2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	:
Name of Study Device: SDT-001	**Page:**	

Study Title: Phase 3 study of SDT-001 in pediatric patients with Attention Deficit/Hyperactivity Disorder consisting of randomized, open-label, treatment as usual-control, comparison part and open-label, repetition part

Investigators and Study Centers: This study was a multicenter study conducted by 45 investigators at 44 sites in Japan.

Publication (reference): Not applicable

Studied Period:

From 12 May 2022 to 25 Dec 2023

(Study complete date is the date of evaluation for last participant tracking questionnaire about post-treatment)

Phase of Development: Phase 3

Objectives:

Comparison part

Primary objective

- To verify the efficacy (in terms of the change in Attention Deficit/Hyperactivity Disorder Rating Scale IV [ADHD-RS-IV] [physician's assessment] inattentive subscale score) of SDT-001 when used for 6 weeks as compared with the treatment as usual (TAU) group* in pediatric ADHD patients.

  *: Control group for comparison, provided with environmental control and/or psychosocial treatment only.

Key secondary objective

- To verify the efficacy (in terms of the changes in ADHD-RS-IV [physician's assessment] total score and hyperactivity/impulsivity subscale score) of SDT-001 when used for 6 weeks as compared with TAU group in pediatric ADHD patients.

Other secondary objectives

- To evaluate the efficacy of SDT-001 when used for 6 weeks as compared with the TAU group in pediatric ADHD patients.
- To evaluate the safety of SDT-001 when used for 6 weeks in pediatric patients with ADHD.
- To explore the possibility of SDT-001 causing gaming disorder.

Exploratory objective

- To collect exploratory information for estimating the effects of SDT-001 when used for 6 weeks in pediatric ADHD patients.

Repetition part

Secondary objectives

- To evaluate the efficacy of SDT-001 when used for another 6 weeks (additional 1 cycle) in pediatric ADHD patients who have used SDT-001 for 6 weeks (1 cycle).
- To evaluate the efficacy of SDT-001 when used for 6 weeks in pediatric ADHD patients.
- To evaluate the safety of SDT-001 when used for another 6 weeks (additional 1 cycle) in pediatric ADHD patients who have used SDT-001 for 6 weeks (1 cycle).
- To evaluate the safety of SDT-001 when used for 6 weeks in pediatric ADHD patients.
- To explore the possibility of SDT-001 causing gaming disorder.

Exploratory objectives

- To collect exploratory information for estimating the effect of SDT-001 when used for another 6 weeks (additional 1 cycle) in pediatric ADHD patients who have used SDT-001 for 6 weeks (1 cycle).
- To collect exploratory information for estimating the effects of SDT-001 when used for 6 weeks in pediatric ADHD patients.

Methodology:

This study was a multicenter, open-label study in male and female outpatients who were school children or students aged 6 to 17 years with a diagnosis of ADHD. The study consisted of 2 parts: a randomized, TAU group-controlled, parallel-group comparison part and a single-group repetition part.

Comparison part

The comparison part had 2 treatment groups: SDT-001 group and TAU group. The comparison part consisted of a screening period (2 to 4 weeks), a treatment period (6 weeks), and a follow-up period (4 weeks, SDT-001 group only). Participants who were considered eligible for participation during the screening period and enrolled in the study were randomized to either SDT-001 group or TAU group in a 2:1 ratio. Both 2 groups were allowed to receive environmental control and/or psychosocial treatment as performed in the real clinical practice setting during the study period. Participants randomized to SDT-001 group used SDT-001, the study device, once (approximately 25 minutes) daily for 6 weeks in the treatment period. Participants randomized to TAU group received environmental control and/or psychosocial treatment only. The questionnaire about treatment at the final visit was performed only in participants who did not enter the repetition part at the last visit (or discontinuation). Participants who answered in this questionnaire that they had initiated pharmacotherapy for ADHD terminated the study at that point. On the other hand, participants who had not initiated pharmacotherapy for ADHD (excluding those who had been deemed to need pharmacotherapy but did not initiate it at the request of themselves or their parents/guardians) continued the study and underwent a tracking questionnaire about

treatment post-final visit (hereinafter referred to as "tracking questionnaire") at up to 24 weeks after the last visit (or discontinuation) of the comparison part. The duration of the comparison part was 12 to 38 weeks for SDT-001 group and 8 to 34 weeks for TAU group.

Repetition part

The repetition part consisted of 2 periods: a treatment period (6 weeks) and a follow-up period (12 weeks). All participants who had completed the comparison part and given consent to participation in the repetition part, and were considered eligible, were enrolled for SDT-001 group. In the treatment period, all participants used SDT-001 once (approximately 25 minutes) daily for 6 weeks. The questionnaire about treatment at the final visit was performed at the last visit (or discontinuation). Participants who had not initiated pharmacotherapy for ADHD (excluding those who had been deemed to need pharmacotherapy but did not initiate it at the request of themselves or their parents/guardians) underwent the tracking questionnaire at up to 24 weeks after the last visit (or discontinuation) of the repetition part. The duration of the repetition part was 18 to 42 weeks. A participant who used SDT-001 through the comparison and repetition parts was allowed to have follow-up for up to 52 weeks, including the tracking questionnaire to investigate whether pharmacotherapy for ADHD was to need post-final visit.

Number of Participants (Planned and Analyzed):

Comparison part

Planned: 150 (100 in SDT-001 group, 50 in TAU group)

Randomized: 164 (109 in SDT-001 group, 55 in TAU group)

Analyzed for efficacy:

- Full analysis set (FAS): 163 (109 in SDT-001 group, 54 in TAU group)
- Per protocol set (PPS): 142 (90 in SDT-001 group, 52 in TAU group)

Analyzed for safety: 164 (109 in SDT-001 group, 55 in TAU group)

Repetition part

Planned: Up to 150 participants

Enrolled: 126 (75 in SDT-001/SDT-001 group*, 51 in TAU/SDT-001 group**)

Analyzed for efficacy (FAS): 126 (75 in SDT-001/SDT-001 group, 51 in TAU/SDT-001 group)

Analyzed for safety: 126 (75 in SDT-001/SDT-001 group, 51 in TAU/SDT-001 group)

*: Participants randomized to SDT-001 group, who had completed the comparison part and then entered the repetition part to use SDT-001.

**: Participants randomized to TAU group, who had completed the comparison part and then entered the repetition part to use SDT-001.

Diagnosis and Main Criteria for Inclusion:

Comparison part

1. Inclusion criteria

- Male or female outpatients who were school children or students aged 6 to 17 years at the time of informed consent.
- Patients whose primary diagnosis* according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) was ADHD and who met any of the following disease type classification codes of ADHD at the time of informed consent.
  - 314.01 (F90.2) Combined presentation
  - 314.00 (F90.0) Predominantly inattentive presentation
  - 314.01 (F90.1) Predominantly hyperactive-impulsive presentation

  *: Disease which was the main factor requiring outpatient medical care in patients with more than 1 diagnosis made in the outpatient setting.
- Patients who were confirmed at the time of informed consent to had received environmental control and/or psychosocial treatment for ADHD for a sufficient period and were considered unlikely to have a sufficient effect.
- Patients who had not received pharmacotherapy for ADHD within 7 days before informed consent.
- Patients whose ADHD-RS-IV (physician's assessment) inattentive subscale scores at both Visit 1 and Visit 2 were 15 points or higher.
- A patient who could obtain acceptance from his/her teacher to perform assessments and for whom the results of teacher's assessments could be confirmed at day 1.

2. Exclusion criteria
   - Patients with psychiatric disease such as schizophrenia spectrum disorder, depression, or bipolar disorder. However, patients with concurrent autism spectrum disorder or localized learning disorder might have been included.
   - Patients with personality disorder or intellectual disability, or, patients with suspected intellectual disability with an intelligence quotient of < 70 in an intelligence test (or a previous intelligence test within the past 1 year, if any and if acceptable in the opinion of the investigator).
   - Patients concurrently or previously with convulsion or severe tic disorder (including Tourette's disorder). However, patients concurrently or previously with febrile convulsion were eligible.
   - Patients whose percent change in ADHD-RS-IV (physician's assessment) inattentive subscale score at day 1 exceeded 30% compared to that at Visit 1.
   - Patients who were considered to be unable to operate the application for physical or other reasons (eg, deafness, color blindness, broken hands or arms, etc.).
   - Patients with suspected gaming disorder (playing games had greatly interfered with everyday life [eg, school life, sleep, etc.])
   - Patients with suicidal tendency meeting any of the followings:
     - A patient previously with suicide attempts.
     - A patient who had answered "Yes" to Question 4 or Question 5 regarding suicidal ideation or any questions regarding suicidal behavior in the

Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 6 months.

- Patients with suspected substance-related disorders within 180 days prior to Visit 1.

Repetition part

1. Inclusion criteria
   - Male or female outpatients who were school children or students aged 6 to 17 years before initiating the treatment period of repetition part (Visit 1).
   - Patients who had participated in the preceding comparison part and who had completed the last visit (at the end of follow-up period for the SDT-001 group and at the end of treatment period for the TAU group).
   - A patient who could obtain acceptance from his/her teacher to continue performing assessments.
2. Exclusion criteria
   - Patients who were considered to be unable to operate the application for physical and other reasons (eg, deafness, color blindness, broken hands or arms, etc.).
   - Patients who were considered by the investigator (subinvestigator) to be inappropriate for participation in the repetition part due to adverse events (AEs) that occurred during the precedent comparison part and were unresolved before initiating the treatment period of repetition part (Visit 1).
   - Patients who had answered "Yes" to Question 4 or Question 5 regarding suicidal ideation or any questions regarding suicidal behavior in the C-SSRS before initiating the treatment period of repetition part (Visit 1).

Study Device and Treatment Method:

The study device used in this study was SDT-001, a software program (application) as medical device which had a core mechanism of dual tasks (performing 2 tasks simultaneously) and task difficulty adjustment for each participant's achievement level.

Participants randomized to SDT-001 group in the comparison part and participants entering the repetition part used the study device according to the following procedures:

- Tap the icon of the SDT-001 application installed on the iPad mini tablet terminal.
- Log in for the first time by entering the code number and the password assigned to the participant on the login screen. Then, change the password (on the first day of use only. The participant can initiate a session only by tapping the icon on subsequent days).
- Follow the navigation and understand the procedures and precautions displayed on the screen.
- Initiate the first session.

- After finishing the scheduled sessions (approximately 25 minutes) assigned for the day, press the home button on the iPad mini tablet terminal to complete the use for the day.

Participants were supposed to do 2 types of operations during the sessions, ie, steering (tilting the tablet to the left and right to drive and move the character along the path as specified on the screen) and tapping (touching anywhere on the screen when a predefined object appeared on the screen). The method of using the study device was not changed.

Duration of Treatment:

SDT-001 was used once (approximately 25 minutes) daily for 6 weeks both in the comparison and repetition parts.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable

Criteria for Evaluation:

Efficacy Assessment:

Measurement scales used in this study for the efficacy assessment included: ADHD-RS-IV (physician's and teacher's assessments) scores, Behavior Rating Inventory of Executive Function (BRIEF) score, Conners third Edition (Conners 3) (parent's assessment) scale score, Impairment Rating Scale (IRS) score, Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, EuroQol Five-Dimensional Questionnaire, Youth Version (EQ-5D-Y) visual analogue scale (VAS) score, Clinical Global Impression-Improvement (CGI-I) scale, and parent's global assessment (PGA) scale.

Comparison part

Primary endpoint

- Change from baseline in ADHD-RS-IV (physician's assessment) inattentive subscale score at the end of 6-week use of SDT-001 (week 6)

Key secondary endpoints

- Change from baseline in ADHD-RS-IV (physician's assessment) total score at week 6
- Change from baseline in ADHD-RS-IV (physician's assessment) hyperactivity/impulsivity subscale score at week 6

Other secondary endpoints

- Changes from baseline in ADHD-RS-IV (physician's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score at each assessment time point (excluding week 6)
- Proportion of participants with improvement of 30% from baseline in ADHD-RS-IV (physician's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score at each assessment time point
- Changes from baseline in the following measures at each assessment time point: ADHD-RS-IV (teacher's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score; BRIEF score; Conners 3

(parent's assessment) scale score; IRS score; PedsQL Generic Core Scales; and EQ-5D-Y score

- Proportion of participants with improvement ("very much improved" or "much improved") in CGI-I at each assessment time point
- Proportion of participants with improvement ("very much improved" or "much improved") in PGA at each assessment time point

Repetition part

Secondary endpoints

- Changes from baseline in the following measures at each assessment time point: ADHD-RS-IV (physician's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score; ADHD-RS-IV (teacher's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score; BRIEF score; Conners 3 (parent's assessment) scale score; IRS score; PedsQL Generic Core Scales; and EQ-5D-Y score
- Proportion of participants with improvement of 30% from baseline in ADHD-RS-IV (physician's assessment) total score, inattentive subscale score, and hyperactivity/impulsivity subscale score at each assessment time point
- Proportion of participants with improvement ("very much improved" or "much improved") in CGI-I at each assessment time point
- Proportion of participants with improvement ("very much improved" or "much improved") in PGA at each assessment time point

Safety Assessment:

AEs, adverse device effects (ADEs), device deficiencies, C-SSRS, and questionnaire about gaming disorder

Statistical Methods:

Efficacy Analyses:

Efficacy analyses for each part were performed in the FAS population. The analysis of the primary endpoint was performed also in the PPS population. All statistical tests were performed at the 2-sided significance level of 0.05, unless otherwise stated.

Comparison part

For the primary endpoint, the changes from baseline in ADHD-RS-IV (physician's assessment) inattentive subscale scores observed at weeks 2, 4 and 6 were analyzed using the mixed-effects models for repeated measures (MMRM). The MMRM model with unstructured covariance was fitted to estimate group difference between SDT-001 and TAU groups, with change from baseline as the response variable; treatment group, assessment time point, and the interaction between treatment group and assessment time point as fixed effects; and baseline value, age category, presence or absence of prior pharmacotherapy indicated for ADHD, and type of ADHD as covariates. The degree of freedom was calculated using the Kenward-Roger method. The difference between the 2 groups in the change from baseline at week 6 and its 95% CI were calculated to test the superiority of SDT-001 group over TAU group.

The key secondary endpoints were analyzed using the MMRM as was for the primary endpoint. If the primary endpoint was met, the key secondary endpoints were to be analyzed in the following order using the fixed sequence procedure: (1) Comparison between the groups for the change from baseline in ADHD-RS-IV (physician's assessment) total score at week 6; (2) Comparison between the groups for the change from baseline in ADHD-RS-IV (physician's assessment) hyperactivity/impulsivity subscale score at week 6.

For the other secondary endpoints observed at various assessment time points, the changes from baseline were analyzed using the MMRM as was for the primary endpoint. The changes from baseline in ADHD-RS-IV (teacher's assessment) scores, Conners 3 (parent's assessment) scale score, and BRIEF score were analyzed using the analysis of covariance (ANCOVA) with baseline value, age category, presence or absence of prior pharmacotherapy indicated for ADHD, and type of ADHD as covariates, and between-group differences and their 95% CIs at week 6 were calculated.

The number and proportion of participants with improvement were calculated by group. In addition, between-group differences were estimated by the Cochran-Mantel-Haenszel (CMH) method stratified by the age category, presence or absence of prior pharmacotherapy indicated for ADHD, and type of ADHD, and the 95% CIs were calculated.

Subgroup analyses were performed for the primary and key secondary endpoints by presence or absence of prior pharmacotherapy indicated for ADHD, age category, sex, and type of ADHD.

Repetition part

Analyses using descriptive statistics were performed by randomized group in the comparison part. The endpoints analyzed were the same as those for the comparison part. For variables observed as continuous values, summary statistics at each assessment time point were calculated. For variables observed as discrete values, the number and proportion of participants by category were calculated. For the changes from baseline, in addition to the analyses using the baseline of the repetition part, analyses using the assessment at day 1 of the comparison part as the baseline data were performed. The change from baseline in ADHD-RS-IV (teacher's assessment) scores was analyzed using the assessment at day 1 of the comparison part as the baseline data because there was no assessment at day 1 of the repetition part.

Safety Analyses:

Adverse events were classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1. Adverse events occurring after enrollment were used for the safety analyses.

Separate summaries by the groups of comparison part were provided for the number and proportion of participants with AEs, AEs leading to discontinuation of using the study device, and serious adverse events (SAEs) for each part. Adverse events considered related to the study device were regarded as ADEs and summarized in the same manner as for AEs. For AEs summarized by SOC and by PT, the number and proportion of participants with event were further summarized for each treatment group

of the comparison part. In addition, the AEs were further summarized by severity and by outcome. Adverse device effects were summarized in the same manner as for AEs.

Device deficiencies were referring to the terminology which was determined by the sponsor with reference to the International Medical Device Regulators Forum (IMDRF), and the number of deficiencies was tabulated separately for the comparison and repetition parts. For C-SSRS, the distribution of presence/absence of suicidal ideation and suicide behavior at each assessment time point were summarized separately for the comparison and repetition parts. For the questionnaire about gaming disorder, the results of the questionnaire about gaming disorder at each assessment time point were tabulated separately for the comparison and repetition parts.

Exploratory Analyses:

The results of each questionnaire were tabulated separately for the comparison and repetition parts.

Summary of Results:

Efficacy:

Comparison part

In the FAS population (109 and 54 in SDT-001 and TAU groups, respectively), the mean (SD) duration using the study device in SDT-001 group was 35.3 (7.3) days with the mean study device compliance rate of 84.1%. The median age was 9.0 (range: 6 to 17) years in both groups with most participants (> 80%) aged ≥ 6 to ≤ 12 years. Male participants account for 74.3% and 74.1% of the participants in SDT-001 and TAU group, respectively. The participants had predominantly inattentive or combined presentation type of ADHD, and all underwent psychosocial treatment including environmental control. Approximately one-fourth of the participants had received prior pharmacotherapies with the indication for ADHD. The mean (SD) ADHD-RS-IV (physician's assessment) inattentive subscale score at baseline was 20.8 (3.3) in SDT-001 group and 21.3 (3.3) in TAU group. The following efficacy results were obtained.

Primary endpoint

- In the FAS population, the difference in the adjusted mean change from baseline in ADHD-RS-IV (physician's assessment) inattentive subscale score between SDT-001 and TAU groups at week 6 was −2.97 (95% CI: −4.38, −1.56; $p < 0.0001$ by MMRM analysis), which was statistically significant. This demonstrated the superiority of SDT-001 group over TAU group in improving ADHD-RS-IV (physician's assessment) inattentive subscale score in pediatric ADHD patients, and thus the primary objective of the study was met.
- In the PPS population (90 and 52 in SDT-001 and TAU groups, respectively), the difference in the adjusted mean change from baseline in ADHD-RS-IV (physician's assessment) inattentive subscale score between SDT-001 and TAU groups at week 6 was −2.72 (95% CI: −4.18, −1.26; $p = 0.0003$ by MMRM analysis). This result was similar to that in the FAS population, suggesting that the important protocol deviations did not have a significant impact on the primary endpoint.

Key secondary endpoints

- The difference in the adjusted mean change from baseline in ADHD-RS-IV (physician's assessment) total score between SDT-001 and TAU groups at week 6 was −4.56 (95% CI; −6.75, −2.38; $p < 0.0001$ by MMRM analysis), which was statistically significant. This indicated that SDT-001 group had a statistically significantly greater improvement in the total score compared with TAU group.
- The difference in the adjusted mean change from baseline in ADHD-RS-IV (physician's assessment) hyperactivity/impulsivity subscale score between SDT-001 and TAU groups at week 6 was −1.55 (95% CI; −2.64, −0.46; $p = 0.0056$ by MMRM analysis), which was statistically significant. This result indicated that SDT-001 group had a statistically significantly greater improvement in the hyperactivity/impulsivity subscale score compared with TAU group.

Repetition part

In the FAS population (126; 75 in SDT-001/SDT-001 group and 51 in TAU/SDT-001 group), the mean (SD) duration using the study device was 35.0 (8.6) days in SDT-001/SDT-001 group and 34.6 (8.3) days in TAU/SDT-001 group. The mean study device compliance rate was 83.8% and 82.3%, respectively. The following efficacy results were obtained.

Secondary Endpoints

SDT-001/SDT-001 group

- A consistent decreasing trend in each ADHD-RS-IV (physician's assessment) score was observed throughout the treatment period, after transitioning to the repetition part. And the improvement in each score was maintained throughout the follow-up period.
  - The mean (SD) changes from baseline of the repetition part in total score were: −2.0 (4.4), −3.1 (4.1), and −3.7 (5.4) at weeks 2, 4, and 6, respectively; −3.9 (5.5), −4.5 (5.7), −4.8 (5.9), and −5.9 (7.2) at weeks 8, 10, 14, and 18, respectively.
  - The mean (SD) changes from baseline of the repetition part in inattentive subscale score were: −1.3 (3.0), −2.1 (3.1), and −2.3 (3.6) at weeks 2, 4, and 6, respectively; −2.8 (4.0), −3.2 (3.9), −3.2 (4.3), and −3.9 (4.5) at weeks 8, 10, 14, and 18, respectively.
  - The mean (SD) changes from baseline of the repetition part in hyperactivity/impulsivity subscale score were: −0.7 (2.6), −1.0 (2.0), and −1.4 (2.7) at weeks 2, 4, and 6, respectively; −1.0 (2.7), −1.3 (3.0), −1.6 (3.0), and −2.0 (3.8) at weeks 8, 10, 14, and 18, respectively.

TAU/SDT-001 group

- A consistent decreasing trend in each ADHD-RS-IV (physician's assessment) score was observed during the treatment period, after transitioning to the repetition part. And the improvement in each score was maintained throughout the follow-up period.
  - The mean (SD) changes from baseline of the repetition part in total score were: −3.1 (5.8), −3.6 (5.9) and −6.9 (6.5) at weeks 2, 4, and 6,

respectively; −6.6 (6.0), −7.6 (7.7), −7.4 (7.4), and −7.8 (6.8), at weeks 8, 10, 14, and 18, respectively.

– The mean (SD) changes from baseline of the repetition part in inattentive subscale score were: −2.1 (3.7), −2.6 (3.8) and −4.7 (4.4) at weeks 2, 4, and 6, respectively; −4.2 (4.0), −4.9 (5.0), −4.7 (4.8), and −4.6 (4.6), at weeks 8, 10, 14, and 18, respectively.
– The mean (SD) changes from baseline of the repetition part in hyperactivity/impulsivity subscale score were: −1.0 (2.8), −1.0 (2.9) and −2.3 (2.9) at weeks 2, 4, and 6, respectively; −2.4 (3.0), −2.7 (3.6), −2.8 (3.6), and −3.2 (3.4), at weeks 8, 10, 14, and 18, respectively.

Safety:

Comparison part

The safety analysis population included all randomized participants (109 and 55 in SDT-001 and TAU groups, respectively). The mean (SD) duration using the study device in SDT-001 group was 35.3 (7.3) days. The following safety results were obtained:

- Neither deaths nor nonfatal SAEs were reported.
- In SDT-001 group, 64 events of AEs occurred in 44 participants (40.4%), and 3 events of ADEs occurred in 3 participants (2.8%), during the treatment and follow-up periods. Most AEs (47 events occurred in 33 participants [30.3%]) and all ADEs occurred during the treatment period.
- The more frequently observed AEs (occurring in 3 or more participants) in SDT-001 group during the treatment period were nasopharyngitis (9 events in 9 participants [8.3%]), COVID-19 (8 events in 8 participants [7.3%]), upper respiratory tract inflammation (4 events in 3 participants [2.8%]), and headache (3 events in 3 participants [2.8%]). The 3 events of ADEs were frustration tolerance decreased, headache, and nausea (1 participant [0.9%] each).
- In TAU group, a total of 12 events of AEs occurred in 10 participants (18.2%) during the treatment period. All of the AEs, except for nasopharyngitis (occurring in 2 participants [3.6%]), were observed in 1 participant (1.8%) each.
- No severe AEs occurred in any of the 2 groups. All AEs were mild in severity, with the exception of 2 moderate AEs that occurred in 2 participants (1.8%) in SDT-001 group: nasopharyngitis and gastroenteritis (1 participant each).
- Adverse events with outcome of "not recovered/not resolved" occurred in 3 participants (2.8%) in SDT-001 group (periodontitis, insomnia, urticaria, and haematuria), and in 1 participant (1.8%) in TAU group (iron deficiency anaemia). All of the other AEs were recovered/resolved.
- One participant (0.9%) in SDT-001 group experienced an AE that led to discontinuation of using the study device. The AE (frustration tolerance decreased) was reported as a mild ADE which resolved without treatment.
- A total of 6 events of device deficiency (malfunction after login) were reported in 6 participants (5.5%) in SDT-001 group: the scheduled sessions could not be performed (4 participants), and sometimes the screen failed to respond to tilt or

taps during missions (2 participants). All of the events were considered to be not related to the study device, and none were deemed to be associated with SAEs, in the opinion of the investigator (subinvestigator).

- Throughout the comparison part, no participants in SDT-001 and TAU groups shifted from the "no suicidal ideation" category at baseline to a higher risk category. No suicidal ideation or behavior of C-SSRS was observed in any of the 2 groups.
- According to the questionnaire about gaming disorder, there was no indication of a trend towards gaming disorder after using the study device.

Repetition part

The safety analysis population included all 126 enrolled participants (75 in SDT-001/SDT-001 group and 51 in TAU/SDT-001 group). The mean (SD) duration using the study device during the repetition part was 35.0 (8.6) days in SDT-001/SDT-001 group and 34.6 (8.3) days in TAU/SDT-001 group. The following safety results were obtained:

- Neither deaths nor AEs leading to discontinuation of using the study device were reported.
- A nonfatal SAE (cyclic vomiting syndrome) was reported in 1 participant (1.3%) in SDT-001/SDT-001 group during the follow-up period and was resolved through hospitalization and treatment. This SAE was considered to be moderate in severity and not related to the study device by the investigator (subinvestigator).
- Overall, 106 events of AEs occurred in 63 participants (50.0%) during the treatment and follow-up periods. An AE was reported as ADE (0.8%).
- In SDT-001/SDT-001 group, 62 events of AEs occurred in 36 participants (48.0%) during the treatment and follow-up periods. Among which, 42 events in 27 participants (36.0%) were observed during the initial 10-week period of the repetition part.
- The more frequently observed AEs (occurring in 3 or more participants) in SDT-001/SDT-001 group during the treatment and follow-up periods were nasopharyngitis, COVID-19 (7 events in 7 participants [9.3%] each), pyrexia (4 events in 4 participants [5.3%]), and upper respiratory tract inflammation (3 events in 3 participants [4.0%]).
- The incidences of AEs during the 10-week period in the comparison and repetition parts were 40.4% (44/109) for SDT-001 group and 36.0% (27/75) for SDT-001/SDT-001 group, respectively. This indicated that an increase in the number of device usage cycles did not result in a marked increase in the occurrence of AE.
- In TAU/SDT-001 group, 44 events of AEs occurred in 27 participants (52.9%) during the treatment and follow-up periods, and 1 event (vomiting) was reported as ADE (2.0%). Among which, 27 events of AEs in 21 participants (41.2%) and the ADE were observed during the initial 10-week period of the repetition part.

- The more frequently observed AEs (occurring in 3 or more participants) in TAU/SDT-001 group during the treatment and follow-up periods were nasopharyngitis (14 events in 10 participants [19.6%]), COVID-19 (6 events in 6 participants [11.8%]), and pyrexia (3 events in 3 participants [5.9%]). All of the other AEs were observed in 1 (2.0%) or 2 (3.9%) participants each.
- No severe AEs occurred. All AEs were mild in severity, with the exception of 3 moderate AEs (COVID-19, cyclic vomiting syndrome, and foot fracture) occurred in SDT-001/SDT-001 group, and 2 moderate AEs (COVID-19 and gastroenteritis) occurred in TAU/SDT-001 group.
- Most AEs were recovered/resolved. Adverse events with outcome of "not recovered/not resolved" occurred in 4 participants (5.3%) in SDT-001/SDT-001 group (seasonal allergy, tic, upper respiratory tract inflammation, and foot fracture).
- A total of 7 events of device deficiency (non activation [the application did not start]) were reported in 7 participants (9.3%) in SDT-001/SDT-001 group, and 2 events of device deficiency (1 event each of incorrect display [the application was frozen during missions] and malfunction after login [sometimes the screen failed to respond to taps during missions]) in 2 participants (3.9%) in TAU/SDT-001 group. None of the events were considered to be related to the study device and associated with SAEs in the opinion of the investigator (subinvestigator).
- Throughout the repetition part, there was no suicidal ideation or behavior as assessed by the C-SSRS.
- According to the questionnaire about gaming disorder, there was no indication of a trend towards gaming disorder after using the study device for 1 cycle or for an additional cycle.

CONCLUSIONS

Efficacy Conclusions:

Comparison part

The efficacy findings demonstrated that the treatment with the study device SDT-001 was more effective than TAU in improving pediatric ADHD symptoms, particularly for ADHD-RS-IV (physician's assessment) inattentive subscale score, total score, and hyperactivity/impulsivity subscale score, when used once (approximately 25 minutes) daily for 6 weeks in pediatric ADHD patients.

Repetition part

The efficacy findings demonstrated that the study device has sustained efficacy in improving pediatric ADHD symptoms, when used repeatedly for an additional 6 weeks by patients who had already used it for 6 weeks, or used initially for 6 weeks by patients who had received TAU for the same duration.

Safety Conclusions:

Comparison part

Based on the safety results, there was no significant safety concerns identified in the comparison part, during and after the 6-week use of this device in pediatric patients with ADHD.

Repetition part

Based on the safety results, there was no significant safety concerns suggested in the repetition part, when the study device was used repeatedly for an additional 6 weeks (1 more cycle) by pediatric ADHD patients who had used it for 6 weeks, nor when the study device was initially used for 6 weeks by those who had received only TAU for 6 weeks (1 cycle).

For the results of the questionnaire about treatment at the final visit and the tracking questionnaire, a report is attached to Appendix 16.1.9 of this clinical study report (CSR).

Date of Report: 6 Feb 2024