lifetime.
- [0121] In some embodiments, the patient is female. In some embodiments, the patient is male. In some embodiments, patient is Caucasian. In some embodiments, the patient is not Hispanic or Latino.
- [0122] Reduction of ADHD Symptoms
- [0123] The disclosure provides methods of treating ADHD and reducing ADHD symptoms in a patient. In some embodiments, the disclosed methods provide treatment of ADHD and a reduction in ADHD systems in a child or adolescent patient having ADHD. The reduction in ADHD symptoms is measured using an assessment tool suitable for the patient population. In some embodiments, the reduction of symptoms is measured using an ADHD-RS-5 assessment. In some embodiments, the reduction of symptoms is measured using a CGI-S-ADHD assessment. In some embodiments, the patient having ADHD has an ADHD-RS-5 total raw score at initiation of treatment of at least 28. In some embodiments, the patient having ADHD has a CGI-S score at initiation of treatment of at least 4.
- [0124] In some embodiments, the disclosed methods comprise measuring the treatment of ADHD and/or reduction of ADHD symptoms by a Conners-3 assessment. In embodiments using a Conners-3 assessment, the assessment is used to evaluate one or more the following aspects of ADHD: hyperactivity; inattention; defiance/aggression; executive function; learning problems; and peer relations. In some embodiments, the treatment and/or reduction of symptoms is measured using a Conners-3 Parent Short-t-score of the attribute being assessed. In some embodiments, the treatment and/or reduction of symptoms is measured using a Conners-3 Self Report t-score of the attribute being assessed. For example, in some embodiments, a Conners-3 assessment comprises Conners-3 Parent Short t-score Executive Functioning Content Scale. As used herein, "a Conners-3 assessment" refers to either the Parent Short t-score or the Self Report t-score assessment, as appropriate, for the given assessment.
- [0125] In some embodiments, the reduction of ADHD symptoms is achieved as soon as one week after administration. In some embodiments, the reduction of symptoms is

achieved at week 6 after beginning treatment. In some embodiments, the reduction of symptoms is achieved at week 5 after beginning treatment. In some embodiments, the reduction of symptoms is achieved at week 4 after beginning treatment. In some embodiments, the reduction of symptoms is achieved at week 3 after beginning treatment. In some embodiments, the reduction of symptoms is achieved at week 2 after beginning treatment. In some embodiments, the reduction of symptoms is achieved at week 1 after beginning treatment.

- [0126] In some embodiments, the assessment comprises a Conners-3 Parent Short t-score Executive Functioning Content Scale. In some embodiments, comprising a Conners-3 Parent Short t-score Executive Functioning Content Scale, the mean score of the Conners-3 Parent Short t-score Executive Functioning Content Scale is reduced by at least 4 after 6 weeks of treatment.
- [0127] The disclosed methods can provide a statistically significant reduction in ADHD symptoms compared to placebo. The reduction of ADHD symptoms is considered statistically significant when the p-value is less than 0.05 as compared to placebo. In some embodiments, the reduction of ADHD symptoms compared to placebo has a p-value of less than 0.01. In some embodiments, the reduction of ADHD symptoms compared to placebo has a p-value of 0.0003 or less (e.g., 0.0002 or 0.0001 or less).
- [0128] In some embodiments, the disclosed methods provide a statistically significant (e.g., p-value of less than 0.05) reduction of ADHD symptoms compared to placebo by week 6 after beginning treatment. In some embodiments, the disclosed methods provide a statistically significant (e.g., p-value of less than 0.05) reduction of ADHD symptoms compared to placebo at week 1 after beginning treatment. In some embodiments, the disclosed methods provide a statistically significant reduction of ADHD symptoms compared to placebo at week 1 after beginning treatment, wherein the p-value is less than 0.01.
- [0129] In some embodiments, the reduction of ADHD symptoms is self-reported from the patient using a suitable Self Report t-score corresponding to the attribute being evaluated (e.g., Conners-3 Self Report Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Self Report Short t-score Inattentive Content Scale, Conners-3 Self Report Short t-score Defiance/Aggression Content Scale, Conners-3 Self Report Short t-score Executive Functioning Content Scale, Conners-3 Self Report Short t-score Learning Problems Content Scale, Conners-3 Self Report Short t-score Peer Relations Content Scale, and a combination thereof).
- [0130] In some embodiments, the reduction of ADHD symptoms is reported by a parent using a suitable Parent Report t-score corresponding to the attribute being evaluated (e.g., a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score

Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, Conners-3 Parent Short t-score Peer Relations Content Scale, and a combination thereof).

- [0131] In some embodiments, the reduction of symptoms is both self-reported and reported by the parent using the t-scores from the corresponding reporting tools. For example, in some embodiments the disclosed methods comprise administering centanafadine or a pharmaceutically acceptable salt thereof, wherein the patient is 5 to 12 years of age, the reduction of symptoms is self-reported from the patient and separately reported by the parent. In addition, in some embodiments, the patient is an adolescent having an age of 13 to 17 years and the reduction of symptoms is self-reported from the patient and separately reported by a parent.
- [0132] Applicant has surprisingly discovered that in some embodiments that the reduction of symptoms reported by the parent correlate to the reduction of symptoms reported by the patient (e.g., child or adolescent). This contrasts with typical assessments in methods of treating ADHD using other active agents. It is well established when assessing indicators of children's mental health that discrepancies between self-reported results and those of a caregiver or parent can be problematic (e.g., Caqueo-Urizar, Alejandra, et al. "Children's mental health: Discrepancy between child self-reporting and parental reporting." Behavioral Sciences 12.10 (2022): 401). As such, correlation between child self-reports and caregiver (e.g. parent) reports is desirable. The statistical correlation is measured using a suitable statistical analysis (e.g., Pearson's Correlation Coefficient, Spearman's Rank Correlation, Kendall's Tau, Coefficient of Determination, Regression Analysis, Analysis of Variance (ANOVA)). In some embodiments, the statistically significant correlation is observed as soon as week 1 after administration of CTN and is observed thereafter (e.g., 2, 3, 4, 5, 6 weeks after administration).
- [0133] In some embodiments, the Conners-3 Parent Short t-score Inattention Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0134] In some embodiments, the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0135] In some embodiments, the Conners-3 Parent Short t-score Executive Functioning Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical sig-

nificance is determined by a p-value of less than 0.05.

- [0136] In some embodiments, the Conners-3 Parent Short t-score Learning Problems Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0137] In some embodiments, the Conners-3 Parent Short t-score Inattention Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0138] In some embodiments, the Conners-3 Self Report Short t-score Inattention Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0139] In some embodiments, the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0140] In some embodiments, the Conners-3 Self Report Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0141] In some embodiments, the Conners-3 Parent Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0142] In some embodiments, the Conners-3 Parent Short t-score Learning Problems Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0143] In some embodiments, the Conners-3 Self Report Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0144] In some embodiments, adolescents receiving 328.8 mg CTN QD self-report a reduction of ADHD symptoms (e.g., hyperactive/impulsive) using the Conners-3 parent short t-score, which correlate with the reporting of reduction of symptoms by the caregiver (p value of less than 0.05, less than 0.01, less than 0.001, or less than 0.0001). See Figure 18. The statistically significant correlation is observed even after 1

week of treatment.

- [0145] In some embodiments, adolescents receiving 328.8 mg CTN self-report a reduction of ADHD symptoms (e.g., inattention) using the Conners-3 parent short t-score inattentive content scale (MMRM) assessment, which correlate with the reporting of reduction of symptoms by the caregiver (p value of less than 0.05, less than 0.01, less than 0.001, or less than 0.0001). See Figure 21. The statistically significant correlation is observed even after 1 week of treatment.
- [0146] Dosing
- [0147] The disclosed methods comprise administering an effective amount of CTN or a pharmaceutical salt thereof. In some embodiments, the disclosed methods comprise administering a daily dose of about 150 mg to about 600 mg of centanafadine or a pharmaceutically acceptable salt thereof. In some embodiments, the disclosed methods comprise administering a daily dose of at least 165 mg. For example, in some embodiments, the disclosed methods comprise administering a daily dose of 165 mg to 600 mg CTN, or 200 mg to 400 mg CTN, or 300 mg to 350 mg CTN. In some embodiments, the disclosed methods comprise administering about 330 mg CTN. For example, in some embodiments, the disclosed methods comprise administering 328.8 mg CTN.
- [0148] An effective amount of CTN is based on the patient's weight. By way of example, in some embodiments a patient weighing at least 20 kg and less than 35 kg is administered a dose of at least 150 mg CTN, or at least 150 mg and less than 240 mg CTN, or in a range of 150 mg to 160 mg CTN, or about 165 mg (e.g., 164.4 mg) CTN.
- [0149] In some embodiments, a patient weighing at least 35 kg and up to 50 kg is administered a dose of at least 240 mg CTN, or at least 240 mg and up to 320 mg CTN, or in a range of 240 mg to 260 mg CTN, or about 245 mg (e.g., 246.6 mg).
- [0150] In some embodiments, a patient weighing at least 50 kg is administered a dose of greater than 240 mg CTN, or greater than 240 mg and up to 400 mg CTN, or in a range of 320 mg to 340 mg CTN, or about 330 mg (e.g., 328.8 mg) CTN.
- [0151] In some embodiments, the disclosed methods comprise administering a daily dose of about 150 mg to about 600 mg of centanafadine or a pharmaceutically acceptable salt thereof, wherein the patient is 5 to 17 years of age.
- [0152] In some embodiments, the disclosed methods comprise administering CTN once-daily (QD) to provide the daily dose. In some embodiments, the disclosed methods comprise administering CTN twice-daily (BID) to provide the daily dose.
- [0153] The disclosed methods comprise administering CTN in a suitable manner in accordance with dosage form administered. In some embodiments, the daily dose is administered once per day. In some embodiments, the effective amount or at least a portion is administered in an extended-release dosage form. Examples of suitable

dosage extended-release dosage forms are described in U.S. Patent Nos. 11,564,885, and 11,759,426, or in U.S. Patent Publication No. 2023/0338293 A1.

[0154] The methods are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described below (including those shown in the figures), unless stated otherwise.

[0155] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique (e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[0156] As used herein, the term “comprising” indicates the potential inclusion of other agents, elements, steps, or features, in addition to those specified.

[0157] Centanafadine, including its pharmaceutically acceptable salts, has been reported to be useful in treatment of ADHD. Described herein are methods of using centanafadine, and effective dosing thereof, to achieve reduction in particular ADHD symptoms in children and adolescents.

[0158] **EMBODIMENTS**

1. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0159] 2. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0160] 3. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0161] 4. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

[0162] 5. In an embodiment, the disclosure provides a method of treating ADHD and

reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

- [0163] 6. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0164] 7. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0165] 8. In an embodiment, the disclosure provides a method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0166] 9. In an embodiment, the disclosure provides the method of any one of embodiments 1-8, wherein the reduction of symptoms is achieved at week 6 after beginning treatment.
- [0167] 10. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the reduction of symptoms is achieved at week 5 after beginning treatment.
- [0168] 11. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the reduction of symptoms is achieved at week 4 after beginning treatment.
- [0169] 12. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the reduction of symptoms is achieved at week 3 after beginning treatment.
- [0170] 13. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the reduction of symptoms is achieved at week 2 after beginning treatment.
- [0171] 14. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the reduction of symptoms is achieved at week 1 after beginning treatment.
- [0172] 15. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is an adolescent having an age in a range of 13 to 17 years.
- [0173] 16. In an embodiment, the disclosure provides the method of any one of embodiments 1-14, wherein the patient is a child having an age in a range of 6 to 12 years.

- [0174] 17. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is a child having an age in a range of 4 to 5 years.
- [0175] 18. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the effective amount is a daily dose of at least 165 mg, or in a range of 165 mg to 600mg, or 200 mg to 400 mg, or 300 mg to 350 mg, or about 330 mg, or 328.8 mg.
- [0176] 19. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the effective amount is a daily dose based on the patient's weight.
- [0177] 20. In an embodiment, the disclosure provides the method of embodiment 18, wherein a patient with weight at least 20 kg and less than 35 kg is administered a dose of at least 150 mg, or at least 150 mg and less than 240 mg, or in a range of 150 mg to 160 mg, or about 165 mg, or 164.4mg.
- [0178] 21. In an embodiment, the disclosure provides the method of embodiment 18, wherein a patient with weight at least 35 kg and up to 50 kg is administered a dose of at least 240 mg, or at least 240 mg and up to 320 mg, or in a range of 240 mg to 260 mg, or about 245 mg, or 246.6 mg.
- [0179] 22. In an embodiment, the disclosure provides the method of embodiment 18, wherein a patient with weight at least 50 kg is administered a dose of greater than 240 mg, or greater than 240 mg and up to 400 mg, or in a range of 320 mg to 340 mg, or about 330 mg, or 328.8 mg.
- [0180] 23. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the daily dose is administered once per day.
- [0181] 24. The method of any one of the preceding embodiments, wherein the effective amount or at least a portion thereof is administered in an extended release dosage form.
- [0182] 25. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the extended release dosage form is a dosage form described in, or has a formulation as described in US Patent No. 11,564,885, or US Patent No. 11,759,426, or US Patent Publication 2023/0338293 A1.
- [0183] 26. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient having ADHD has a ADHD-RS-5 total raw score at initiation of treatment of at least 28.
- [0184] 27. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient having ADHD has a CGI-S score at initiation of treatment of at least 4.
- [0185] 28. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient having ADHD does not have a comorbid

diagnosis of: Tourette's Disorder, severe GAD, panic disorder, conduct disorder, psychosis, PTSD, bipolar disorder, ASD, severe ODD, severe OCD, or MDD with current MDE.

- [0186] 29. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient has not derived a therapeutic benefit from adequate courses of 2 classes of therapy for ADHD during the subject's lifetime.
- [0187] 30. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is female.
- [0188] 31. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is male.
- [0189] 32. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is Caucasian.
- [0190] 33. In an embodiment, the disclosure provides the method of any one of the preceding embodiments, wherein the patient is not Hispanic or Latino.
- [0191] 34. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0192] 35. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0193] 36. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0194] 37. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0195] 38. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

- [0196] 39. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0197] 40. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0198] 41. In an embodiment, the disclosure provides the use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0199] 42. In an embodiment, the disclosure provides the use of any one of embodiments 34- 41, wherein the reduction of symptoms is achieved at week 6 after beginning treatment.
- [0200] 43. In an embodiment, the disclosure provides the use of any one of embodiments 34- 42, wherein the reduction of symptoms is achieved at week 5 after beginning treatment.
- [0201] 44. In an embodiment, the disclosure provides the use of any one of embodiments 34- 43, wherein the reduction of symptoms is achieved at week 4 after beginning treatment.
- [0202] 45. In an embodiment, the disclosure provides the use of any one of embodiments 34- 44, wherein the reduction of symptoms is achieved at week 3 after beginning treatment.
- [0203] 46. In an embodiment, the disclosure provides the use of any one of embodiments 34- 45, wherein the reduction of symptoms is achieved at week 2 after beginning treatment.
- [0204] 47. In an embodiment, the disclosure provides the use of any one of embodiments 34- 46, wherein the reduction of symptoms is achieved at week 1 after beginning treatment.
- [0205] 48. In an embodiment, the disclosure provides the use of any one of embodiments 34- 47, wherein the patient is an adolescent having an age in a range of 13 to 17 years.
- [0206] 49. In an embodiment, the disclosure provides the use of any one of embodiments 34- 48, wherein the patient is a child having an age in a range of 6 to 12 years.
- [0207] 50. In an embodiment, the disclosure provides the use of any one of embodiments

- 34- 49, wherein the patient is a child having an age in a range of 4 to 5 years.
- [0208] 51. In an embodiment, the disclosure provides the use of any one of embodiments 34- 50, wherein the effective amount is a daily dose of at least 165 mg, or in a range of 165 mg to 600mg, or 200 mg to 400 mg, or 300 mg to 350 mg, or about 330 mg, or 328.8 mg.
- [0209] 52. In an embodiment, the disclosure provides the use of any one of embodiments 34- 51, wherein the effective amount is a daily dose based on the patient's weight.
- [0210] 53. In an embodiment, the disclosure provides the use of embodiment 52, wherein a patient with weight at least 20 kg and less than 35 kg is administered a dose of at least 150 mg, or at least 150 mg and less than 240 mg, or in a range of 150 mg to 160 mg, or about 165 mg, or 164.4mg.
- [0211] 54. In an embodiment, the disclosure provides the use of embodiment 52, wherein a patient with weight at least 35 kg and up to 50 kg is administered a dose of at least 240 mg, or at least 240 mg and up to 320 mg, or in a range of 240 mg to 260 mg, or about 245 mg, or 246.6 mg.
- [0212] 55. In an embodiment, the disclosure provides the use of embodiment 52, wherein a patient with weight at least 50 kg is administered a dose of greater than 240 mg, or greater than 240 mg and up to 400 mg, or in a range of 320 mg to 340 mg, or about 330 mg, or 328.8 mg.
- [0213] 56. In an embodiment, the disclosure provides the use of any one of embodiments 34- 55, wherein the daily dose is administered once per day.
- [0214] 57. In an embodiment, the disclosure provides the use of any one of embodiments 34- 56, wherein the effective amount or at least a portion thereof is administered in an extended release dosage form.
- [0215] 58. In an embodiment, the disclosure provides the use of any one of embodiments 34- 57, wherein the extended release dosage form is a dosage form described in, or has a formulation as described in US Patent No. 11,564,885, or US Patent No. 11,759,426, or US Patent Publication 2023/0338293 A1.
- [0216] 59. In an embodiment, the disclosure provides the use of any one of embodiments 34- 58, wherein the patient having ADHD has a ADHD-RS-5 total raw score at initiation of treatment of at least 28.
- [0217] 60. In an embodiment, the disclosure provides the use of any one of embodiments 34- 59, wherein the patient having ADHD has a CGI-S score at initiation of treatment of at least 4.
- [0218] 61. In an embodiment, the disclosure provides the use of any one of embodiments 34- 60, wherein the patient having ADHD does not have a comorbid diagnosis of: Tourette's Disorder, severe GAD, panic disorder, conduct disorder, psychosis, PTSD, bipolar disorder, ASD, severe ODD, severe OCD, or MDD with current MDE.

- [0219] 62. In an embodiment, the disclosure provides the use of any one of embodiments 34- 61, wherein the patient has not derived a therapeutic benefit from adequate courses of 2 classes of therapy for ADHD during the subject's lifetime.
- [0220] 63. In an embodiment, the disclosure provides the use of any one of embodiments 34- 62, wherein the patient is female.
- [0221] 64. In an embodiment, the disclosure provides the use of any one of embodiments 34- 63, wherein the patient is male.
- [0222] 65. In an embodiment, the disclosure provides the use of any one of embodiments 34- 64, wherein the patient is Caucasian.
- [0223] 66. In an embodiment, the disclosure provides the use of any one of embodiments 34- 65, wherein the patient is not Hispanic or Latino.
- [0224] 67. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by an ADHD-RS-5 total raw score at 1 week after beginning treatment by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0225] 68. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a CGI-S-ADHD score by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0226] 69. In an embodiment, the disclosure provides entanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0227] 70. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Inattentive Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0228] 71. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Defiance/Aggression Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0229] 72. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Executive Functioning Content Scale by

administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.

- [0230] 73. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Learning Problems Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0231] 74. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use in treating ADHD and reducing ADHD symptoms as measured by a Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof.
- [0232] 75. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof for use in any one of embodiments 67- 74, wherein the reduction of symptoms is achieved at week 6 after beginning treatment.
- [0233] 76. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 75, wherein the reduction of symptoms is achieved at week 5 after beginning treatment.
- [0234] 77. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 76, wherein the reduction of symptoms is achieved at week 4 after beginning treatment.
- [0235] 78. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 77, wherein the reduction of symptoms is achieved at week 3 after beginning treatment.
- [0236] 79. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 78, wherein the reduction of symptoms is achieved at week 2 after beginning treatment.
- [0237] 80. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 79, wherein the reduction of symptoms is achieved at week 1 after beginning treatment.
- [0238] 81. The centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 80, wherein the patient is an adolescent having an age in a range of 13 to 17 years.
- [0239] 82. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 81, wherein the patient is a child having an age in a range of 6 to 12 years.
- [0240] 83. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 82, wherein the

patient is a child having an age in a range of 4 to 5 years.

- [0241] 84. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 83, wherein the effective amount is a daily dose of at least 165 mg, or in a range of 165 mg to 600mg, or 200 mg to 400 mg, or 300 mg to 350 mg, or about 330 mg, or 328.8 mg.
- [0242] 85. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 84, wherein the effective amount is a daily dose based on the patient's weight.
- [0243] 86. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of embodiment 85, wherein a patient with weight at least 20 kg and less than 35 kg is administered a dose of at least 150 mg, or at least 150 mg and less than 240 mg, or in a range of 150 mg to 160 mg, or about 165 mg, or 164.4mg.
- [0244] 87. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of embodiment 85, wherein a patient with weight at least 35 kg and up to 50 kg is administered a dose of at least 240 mg, or at least 240 mg and up to 320 mg, or in a range of 240 mg to 260 mg, or about 245 mg, or 246.6 mg.
- [0245] 88. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of embodiment 85, wherein a patient with weight at least 50 kg is administered a dose of greater than 240 mg, or greater than 240 mg and up to 400 mg, or in a range of 320 mg to 340 mg, or about 330 mg, or 328.8 mg.
- [0246] 89. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 88, wherein the daily dose is administered once per day.
- [0247] 90. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 89, wherein the effective amount or at least a portion thereof is administered in an extended release dosage form.
- [0248] 91. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 90, wherein the extended release dosage form is a dosage form described in, or has a formulation as described in US Patent No. 11,564,885, or US Patent No. 11,759,426, or US Patent Publication 2023/0338293 A1.
- [0249] 92. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 91, wherein the patient having ADHD has a ADHD-RS-5 total raw score at initiation of treatment of at least 28.

- [0250] 93. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 92, wherein the patient having ADHD has a CGI-S score at initiation of treatment of at least 4.
- [0251] 94. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 93, wherein the patient having ADHD does not have a comorbid diagnosis of: Tourette's Disorder, severe GAD, panic disorder, conduct disorder, psychosis, PTSD, bipolar disorder, ASD, severe ODD, severe OCD, or MDD with current MDE.
- [0252] 95. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 94, wherein the patient has not derived a therapeutic benefit from adequate courses of 2 classes of therapy for ADHD during the subject's lifetime.
- [0253] 96. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 95, wherein the patient is female.
- [0254] 97. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 96, wherein the patient is male.
- [0255] 98. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 97, wherein the patient is Caucasian.
- [0256] 99. In an embodiment, the disclosure provides the centanafadine or a pharmaceutically acceptable salt thereof use of any one of embodiments 67- 98, wherein the patient is not Hispanic or Latino.
- [0257] 100. In an embodiment, the disclosure provides centanafadine or a pharmaceutically acceptable salt thereof for use or in a method of use described herein.
- [0258] 101. The method of any one of the preceding embodiments, wherein the reduction of symptoms is self-reported from the patient.
- [0259] 102. The method of any one of the preceding embodiments, wherein the reduction of symptoms is reported by a parent.
- [0260] 103. The method of embodiment 102, wherein the reduction of symptoms reported by a parent correlate with the reduction of symptoms reported by the patient.
- [0261] 104. The method of embodiment 103, wherein the correlation is statistically significant.
- [0262] 105. A method of treating ADHD and reducing ADHD symptoms comprising administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof, wherein symptoms of ADHD are reduced at 1 week after beginning treatment, as assessed by a method selected from the group consisting

of ADHD-RS-5 total raw score, CGI-S-ADHD score, Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, and Conners-3 Parent Short t-score Peer Relations Content Scale.

- [0263] 106. The method of any one of the preceding embodiments 105, wherein the symptoms are further reduced at week 6 after beginning treatment.
- [0264] 107. The method of embodiment 105 or 106, wherein the symptoms are further reduced at week 5 after beginning treatment.
- [0265] 108. The method of any one of embodiments 105-107, wherein the symptoms are further reduced at week 4 after beginning treatment.
- [0266] 109. The method of any one of embodiments 105-108, wherein the symptoms are further reduced at week 3 after beginning treatment.
- [0267] 110. The method of any one of embodiments 105-109, wherein the symptoms are further reduced at week 2 after beginning treatment.
- [0268] 111. The method of any one of embodiments 105-110, wherein the patient is an adolescent having an age in a range of 13 to 17 years.
- [0269] 112. The method of any one of embodiments 105-111, wherein the patient is a child having an age in a range of 6 to 12 years.
- [0270] 113. The method of any one of embodiments 105-112, wherein the patient is a child having an age in a range of 4 to 5 years.
- [0271] 114. The method of any one of embodiments 105-113, wherein the effective amount is a daily dose of at least 165 mg, or in a range of 165 mg to 600 mg, or 200 mg to 400 mg, or 300 mg to 350 mg, or about 330 mg, or 328.8 mg.
- [0272] 115. The method of any one of embodiments 105-114, wherein the effective amount is a daily dose based on the patient's weight.
- [0273] 116. The method of embodiment 115, wherein a patient with weight at least 20 kg and less than 35 kg is administered a dose of at least 150 mg, or at least 150 mg and less than 240 mg, or in a range of 150 mg to 160 mg, or about 165 mg, or 164.4mg.
- [0274] 117. The method of embodiment 115, wherein a patient with weight at least 35 kg and up to 50 kg is administered a dose of at least 240 mg, or at least 240 mg and up to 320 mg, or in a range of 240 mg to 260 mg, or about 245 mg, or 246.6 mg.
- [0275] 118. The method of embodiment 115, wherein a patient with weight at least 50 kg is administered a dose of greater than 240 mg, or greater than 240 mg and up to 400 mg, or in a range of 320 mg to 340 mg, or about 330 mg, or 328.8 mg.
- [0276] 119. The method of any one of embodiments 1-118, wherein the daily dose is administered once per day.

- [0277] 120. The method of any one of embodiments 24-119, wherein the extended release dosage form comprises a plurality of centanafadine (CTN) beads, the plurality of CTN beads each comprising a core particle comprising CTN or a pharmaceutically acceptable salt thereof and an excipient.
- [0278] 121. The method of any one of embodiments 1-120, wherein the patient has an ADHD-RS-5 total raw score at initiation of treatment of at least 28.
- [0279] 122. The method of any one of embodiments 1-121, wherein the patient has a CGI-S score at initiation of treatment of at least 4.
- [0280] 123. The method of any one of embodiments 1-122, wherein the patient does not have a comorbid diagnosis selected from: Tourette's Disorder, severe GAD, panic disorder, conduct disorder, psychosis, PTSD, bipolar disorder, ASD, severe ODD, severe OCD, and MDD with current MDE.
- [0281] 124. The method of any one of embodiments 1-123, wherein the patient has not derived a therapeutic benefit from adequate courses of 2 classes of therapy for ADHD during the patient's lifetime.
- [0282] 125. The method of any one of embodiments 1-124, wherein the patient is female.
- [0283] 126. The method of any one of embodiments 1-124, wherein the patient is male.
- [0284] 127. The method of any one of embodiments 1-126, wherein the patient is Caucasian.
- [0285] 128. The method of any one of embodiments 1-127, wherein the patient is not Hispanic or Latino.
- [0286] 129. The use of centanafadine or a pharmaceutically acceptable salt thereof for treating ADHD as assessed by a method selected from the group consisting of ADHD-RS-5 total raw score, CGI-S-ADHD score, Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, and Conners-3 Parent Short t-score Peer Relations Content Scale by administering to a patient having ADHD an effective amount of centanafadine or a pharmaceutical acceptable salt thereof, wherein symptoms of ADHD are reduced at 1 week after beginning administration.
- [0287] 130. A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 assessment by administering to a patient having ADHD a daily dose of about 150 mg to about 600 mg of centanafadine or a pharmaceutical acceptable salt thereof, wherein the patient is 5 to 17 years of age.
- [0288] 131. The method of embodiment 130, wherein the Conners-3 assessment is selected from the group consisting of a Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-

score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, Conners-3 Parent Short t-score Peer Relations Content Scale, and a combination thereof.

- [0289] 132. The method of any one of the preceding embodiments, wherein the Conners-3 assessment is selected from the group consisting of a Conners-3 Self Report Short t-score Hyperactive/Impulsive Content Scale, Conners-3 Self Report Short t-score Inattentive Content Scale, Conners-3 Self Report Short t-score Defiance/Aggression Content Scale, Conners-3 Self Report Short t-score Executive Functioning Content Scale, Conners-3 Self Report Short t-score Learning Problems Content Scale, Conners-3 Self Report Short t-score Peer Relations Content Scale, and a combination thereof.
- [0290] 133. The method of any one of the preceding embodiments, wherein the Conners-3 assessment comprises Conners-3 Parent Short t-score Executive Functioning Content Scale.
- [0291] 134. The method of any one of the preceding embodiments, wherein the mean score of the Conners-3 Parent Short t-score Executive Functioning Scale is reduced by at least 4 after 6 weeks of treatment.
- [0292] 135. The method of any one of the preceding embodiments, wherein the reduction of symptoms is statistically significant compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0293] 136. The method of any one of the preceding embodiments, wherein the reduction of symptoms is statistically significant compared to placebo at week 1 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0294] 137. The method of any one of the preceding embodiments, wherein the reduction of symptoms is statistically significant compared to placebo at week 1 after beginning treatment, wherein the statistical significance is determined by a p-value of less than 0.01.
- [0295] 138. The method according to embodiments 129 to 132, wherein the patient is 5 to 12 years of age, and the reduction of symptoms is self-reported from the patient and separately reported by a parent.
- [0296] 139. The method according to embodiments 129 to 132, wherein the patient is an adolescent having an age of 13 to 17 years and the reduction of symptoms is self-reported from the patient and separately reported by a parent.
- [0297] 140. The method according to embodiments 138 to 139, wherein the reduction of symptoms self-reported by the patient and a parent are correlated.
- [0298] 141. The method of embodiment 138, wherein the Conners-3 Parent Short t-score Inattention Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.

- [0299] 142. The method of embodiment 138, wherein the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0300] 143. The method of embodiment 138, wherein the Conners-3 Parent Short t-score Executive Functioning Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0301] 145. The method of embodiment 138, wherein the Conners-3 Parent Short t-score Learning Problems Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0302] 146. The method of embodiment 139, wherein the Conners-3 Parent Short t-score Inattention Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0303] 147. The method of embodiment 139, wherein the Conners-3 Self Report Short t-score Inattention Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0304] 148. The method of embodiment 139, wherein the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0305] 149. The method of embodiment 139, wherein the Conners-3 Self Report Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0306] 150. The method of embodiment 139, wherein the Conners-3 Parent Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0307] 151. The method of embodiment 139, wherein the Conners-3 Parent Short t-score Learning Problems Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [0308] 152. The method of embodiment 10, wherein the Conners-3 Self Report Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant

reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.

Examples

[0309] The following examples are provided for illustration and are not intended to limit the scope of the invention. In the examples, centanafadine was formulated and administered as centanafadine hydrochloride, unless otherwise indicated.

[0310] The following abbreviations are used herein:

[Table 1]

ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-5	ADHD Rating Scale-5
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CGI-C-ADHD	Clinical Global Impression - Change - Attention-Deficit/Hyperactivity Disorder
CGI-S-ADHD	Clinical Global Impression - Severity - Attention-Deficit/Hyperactivity Disorder
CI	Confidence interval
Conners 3-P(S)	Conners 3rd Edition - Parent Short form
CTN	centanafadine
DF	Degrees of freedom
ECV	Explained common variance
IRT	Item response theory
PGI-C	Patient Global Impression - Change
PGI-S	Patient Global Impression - Severity
PUC	Percent of uncontaminated correlations
RCI	Reliable change index
RMSEA	Root mean square error of approximation
ROC	Receiver operating characteristic
TLI	Tucker-Lewis index
WPMI	Within-person meaningful improvement

[0311] The examples provide results of a randomized, double-blind placebo-controlled study in adolescents (13 to 17 years of age) and children (6 to 12 years of age) administered CTN QD XR for the treatment of ADHD. The example also provides data regarding the safety and tolerability of CTN QD XR in adolescents or children with ADHD.

[0312] The results of the study are further described in the attached figures, which also further describe the study design.

[0313] In summary, the study comprised three treatment groups for each of the adolescent groups and children group as follows: 1) adolescent subjects administered CTN QD XR high dose (328.8 mg) or low dose (164.4 mg); 2) child subjects administered CTN QD XR high dose or low dose as weight-based dosing; and 3) a placebo group for each of the first two groups. The treatment period was 6 weeks.

[0314] The subjects having ADHD-RS-5 baseline scores greater than or equal to 28 and

CGI-S baseline scores greater than or equal to 4 were randomized into the treatment groups. Inclusion criteria also included a primary diagnosis of ADHD based on the DSM-5 diagnosis criteria and confirmed with the MINI-KID, a minimum symptoms total raw score of ≥ 28 on the ADHD-RS-5 at baseline; and a score of ≥ 4 on the CGI-S-ADHD at baseline.

- [0315] Exclusion criteria included a comorbid diagnosis of: Tourette's Disorder, GAD that was severe enough to interfere with trial procedures, Panic Disorder, Conduct Disorder, Psychosis, PTSD, Bipolar Disorder, ASD, ODD that was severe enough to interfere with trial conduct, OCD that was severe enough to interfere with trial conduct, MDD with current MDE, or required treatment within the 3 months prior to screening. Moreover, subjects were excluded if no suitable therapeutic benefit had been derived from adequate courses of 2 classes of therapy for ADHD during the subject's lifetime, in the investigator's opinion.
- [0316] The primary endpoint was a change from baseline in the ADHD-RS-5 symptoms total raw score at Week 6. Key secondary endpoints included Change from baseline in CGI-S-ADHD at Week 6; change from baseline in Conners 3 Parent Short t-score at Week 6 (e.g., hyperactivity/Impulsivity content scale, inattention content scale, defiance/Aggression content scale, and executive functioning content scale).
- [0317] At Week 6, improvements in the ADHD symptoms of hyperactivity/impulsivity were observed for CTN 328.8 mg vs placebo on the Conners 3-Parent Short (-14.0 vs -8.5 [$p = .0002$]) and the Conners 3-Self Report Scale (-11.6 vs -8.9 [$p = .0282$]) t scores. Improvements were seen in the inattention content scale at Week 6 per Conners 3-Parent Short t scores for CTN 328.8 mg vs placebo (-14.4 vs -8.1 [$p < .0001$]) and per Conners 3-Self Report Scale (-15.3 vs -10.0 [$p = .0001$]). Significance for CTN 328.8 mg vs placebo was observed as early as Week 1 on Conners 3-Parent Scale hyperactive/impulsivity and inattention content scale t scores, and Conners 3-Self Reporting Scale inattention scale t scores.
- [0318] The figures submitted herewith show additional details of the study, including results thereof.

[Table 2]

Conners-3 Parent Short t-score Adolescents

Content Scale	CTN dose (mg)	Treatment Difference	P value*
Hyperactivity/Impulsivity	328.8	-5.52	0.0002*
	164.4	-0.17	0.9108
Inattentive	328.8	-6.33	<0.0001*
	164.4	-1.26	0.3617
Defiance/Aggression	328.8	-1.02	0.3932
	164.4	-0.44	0.7111
Executive Function	328.8	-4.92	0.0003*
	164.4	-1.46	0.2743

*nominally significant

[Table 3]

Conners-3 Parent Short t-score Children

Content Scale	CTN dose (mg)	Treatment Difference	P value*
Hyperactivity/Impulsivity	328.8	-4.56	0.0022*
	164.4	-1.05	0.4804
Inattentive	328.8	-5.50	0.0002*
	164.4	-2.72	0.0704
Defiance/Aggression	328.8	-2.12	0.1854
	164.4	+2.42	0.1332
Executive Function	328.8	-4.56	0.0026*
	164.4	-2.52	0.0977

*nominally significant

[Table 4]

Response Rate Adolescents

Improvement Response Rate	CTN dose (mg)	% Response	P value**
ADHD-RS-5 50%	328.8	47.0	0.0037**
	164.4	34.0	0.6209
	placebo	31.0	
ADHD-RS-5 40%	328.8	57.7	0.0069**
	164.4	42.0	0.9167
	placebo	42.1	
ADHD-RS-5 30%	328.8	69.1	0.0013**
	164.4	56.0	0.3171
	placebo	50.3	
CGI-C 1 or 2	328.8	50.3	0.0075**
	164.4	40.0	0.3420
	placebo	34.5	

*Response rates are at Week 6

*nominally significant

[Table 5]

Response Rate Children

Improvement Response Rate	CTN dose (mg)	% Response	P value**
ADHD-RS-5 50%	328.8	32.5	0.0079**
	164.4	25.9	0.1732
	placebo	19.9	
ADHD-RS-5 40%	328.8	35.7	0.0289**
	164.4	35.0	0.0383**
	placebo	24.5	
ADHD-RS-5 30%	328.8	44.8	0.0250**
	164.4	44.1	0.0411**
	placebo	32.5	
CGI-C 1 or 2	328.8	36.4	0.0128**
	164.4	32.2	0.0697
	placebo	22.5	

*Response rates are at Week 6

*nominally significant

[Table 6]

Quality of Life Assessment at Week 6

Mean change from baseline	Adolescents			Children		
	164.4 mg	328.8 mg	Placebo	164.4 mg	328.8 mg	Placebo
Parent Health Related QoL	7.99 P=0.7468	12.66 P=0.0082*	7.34	9.37 P=0.1070	9.11 P=0.1378	5.82
Family Functioning Summary Score	8.22 P=0.3848	14.29 P=0.0008*	6.15	6.93 P=0.5790	11.61 P=0.0135*	5.60
Total Score	6.87 P=0.5075	11.99 P=0.0006*	5.66	7.09 P=0.1048	8.18 P=0.0309*	3.87

*nominally significant

[Table 7]

ADHD-RS-5 Impairment Subscale Scores at Week 6

Mean change from baseline	Adolescent dose (mg)			Children dose (mg)		
	164.4	328.8	Placebo	164.4	328.8	Placebo
Family relations	-0.81 P=0.6923	-0.90 P=0.2033	-0.78	-0.69 P=0.4164	-0.72 P=0.3009	-0.60
Peer relations	-0.61 P=0.9126	-0.73 P=0.1814	-0.62	-0.64 P=0.7984	-0.77 P=0.1463	-0.61
Homework	-0.97 P=0.9715	-1.15 P=0.2088	-0.96	-0.98 P=0.0217*	-1.12 P=0.0014*	-0.63
Academics	-0.94 P=0.1929	-0.96 P=0.1522	-0.76	-0.84 P=0.4358	-1.12 P=0.0064*	-0.73
Behavior	-0.74 P=0.5523	-0.78 P=0.3807	-0.66	-0.84 P=0.2403	-0.95 P=0.0439*	-0.68
Self esteem	-0.67 P=0.4243	-0.75 P=0.8850	-0.74	-0.68 P=0.9024	-0.73 P=0.5282	-0.67

*nominally significant

- [0319] The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.
- [0320] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise” and variations such as “comprises” and “comprising” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.
- [0321] Throughout the specification, where compositions are described as including components or materials, it is contemplated that the compositions can also consist essentially of, or consist of, any combination of the recited components or materials, unless described otherwise. Likewise, where methods are described as including particular steps, it is contemplated that the methods can also consist essentially of, or consist of, any combination of the recited steps, unless described otherwise. The invention illustratively disclosed herein suitably may be practiced in the absence of any element or step which is not specifically disclosed herein.
- [0322] The practice of a method disclosed herein, and individual steps thereof, can be performed manually and/or with the aid of or automation provided by electronic equipment. Although processes have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used. For example, the order of various of the steps may be changed without departing from the scope or spirit of the method, unless described otherwise. In addition, some of the individual steps can be combined, omitted, or further subdivided into additional steps.

[0323] All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

Claims

- [Claim 1] A method of treating ADHD and reducing ADHD symptoms as measured by a Conners-3 assessment by administering to a patient having ADHD a daily dose of about 150 mg to about 600 mg of cen-tanafadine or a pharmaceutical acceptable salt thereof, wherein the patient is 5 to 17 years of age.
- [Claim 2] The method of claim 1, wherein the Conners-3 assessment is selected from the group consisting of a Conners-3 Parent Short t-score Hy-peractive/Impulsive Content Scale, Conners-3 Parent Short t-score Inattentive Content Scale, Conners-3 Parent Short t-score Defiance/Aggression Content Scale, Conners-3 Parent Short t-score Executive Functioning Content Scale, Conners-3 Parent Short t-score Learning Problems Content Scale, Conners-3 Parent Short t-score Peer Relations Content Scale, and a combination thereof.
- [Claim 3] The method of claim 1, wherein the Conners-3 assessment is selected from the group consisting of a Conners-3 Self Report Short t-score Hy-peractive/Impulsive Content Scale, Conners-3 Self Report Short t-score Inattentive Content Scale, Conners-3 Self Report Short t-score Defiance/Aggression Content Scale, Conners-3 Self Report Short t-score Executive Functioning Content Scale, Conners-3 Self Report Short t-score Learning Problems Content Scale, Conners-3 Self Report Short t-score Peer Relations Content Scale, and a combination thereof.
- [Claim 4] The method of claim 1, wherein the Conners-3 assessment comprises Conners-3 Parent Short t-score Executive Functioning Content Scale.
- [Claim 5] The method of claim 4, wherein the mean score of the Conners-3 Parent Short t-score Executive Functioning Scale is reduced by at least 4 after 6 weeks of treatment.
- [Claim 6] The method of claim 5, wherein the reduction of symptoms is sta-tistically significant compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 7] The method of claim 5, wherein the reduction of symptoms is sta-tistically significant compared to placebo at week 1 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 8] The method of claim 5, wherein the reduction of symptoms is sta-tistically significant compared to placebo at week 1 after beginning

- treatment, wherein the statistical significance is determined by a p-value of less than 0.01.
- [Claim 9] The method according to claims 1 to 3, wherein the patient is 5 to 12 years of age, and the reduction of symptoms is self-reported from the patient and separately reported by a parent.
- [Claim 10] The method according to claims 1 to 3, wherein the patient is an adolescent having an age of 13 to 17 years and the reduction of symptoms is self-reported from the patient and separately reported by a parent.
- [Claim 11] The method according to claims 9 to 10, wherein the reduction of symptoms self-reported by the patient and a parent are correlated.
- [Claim 12] The method of claim 9, wherein the Conners-3 Parent Short t-score Inattention Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 13] The method of claim 9, wherein the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 14] The method of claim 9, wherein the Conners-3 Parent Short t-score Executive Functioning Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 15] The method of claim 9, wherein the Conners-3 Parent Short t-score Learning Problems Content Scale in children shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 16] The method of claim 10, wherein the Conners-3 Parent Short t-score Inattention Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 17] The method of claim 10, wherein the Conners-3 Self Report Short t-score Inattention Content Scale in adolescents shows a statistically sig-

- nificant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 18] The method of claim 10, wherein the Conners-3 Parent Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 19] The method of claim 10, wherein the Conners-3 Self Report Short t-score Hyperactive/Impulsive Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 20] The method of claim 10, wherein the Conners-3 Parent Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 21] The method of claim 10, wherein the Conners-3 Parent Short t-score Learning Problems Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.
- [Claim 22] The method of claim 10, wherein the Conners-3 Self Report Short t-score Executive Functioning Content Scale in adolescents shows a statistically significant reduction of symptoms compared to placebo by week 6 after beginning treatment, wherein statistical significance is determined by a p-value of less than 0.05.