**Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets in Adults   
With Attention-deficit/Hyperactivity Disorder: Results of Two Phase 3, Randomized,   
Double-blind, Multicenter, Placebo-controlled Trials**

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# Supplemental Digital Content 1. Table: Inclusion criteria for Study 1 (NCT03605680) and Study 2 (NCT03605836)

|  |  |
| --- | --- |
| No. | Inclusion criteria |
| Assessed at screening | |
| 1. | Current primary DSM-5 diagnosis of ADHD (including predominantly inattentive, hyperactive, or combined presentations) as confirmed by the ACDS Version 1.2 |
| 2. | AISRS score of ≥28 at screening for subjects not receiving any pharmacological treatment for ADHD; AISRS score of ≥22 at screening for subjects who were receiving pharmacological treatment for ADHD |
| 3. | 18 – 55 years of age, inclusive |
| 4. | BMI 18 – 40, inclusive |
| 5. | Able to swallow multiple tablets |
| 6. | Willing and able to comply with all testing and requirements as defined in the protocol |
| 7. | Able to provide informed consent in accordance with the ICH GCP Guidance E6 and applicable regulations before completing any trial-related procedures |
| 8. | Willing to discontinue all prohibited psychotropic medicationsa starting from the time of signing informed consent form through the 7-day follow-up period |
| 9. | Able to read and communicate in English or Spanish |
| Assessed at baseline | |
| 10. | AISRS score of ≥28 for subjects not receiving any pharmacological treatment for ADHD; AISRS score of ≥28 at screening for subjects who were receiving pharmacological treatment for ADHD |
| 11. | CGI-S score ≥4 (moderate or greater than moderate impairment) |

ACDS, Adult ADHD Clinical Diagnostic Scale; ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; BMI, body mass index; CGI-S, Clinical Global Impression-Severity of Illness Scale; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ICH GCP International Council for Harmonisation Good Clinical Practice.

aAntidepressants, benzodiazepines, hypnotics (including non-benzodiazepine sleep aids), ADHD medications, sedating antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine), antihypertensives (clonidine, propranolol, guanfacine), anorexics (weight loss supplements), and investigational compounds.

# Supplemental Digital Content 2. Table: Exclusion criteria for Study 1 (NCT03605680) and Study 2 (NCT03605836)

|  |  |
| --- | --- |
| No. | Exclusion criteria |
| Screening | |
| 1. | Females who are breast-feeding or who had a positive pregnancy test result prior to receiving study drug. |
| 2. | Sexually active males or FOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the course of the trial and for 30 days after the last dose of study drug for female subjects, and 90 days after the last dose of study drug for male subjects and their partners who are FOCBP. Male subjects who do not agree to refrain from donating sperm from screening through 90 days after the last dose of study drug. |
| 3. | DSM-5 diagnosis of Other Specified or Unspecified Attention-Deficit/Hyperactivity Disorder. |
| 4. | Initiated, changed, or discontinued receiving psychological (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) interventions for ADHD within the 60 days before the screening visit, or are anticipated to start new treatment during the trial. Subjects who are receiving psychotherapy that was initiated >60 days before the screening visit will be allowed to continue to receive their psychotherapy during the trial only if they agree to not make any changes in the frequency or nature of their psychotherapy during the course of this trial. |
| 5. | Lifetime history of electroconvulsive therapy, or a lifetime history of vagal nerve stimulation or deep brain stimulation for the treatment of depression. |
| 6. | Current comorbid psychiatric disorder that either could be expected to require treatment with medications prohibited in this trial, or to confound efficacy or safety assessments. Examples include, but are not limited to, psychotic disorder (current or lifetime), bipolar disorder (current or lifetime), generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a current major depressive episode, or posttraumatic stress disorder, as established by the MINI. |
| 7. | Clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, narcissistic, avoidant, or dependent personality disorders. |
| 8. | Meet criteria for C-SSRS Suicidal Ideation Items 4 and 5 or within the last 6 months prior to screening or meet criteria for any of the 5 C-SSRS Suicidal Behavior Items and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years prior to screening,  **OR**  Who, in the opinion of the investigator, present a serious risk of suicide. |
| 9. | Medical or psychological condition(s) or state(s) that in the investigator’s opinion would prohibit the subject from completing the trial or would go against the subject’s best interest with his/her participation in the trial. This would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. This would also include most bariatric surgeries, with the only exception being those where there has been no breach of the gastrointestinal wall (ie, uncomplicated lap band surgery) AND no sign of malabsorption. |
| 10. | History of epilepsy, seizures (other than infantile febrile seizures), syncope, Tourette’s Disorder, serious neurological disease, history of significant head trauma with clinically significant loss of consciousness, dementia, cerebrovascular disease, Parkinson’s disease, or intracranial lesions. |
| 11. | Lifetime history of a pattern of abuse or diversion of stimulants. |
| 12. | Any current or suspected drug or alcohol use disorder. Has met the DSM-5 criteria for a substance use disorder in the past 6 months. Nicotine use disorder is not exclusionary. |
| 13. | A positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (excluding marijuana). Subjects with a positive drug screen for confirmed prescription or OTC use of ADHD medications at screening will be required to undergo a washout period. NOTE: Subjects that test positive for marijuana may be permitted to be enrolled if they have no evidence of a substance use disorder, and if they agree to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening require explicit approval from the medical monitor. |
| 14. | Known intellectual disability or clinical evidence of intellectual disability based on the opinion of the investigator. |
| 15. | Insulin-dependent diabetes mellitus. Subjects with non-insulin-dependent diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:   * Screening glucose (non-fasting) < 200 mg/dL. (If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. Fasting glucose must be ≤ 125 mg/dL.), * Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, * Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** * Subject’s diabetes is not newly diagnosed during screening for the trial. |
| 16. | Subjects presenting with, or having a history of, uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes standing compared with the previous supine blood pressure, **OR** development of symptoms. |
| 17. | Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, coronary artery bypass surgery, or other serious cardiac problems that would place him/her at increased vulnerability to the sympathomimetic effects of a stimulant medication. |
| 18. | The following laboratory test and ECG results are exclusionary:   1. Platelets ≤ 75,000/mm3 2. Hemoglobin ≤ 9 g/dL 3. Neutrophils, absolute ≤ 1000/mm3 4. AST > 2 × upper limit of normal 5. ALT > 2 × upper limit of normal 6. Creatinine ≥ 2 mg/dL 7. HbA1c ≥ 7% 8. QTcF or QTcB > 450 msec for males or > 470 msec for females   NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator’s judgment are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. |
| 19. | Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) or an abnormal result for free T4 at screening (free T4 is measured only if result for TSH is abnormal). |
| 20. | Subjects receiving any of the prohibited medications within the specified period prior to the start of the single-blind placebo run-in period, or who would be likely to require prohibited concomitant therapy during the trial |
| 21. | Subject has a history of prior exposure to centanafadine. |
| 22. | Subject has a history of dermatologic adverse reactions secondary to any drug exposure or anaphylaxis (or some type of systemic allergic reaction) to any substance. |
| 23. | Subject has participated in a clinical trial involving either an investigational medication or a non-medication intervention within the last 60 days prior to screening or has participated in more than 2 clinical trials involving either an investigational medication or non-medication intervention within the past year. |
| 24. | Subject has previously been randomized in this trial and subsequently withdrawn. |
| 25. | In the opinion of the investigator, subject has not derived significant therapeutic benefit from 2 or more ADHD therapies of 2 different classes (eg, amphetamine and methylphenidate, or amphetamine and atomoxetine) given with an acceptable dose and duration during adulthood (aged 18 or older).  NOTE: If subject has not derived significant therapeutic benefit due to an inability to tolerate side effects, eligibility can be discussed on case-by-case basis with the medical monitor. |
| 26. | Any subject who, in the opinion of the investigator, should not participate in the trial. |
| 27. | Subjects with HIV seropositive status/acquired immunodeficiency syndrome, seropositive status for hepatitis B (ie, HBsAg positive), or hepatitis C (ie, anti-HCV positive and HCV RNA positive). |
| Exclusion Criteria Assessed Prior to Start of the Single-blind Placebo Run-in | |
| 28. | Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to Visit 2 for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be screen failed. This includes medications such as opioids or benzodiazepines taken without prescription. |
| 29 | Subjects with a ≥ 30% improvement in the (18-item) ADHD Symptoms score of the ASRS compared with the score at screening will be screen failed, and not eligible for rescreening. |
| Exclusion Criteria Assessed at Baseline | |
| 30 | Subjects who have a positive alcohol test (via breathalyzer or blood), a positive drug screen assessed prior to the baseline visit for cocaine, other illicit drugs (including marijuana), or prescription or OTC ADHD medications will be early terminated. This includes medications such as opioids or benzodiazepines taken without prescription. |
| 31 | Subjects with a ≥ 30% improvement in the (18-item) ADHD Symptoms score of the ASRS compared with the score at the start of the single-blind placebo run-in will be early terminated. |
| 32 | In the opinion of the investigator, the subject is unable to adhere to the treatment regimen or other requirements outlined in the protocol. |

ADHD, attention-deficit/hyperactivity disorder; ALT, alanine aminotransferase; anti-HCV, hepatitis C antibodies; ASRS, Adult ADHD Self-Report Scale; AST, aspartate aminotransferase; C-SSRS, Columbia-Suicide Severity Rating Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECG, electrocardiogram; FOCBP, females of childbearing potential; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MINI, Mini International Neuropsychiatric Interview; OTC, over-the-counter; QTcB, QT interval corrected for heart rate by the Bazett formula; QTcF, QT interval corrected for heart rate by the Fridericia formula; RNA, ribonucleic acid; T4, thyroxine; TSH, thyroid-stimulating hormone.

# Supplemental Digital Content 3. Table: Summary of mean change from Baseline to Day 42 in AISRS Inattentive Subscale score for Study 1 (NCT03605680), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 147 | 22.01 (3.37) | – | – | – | – | – |
| CTN SR 400 mg/day | 147 | 21.71 (4.04) | – | – | – | – | – |
| Placebo | 144 | 22.10 (3.40) | – | – | – | – | – |
| **Day 7** | | | | | | | |
| CTN SR 200 mg/day | 143 | 18.78 (5.60) | 143 | -2.99 (0.37) | -0.71 | (-1.66, 0.25) | 0.1492 |
| CTN SR 400 mg/day | 144 | 19.24 (5.34) | 144 | -2.10 (0.38) | 0.19 | (-0.77, 1.15) | 0.7019 |
| Placebo | 142 | 19.45 (4.57) | 142 | -2.29 (0.38) | – | – | – |
| **Day 14** | | | | | | | |
| CTN SR 200 mg/day | 133 | 17.89 (5.75) | 133 | -4.02 (0.42) | -0.61 | (-1.72, 0.50) | 0.2817 |
| CTN SR 400 mg/day | 137 | 17.96 (6.05) | 137 | -3.25 (0.43) | 0.16 | (-0.95, 1.27) | 0.7748 |
| Placebo | 136 | 18.37 (5.08) | 136 | -3.41 (0.43) | – | – | – |
| **Day 21** | | | | | | | |
| CTN SR 200 mg/day | 124 | 17.08 (6.26) | 124 | -4.85 (0.47) | -1.40 | (-2.64, -0.17) | **0.0264** |
| CTN SR 400 mg/day | 133 | 16.70 (6.51) | 133 | -4.43 (0.47) | -0.98 | (-2.21, 0.25) | 0.1177 |
| Placebo | 134 | 18.28 (5.72) | 134 | -3.45 (0.47) | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 117 | 16.57 (6.76) | 117 | -5.22 (0.53) | -1.97 | (-3.36, -0.58) | **0.0055** |
| CTN SR 400 mg/day | 124 | 16.23 (6.78) | 124 | -4.85 (0.53) | -1.60 | (-2.98, -0.22) | **0.0231** |
| Placebo | 129 | 18.47 (5.83) | 129 | -3.25 (0.52) | – | – | – |
| **Day 35** | | | | | | | |
| CTN SR 200 mg/day | 113 | 16.24 (6.65) | 113 | -5.64 (0.53) | -1.66 | (-3.06, -0.26) | **0.0200** |
| CTN SR 400 mg/day | 114 | 15.33 (7.06) | 114 | -5.60 (0.53) | -1.63 | (-3.03, -0.24) | **0.0218** |
| Placebo | 122 | 17.79 (6.25) | 122 | -3.97 (0.52) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 109 | 16.15 (7.54) | 109 | -5.58 (0.57) | -1.96 | (-3.47, -0.45) | **0.0110** |
| CTN SR 400 mg/day | 119 | 15.93 (6.92) | 119 | -4.98 (0.56) | -1.35 | (-2.85, 0.14) | 0.0757 |
| Placebo | 119 | 18.22 (6.53) | 119 | -3.62 (0.56) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN-SR, centanafadine sustained release; LS, least- squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 4. Table: Summary of mean change from Baseline to Day 42 in AISRS Inattentive Subscale score for Study 2 (NCT03605836), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 140 | 20.88 (3.82) | – | – | – | – | – |
| CTN SR 400 mg/day | 140 | 21.31 (3.62) | – | – | – | – | – |
| Placebo | 141 | 21.35 (3.16) | – | – | – | – | – |
| **Day 7** | | | | | | | |
| CTN SR 200 mg/day | 137 | 17.68 (5.22) | 137 | -3.63 (0.37) | -1.35 | (-2.29, -0.41) | **0.0050** |
| CTN SR 400 mg/day | 139 | 18.71 (5.00) | 139 | -3.01 (0.37) | -0.73 | (-1.66, 0.21) | 0.1278 |
| Placebo | 139 | 19.40 (5.15) | 139 | -2.28 (0.36) | – | – | – |
| **Day 14** | | | | | | | |
| CTN SR 200 mg/day | 132 | 16.17 (6.28) | 132 | -4.97 (0.44) | -2.14 | (-3.30, -0.98) | **0.0003** |
| CTN SR 400 mg/day | 125 | 17.02 (5.84) | 125 | -4.81 (0.45) | -1.97 | (-3.15, -0.80) | **0.0010** |
| Placebo | 132 | 18.66 (5.49) | 132 | -2.83 (0.44) | – | – | – |
| **Day 21** | | | | | | | |
| CTN SR 200 mg/day | 127 | 15.50 (6.42) | 127 | -5.69 (0.46) | -2.00 | (-3.21, -0.78) | **0.0014** |
| CTN SR 400 mg/day | 116 | 15.80 (6.38) | 116 | -6.00 (0.48) | -2.31 | (-3.54, -1.07) | **0.0003** |
| Placebo | 132 | 17.98 (5.64) | 132 | -3.69 (0.46) | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 122 | 15.20 (6.57) | 122 | -5.94 (0.49) | -1.94 | (-3.23, -0.66) | **0.0031** |
| CTN SR 400 mg/day | 114 | 15.82 (6.32) | 114 | -6.05 (0.50) | -2.06 | (-3.36, -0.75) | **0.0021** |
| Placebo | 130 | 17.59 (5.69) | 130 | -4.00 (0.48) | – | – | – |
| **Day 35** | | | | | | | |
| CTN SR 200 mg/day | 115 | 15.10 (6.85) | 115 | -6.36 (0.53) | -2.08 | (-3.50, -0.66) | **0.0042** |
| CTN SR 400 mg/day | 104 | 14.75 (7.05) | 104 | -7.04 (0.55) | -2.76 | (-4.20, -1.32) | **0.0002** |
| Placebo | 125 | 17.22 (6.20) | 125 | -4.28 (0.52) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 113 | 14.67 (6.91) | 113 | -6.68 (0.54) | -2.42 | (-3.86, -0.98) | **0.0010** |
| CTN SR 400 mg/day | 102 | 15.33 (7.21) | 102 | -6.52 (0.56) | -2.26 | (-3.72, -0.80) | **0.0026** |
| Placebo | 123 | 17.28 (6.42) | 123 | -4.26 (0.53) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN-SR, centanafadine sustained release; LS, least- squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 5. Table: Summary of mean change from Baseline to Day 42 in AISRS Hyperactive-Impulsive Subscale score for Study 1 (NCT03605680), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 147 | 17.59 (4.75) | – | – | – | – | – |
| CTN SR 400 mg/day | 147 | 17.85 (4.95) | – | – | – | – | – |
| Placebo | 144 | 17.43 (5.14) | – | – | – | – | – |
| **Day 7** | | | | | | | |
| CTN SR 200 mg/day | 143 | 14.88 (5.65) | 143 | -2.59 (0.37) | -0.58 | (-1.54, 0.37) | 0.2311 |
| CTN SR 400 mg/day | 144 | 15.44 (5.65) | 144 | -2.08 (0.38) | -0.08 | (-1.04, 0.88) | 0.8736 |
| Placebo | 142 | 15.27 (5.71) | 142 | -2.00 (0.38) | – | – | – |
| **Day 14** | | | | | | | |
| CTN SR 200 mg/day | 133 | 14.08 (5.92) | 133 | -3.52 (0.42) | -0.34 | (-1.45, 0.77) | 0.5441 |
| CTN SR 400 mg/day | 137 | 13.96 (6.07) | 137 | -3.58 (0.43) | -0.40 | (-1.51, 0.71) | 0.4751 |
| Placebo | 136 | 14.08 (5.89) | 136 | -3.17 (0.43) | – | – | – |
| **Day 21** | | | | | | | |
| CTN SR 200 mg/day | 124 | 13.73 (6.07) | 124 | -3.72 (0.44) | -0.53 | (-1.68, 0.63) | 0.3701 |
| CTN SR 400 mg/day | 133 | 13.54 (6.42) | 133 | -3.98 (0.44) | -0.78 | (-1.93, 0.36) | 0.1807 |
| Placebo | 134 | 13.96 (6.09) | 134 | -3.19 (0.44) | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 117 | 12.84 (6.54) | 117 | -4.56 (0.49) | -1.41 | (-2.69, -0.13) | **0.0308** |
| CTN SR 400 mg/day | 124 | 12.52 (6.43) | 124 | -4.90 (0.48) | -1.75 | (-3.01, -0.48) | **0.0071** |
| Placebo | 129 | 14.03 (6.21) | 129 | -3.15 (0.48) | – | – | – |
| **Day 35** | | | | | | | |
| CTN SR 200 mg/day | 113 | 12.82 (6.74) | 113 | -4.78 (0.51) | -1.42 | (-2.76, -0.07) | **0.0392** |
| CTN SR 400 mg/day | 114 | 12.30 (6.50) | 114 | -5.22 (0.51) | -1.85 | (-3.19, -0.51) | **0.0068** |
| Placebo | 122 | 13.73 (6.35) | 122 | -3.37 (0.50) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 109 | 12.71 (6.82) | 109 | -4.69 (0.50) | -1.20 | (-2.53, 0.13) | 0.0775 |
| CTN SR 400 mg/day | 119 | 12.65 (6.14) | 119 | -4.86 (0.50) | -1.36 | (-2.68, -0.04) | **0.0428** |
| Placebo | 119 | 13.97 (6.21) | 119 | -3.49 (0.50) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN-SR, centanafadine sustained release; LS, least- squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

Supplemental Digital Content 6. Table: Summary of mean change from Baseline to Day 42 in AISRS Hyperactive-Impulsive Subscale score for Study 2 (NCT03605836), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 140 | 16.71 (4.57) | – | – | – | – | – |
| CTN SR 400 mg/day | 140 | 17.45 (5.02) | – | – | – | – | – |
| Placebo | 141 | 16.30 (4.88) | – | – | – | – | – |
| **Day 7** | | | | | | | |
| CTN SR 200 mg/day | 137 | 14.54 (4.69) | 137 | -2.61 (0.33) | -0.55 | (-1.38, 0.27) | 0.1897 |
| CTN SR 400 mg/day | 139 | 14.60 (5.56) | 139 | -3.02 (0.33) | -0.96 | (-1.79, -0.13) | **0.0237** |
| Placebo | 139 | 14.66 (5.64) | 139 | -2.06 (0.32) | – | – | – |
| **Day 14** | | | | | | | |
| CTN SR 200 mg/day | 132 | 12.80 (5.76) | 132 | -4.15 (0.40) | -1.44 | (-2.48, -0.39) | **0.0074** |
| CTN SR 400 mg/day | 125 | 13.56 (6.17) | 125 | -4.18 (0.41) | -1.47 | (-2.53, -0.40) | **0.0070** |
| Placebo | 132 | 13.96 (6.03) | 132 | -2.72 (0.40) | – | – | – |
| **Day 21** | | | | | | | |
| CTN SR 200 mg/day | 127 | 11.79 (5.91) | 127 | -5.15 (0.43) | -1.96 | (-3.11, -0.81) | **0.0009** |
| CTN SR 400 mg/day | 116 | 12.72 (6.21) | 116 | -5.28 (0.45) | -2.09 | (-3.26, -0.92) | **0.0005** |
| Placebo | 132 | 13.55 (6.35) | 132 | -3.19 (0.43) | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 122 | 11.84 (6.01) | 122 | -5.13 (0.45) | -1.97 | (-3.16, -0.78) | **0.0013** |
| CTN SR 400 mg/day | 114 | 12.68 (6.67) | 114 | -5.41 (0.47) | -2.25 | (-3.47, -1.03) | **0.0003** |
| Placebo | 130 | 13.58 (6.46) | 130 | -3.16 (0.45) | – | – | – |
| **Day 35** | | | | | | | |
| CTN SR 200 mg/day | 115 | 11.80 (5.97) | 115 | -5.27 (0.45) | -1.65 | (-2.83, -0.46) | **0.0066** |
| CTN SR 400 mg/day | 104 | 12.21 (6.38) | 104 | -5.98 (0.47) | -2.35 | (-3.57, -1.14) | **0.0002** |
| Placebo | 125 | 13.06 (6.34) | 125 | -3.63 (0.44) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 113 | 11.64 (6.28) | 113 | -5.34 (0.49) | -1.47 | (-2.76, -0.18) | **0.0251** |
| CTN SR 400 mg/day | 102 | 12.27 (6.50) | 102 | -5.94 (0.51) | -2.07 | (-3.40, -0.75) | **0.0022** |
| Placebo | 123 | 12.83 (6.70) | 123 | -3.87 (0.48) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN-SR, centanafadine sustained release; LS, least- squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 7. ~~Supplemental Digital Content 9.~~ Figure displaying a summary of proportion of responders\* relative to the end of the single-blind run-in period by study day (LOCF) for Study 1 (NCT03605680).

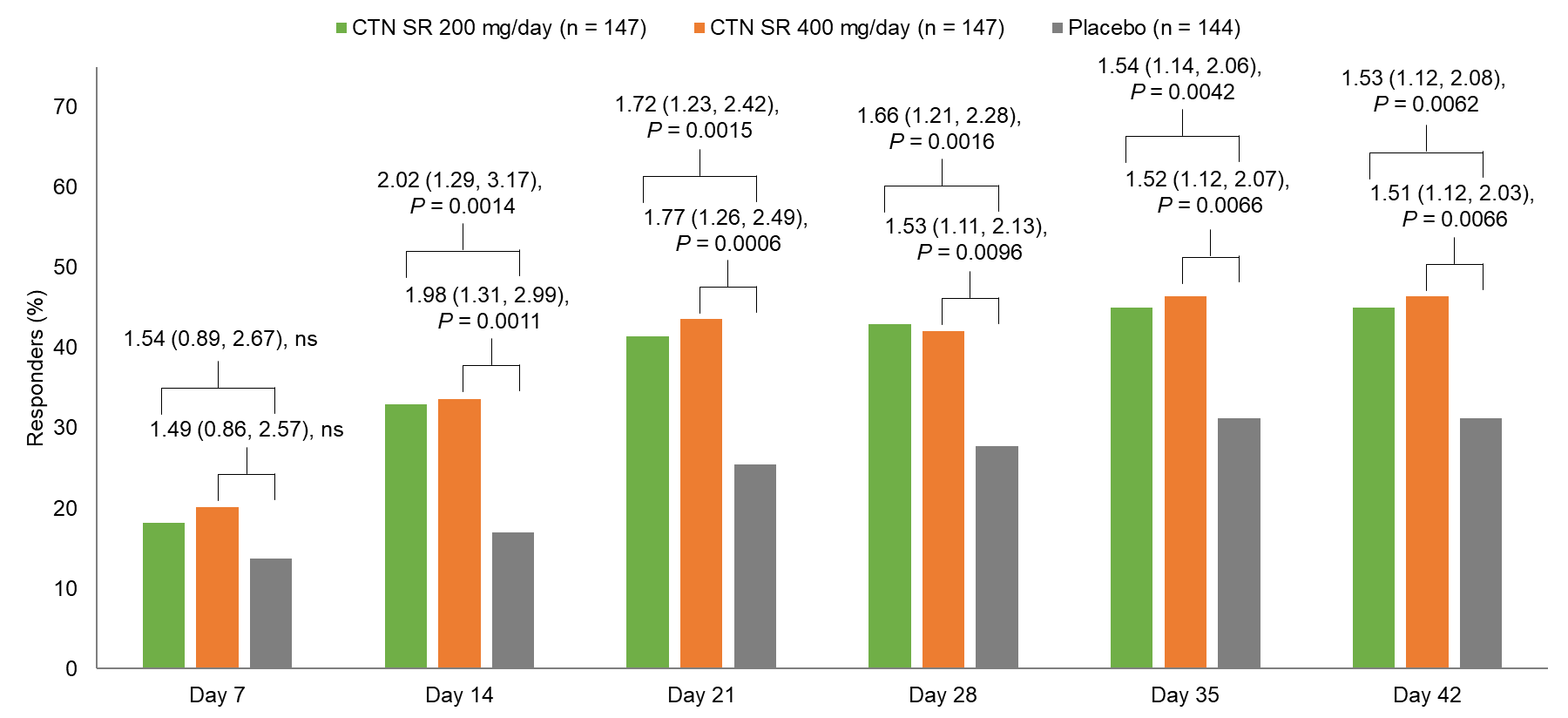
# 

\*Subjects with ≥30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score or CGI-S change from baseline score of 1 or 2.

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness Scale; CMH, Cochran–Mantel–Haenszel test; CTN SR, centanafadine sustained release; LOCF, last observation carried forward; ns, not significant.

In Study 1 the percentage of responders, defined as subjects with CGI-S Change from Baseline score of 1 or 2 or a ≥30% improvement in AISRS score (LOCF), was statistically significantly greater in the centanafadine 400 mg/day dose group compared with placebo at Day 28 and Day 35. The increase in responder rates seen in the centanafadine 200 mg/day dose group at Days 21, 28, 35, and 42 did not reach statistical significance compared with placebo.

# Supplemental Digital Content 8. Figure displaying a summary of proportion of responders\* relative to the end of the single-blind run-in period by study day (LOCF) for Study 2 (NCT03605836).



\*Subjects with ≥30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score or CGI-S change from baseline score of 1 or 2.

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness Scale; CMH, Cochran–Mantel–Haenszel test; CTN SR, centanafadine sustained release; LOCF, last observation carried forward; ns, not significant.

In Study 2, the percentage of responders was statistically significantly greater in the centanafadine 200 mg/day and centanafadine 400 mg/day dose groups compared with placebo at Days 14, 21, 28, 35, and 42. Comparison between treatment groups was carried out using the CMH general association test controlling for study center.

# Supplemental Digital Content 9. Table: Summary of mean change in scores on AIM-A question 9 (impact of symptoms on daily life) from Baseline to Day 42 for Study 1 (NCT03605680), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change From Baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **How much does the symptom bother or concern you?** | | | | | | | |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 118 | 61.3 (19.1) | – | – | – | – | – |
| CTN SR 400 mg/day | 126 | 62.6 (20.0) | – | – | – | – | – |
| Placebo | 131 | 59.8 (22.4) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 115 | 49.7 (22.7) | 115 | -12.3 (1.94) | -5.60 | (-10.5, -0.71) | **0.0251** |
| CTN SR 400 mg/day | 122 | 50.1 (22.6) | 122 | -12.0 (1.94) | -5.34 | (-10.2, -0.53) | **0.0298** |
| Placebo | 126 | 54.0 (23.6) | 126 | -6.67 (1.91) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 109 | 46.7 (24.1) | 109 | -14.8 (1.94) | -7.86 | (-12.8, -2.96) | **0.0018** |
| CTN SR 400 mg/day | 117 | 50.4 (23.9) | 117 | -12.4 (1.94) | -5.42 | (-10.2, -0.60) | **0.0275** |
| Placebo | 118 | 54.2 (23.0) | 118 | -6.95 (1.92) | – | – | – |
| **How much does the symptom interfere with your daily life?** | | | | | | | |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 118 | 57.3 (20.1) | – | – | – | – | – |
| CTN SR 400 mg/day | 126 | 58.5 (20.5) | – | – | – | – | – |
| Placebo | 131 | 57.0 (24.0) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 115 | 45.9 (21.1) | 115 | -12.0 (1.95) | -5.27 | (-10.2, -0.34) | **0.0363** |
| CTN SR 400 mg/day | 122 | 45.9 (23.9) | 122 | -12.2 (1.96) | -5.39 | (-10.2, -0.54) | **0.0296** |
| Placebo | 126 | 50.6 (23.5) | 126 | -6.76 (1.93) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 109 | 44.1 (23.3) | 109 | -13.3 (2.00) | -4.94 | (-10.0, 0.13) | 0.0561 |
| CTN SR 400 mg/day | 117 | 47.3 (25.1) | 117 | -11.2 (2.00) | -2.84 | (-7.82, 2.14) | 0.2621 |
| Placebo | 118 | 49.7 (23.8) | 118 | -8.39 (1.98) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AIM-A, Attention-Deficit/Hyperactivity Disorder Impact Module - Adult; CTN-SR, centanafadine sustained release; LS, least- squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 10. Table: Summary of mean change in scores on AIM-A question 9 (impact of symptoms on daily life) from Baseline to Day 42 for Study 2 (NCT03605836), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **How much does the symptom bother or concern you?** | | | | | | | |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 124 | 59.5 (20.1) | – | – | – | – | – |
| CTN SR 400 mg/day | 113 | 61.7 (18.1) | – | – | – | – | – |
| Placebo | 130 | 59.8 (19.2) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 120 | 49.5 (22.8) | 120 | -12.0 (1.62) | -4.97 | (-8.98, -0.96) | **0.0153** |
| CTN SR 400 mg/day | 112 | 52.9 (20.1) | 112 | -9.98 (1.69) | -2.92 | (-7.02, 1.19) | 0.1631 |
| Placebo | 126 | 55.1 (21.6) | 126 | -7.06 (1.60) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 112 | 45.5 (21.9) | 113 | -15.7 (1.86) | -8.46 | (-13.2, -3.70) | **0.0005** |
| CTN SR 400 mg/day | 98 | 50.7 (22.4) | 98 | -12.9 (1.97) | -5.60 | (-10.5, -0.68) | **0.0257** |
| Placebo | 116 | 55.0 (23.3) | 116 | -7.26 (1.84) | – | – | – |
| **How much does the symptom interfere with your daily life?** | | | | | | | |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 124 | 56.4 (20.8) | – | – | – | – | – |
| CTN SR 400 mg/day | 113 | 58.3 (18.7) | – | – | – | – | – |
| Placebo | 129 | 56.8 (21.1) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 120 | 45.4 (23.4) | 120 | -11.9 (1.66) | -6.87 | (-11.0, -2.74) | **0.0012** |
| CTN SR 400 mg/day | 112 | 47.0 (18.5) | 112 | -11.6 (1.73) | -6.52 | (-10.7, -2.29) | **0.0026** |
| Placebo | 125 | 53.1 (21.6) | 125 | -5.06 (1.64) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 113 | 41.6 (22.4) | 113 | -15.3 (1.95) | -8.66 | (-13.6, -3.67) | **0.0007** |
| CTN SR 400 mg/day | 98 | 45.2 (22.3) | 98 | -13.8 (2.06) | -7.12 | (-12.3, -1.96) | **0.0069** |
| Placebo | 116 | 50.5 (23.9) | 116 | -6.68 (1.93) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; AIM-A, Attention-Deficit/Hyperactivity Disorder Impact Module - Adult; CTN-SR, centanafadine sustained release; LS, least-squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 11. Table: Summary of mean change in scores on the ASRS Scale from Baseline to Day 42 for Study 1 (NCT03605680), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment Group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 118 | 52.2 (9.43) | – | – | – | – | – |
| CTN SR 400 mg/day | 127 | 52.1 (10.2) | – | – | – | – | – |
| Placebo | 131 | 51.7 (10.5) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 116 | 42.5 (14.3) | 116 | -9.50 (1.18) | -3.06 | (-6.00, -0.12) | **0.0414** |
| CTN SR 400 mg/day | 124 | 40.8 (13.2) | 124 | -10.6 (1.19) | -4.12 | (-7.00, -1.24) | **0.0051** |
| Placebo | 129 | 44.7 (13.2) | 129 | -6.44 (1.17) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 109 | 40.5 (16.9) | 109 | -11.3 (1.30) | -4.60 | (-7.88, -1.31) | **0.0062** |
| CTN SR 400 mg/day | 118 | 39.0 (13.6) | 118 | -12.0 (1.29) | -5.28 | (-8.50, -2.07) | **0.0014** |
| Placebo | 119 | 45.0 (13.6) | 119 | -6.70 (1.28) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale; CTN-SR, centanafadine sustained release; LS, least-squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 12. Table: Summary of mean change in scores on the ASRS Scale from Baseline to Day 42 for Study 2 (NCT03605836), MMRM analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Change from baseline** | | | | |
| **Visit**  Treatment Group | **N** | **Mean (SD)** | **N** | **LS mean**  **(SE)a** | **LS mean diffa** | **95% CI** | ***P* valuea** |
| **Baseline** | | | | | | | |
| CTN SR 200 mg/day | 124 | 48.4 (10.9) | – | – | – | – | – |
| CTN SR 400 mg/day | 114 | 49.8 (9.32) | – | – | – | – | – |
| Placebo | 130 | 50.2 (10.5) | – | – | – | – | – |
| **Day 28** | | | | | | | |
| CTN SR 200 mg/day | 121 | 39.7 (14.3) | 121 | -10.1 (1.06) | -4.55 | (-7.17, -1.93) | **0.0007** |
| CTN SR 400 mg/day | 113 | 41.1 (13.6) | 113 | -10.1 (1.10) | -4.49 | (-7.16, -1.82) | **0.0010** |
| Placebo | 128 | 45.9 (13.1) | 128 | -5.57 (1.05) | – | – | – |
| **Day 42** | | | | | | | |
| CTN SR 200 mg/day | 113 | 37.1 (16.4) | 113 | -12.2 (1.20) | -4.91 | (-7.96, -1.87) | **0.0016** |
| CTN SR 400 mg/day | 100 | 38.7 (13.2) | 100 | -12.6 (1.26) | -5.33 | (-8.44, -2.21) | **0.0009** |
| Placebo | 120 | 43.9 (15.2) | 120 | -7.28 (1.18) | – | – | – |

ADHD, attention-deficit/hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale; CTN-SR, centanafadine sustained release; LS, least-squares; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error.

aLS mean difference = difference in LS mean change.

Comparison between treatment groups was carried out using MMRM, with study center, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

# Supplemental Digital Content 13. Table: Incidence of TEAEs of special interest during the double-blind treatment period in Study 1 (NCT03605680) and Study 2 (NCT03605836)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CTN SR  200 mg/day**  **(n = 294)** | **CTN SR  400 mg/day**  **(n = 292)** | **Placebo**  **(n = 290)** | **Total**  **(N = 876)** |
| **Subject with any treatment-emergent AESIsa** | 7 (2.4) | 16 (5.5) | 7 (2.4) | 30 (3.4) |
| **Infections and infestations** | 1 (0.3) | 0 (0.0) | 1 (0.3) | 2 (0.2) |
| Impetigo | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Pustule | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| **Nervous system disorder** | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Somnolence | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| **Psychiatric disorder** | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) |
| Irritability | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) |
| **Skin and subcutaneous tissue disorders** | 6 (2.0) | 15 (5.1) | 6 (2.1) | 27 (3.1) |
| Dermatitis, atopicb | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Dermatitis, contact | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Psoriasis | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) |
| Rash | 4 (1.4) | 11 (3.8) | 2 (0.7) | 17 (1.9) |
| Rash, erythematous | 1 (0.3) | 0 (0.0) | 1 (0.3) | 2 (0.2) |
| Rash, maculo-papular | 1 (0.3) | 1 (0.3) | 0 (0.0) | 2 (0.2) |
| Rash, morbilliform | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Rash, papular | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) |
| Rash, pruritic | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Skin lesion | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) |

AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment emergent adverse event.

Note: All AEs which started after start of trial drug treatment; or if the event was continuous from baseline and was serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial therapy.

aSubjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

bOne subject randomized into the placebo group experienced the TEAE of atopic dermatitis, which was incorrectly categorized as an AESI.