2. Synopsis

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Brand name: To be determined		
Device name: SDT-001		

Study title: Phase 2 Study of SDT-001 in Pediatric Patients with Attention-deficit/Hyperactivity Disorder

Participating medical institutions and investigators: This study was a multicenter clinical study implemented by 66 investigators in 64 medical institutions in Japan.

Publication: None

Study duration: Date of study initiation: 7 Jul 2020 Date of study completion: 7 Jul 2021	Development phase: Phase 2

Objectives:

Efficacy

- To compare the efficacy of SDT-001 with that of Sham in pediatric patients with ADHD.
- To collect reference information from the observation group to evaluate efficacy of SDT-001 and the validity of Sham.

Safety

- To evaluate the safety of SDT-001 in pediatric patients with ADHD.
- To explore the possibility of SDT-001 causing gaming addiction.

Other

- To collect secondary information for estimating the efficacy of SDT-001.

Study methodology:

The study design and the study plan are outlined below. The study protocol that was provided to the medical institutions is attached as Appendix 16.1.1, and a sample case report form (CRF) is attached as Appendix 16.1.2.

This study was a multicenter, randomized, double-blind, sham-controlled study in male and female outpatients who were pupils and students aged 6 years or older and younger than 18 years and had been diagnosed with ADHD. In addition, another observation group was set as a reference, and data were collected in an unblinded manner without randomization.

The study consisted of 3 periods (12 to 14 weeks in total), ie, the screening period for 2 to 4 weeks, the treatment period for 6 weeks, and the follow-up period for 4 weeks. No follow-up period was set for the observation group.

SDT-001 group and Sham group

Screening period (Visits 1 to 2)

After acquisition of consent and assent, patients were enrolled in the “double-blind group

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(SDT-001 group or Sham group)" in the screening period, and the patient's eligibility was confirmed. After completion of the screening period, patients who were confirmed to be eligible were enrolled in the treatment period. The screening period was 2 weeks in principle, but if it took time to request teacher's assessment and receive the returned assessment results, up to 4 weeks was allowed.

Treatment period (Visits 2 to 5)

After enrollment in the treatment period, participants were assigned to either the SDT-001 group or the Sham group by the stochastic minimization method with the presence/absence of a history of pharmacotherapy indicated for ADHD and age as factors. Participants were randomized in a ratio of 1:1. SDT-001 or Sham was used once daily (5 sessions*/approximately 25 minutes) for 7 days per week in a double-blind manner. Psychosocial treatment (including environmental adjustment) being performed at the time of informed consent was also continued.

Follow-up period (Visits 6 to 7)

Participants visited the study site once every 2 weeks to undergo various assessments.

*: Details are provided in Section **Error! Reference source not found.**.

Observation group

Screening period (Visits 1 to 2)

After acquisition of consent and assent, patients were enrolled in the "observation group" in the screening period, and the patient's eligibility was confirmed. After completion of the screening period, patients who were confirmed to be eligible were enrolled in the treatment period. The screening period was 2 weeks in principle, but if it took time to request teacher's assessment and receive the returned assessment results, up to 4 weeks was allowed.

Treatment period (Visits 2 to 5)

Psychosocial treatment (including environmental adjustment) being performed at the time of informed consent alone was continued in the treatment period after enrollment.

Sample size:

Number of participants targeted: 247 (106, 106 and 35 in the SDT-001 group, the Sham group and the observation group, respectively)

Number of participants enrolled: 262 (108, 108 and 46 in the SDT-001 group, the Sham group and the observation group, respectively)

Number of participants analyzed

Number of participants for efficacy analyses: 261 in the full analysis set (FAS)
(108, 107 and 46 in the SDT-001 group, the Sham group and the observation group, respectively)
245 in the per protocol set (PPS)

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(98, 103 and 44 in the SDT-001 group, the Sham group and the observation group, respectively)

Number of participants for safety analyses: 261 (108, 107 and 46 in the SDT-001 group, the Sham group and the observation group, respectively)

Diagnosis and major inclusion criteria:

1. Inclusion criteria

- Male and female outpatients who were pupils and students aged 6 years or older and younger than 18 years at the time of informed consent.
- Patients whose primary diagnosis* based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) was ADHD and who met any of the following disease type classification codes of ADHD at the time of obtaining informed consent.
  - 314.01 (F90.2) Combined
  - 314.00 (F90.0) Predominantly inattentive
  - 314.01 (F90.1) Predominantly hyperactive-impulsive

  * The disease chiefly requiring outpatient medical care in patients with more than one diagnosis.
- Patients who were confirmed to have received psychosocial treatment (including environmental adjustment) for ADHD for a sufficient period at the time of informed consent and were considered not to have a sufficient effect.
- Patients who had not received pharmacotherapy for ADHD within 7 days before informed consent. The observation group enrolled patients who had never received pharmacotherapy for ADHD.
- Patients whose Attention Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) inattentive subscale scores (physician's assessment) at both Visit 1 and Visit 2 were 15 points or higher.
- Patients whose teachers could be requested to cooperate, and for whom the results of the teacher's assessment could be confirmed at Visit 2.

2. Exclusion criteria

- Patients with psychiatric disease such as schizophrenia spectrum, depression, or bipolar disorder. However, patients with concurrent autism spectrum disorder or localized learning disorder might be 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 last 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 who had participated in this study. Or, patients whose siblings were participating or had participated in this study.
- Patients whose change rates in the ADHD-RS-IV inattentive subscale score (physician's assessment) at Visit 2 exceeded 30% compared to that at Visit 1.

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- Patients who were considered to be unable to undergo assessments (eg, the Test of Variables of Attention; T.O.V.A) requiring operation of the application and study-specific activities for physical and other reasons. For example, deafness, color blindness, broken hands or arms.
- Patients with suspected gaming disorder (playing games greatly interfered with everyday life [eg, school life, sleep, etc.]).
- Patients with suicidal tendency meeting any of the followings;
  - A patient previously with suicide attempt
  - A patient concurrently or previously with suicidal ideation
  - A patient who had answered "Yes" to Question 4 or Question 5 of suicidal ideation or any questions of suicidal behavior in the Columbia-Suicide Severity Rating Scale (C-SSRS) within the last 6 months.
- Patients with suspected substance-related disorder within 180 days before Visit 1.

Study device and treatment method:

1. Study device

The study devices manufactured by Akili Interactive Labs, Inc. for this study were SDT-001 and Sham. The study devices are overviewed below.

Study group	SDT-001 group	Sham group
Name of study device	SDT-001	Sham
Type	Programmed medical device	Programmed medical device
Classification	Software program (Application)	Software program (Application)
Treatment frequency and duration	Once daily for 6 weeks (5 sessions */about 25 minutes)	Once daily for 6 weeks (5 sessions */about 25 minutes)
Use	Investigational device	Control device
Specifications	• Dual tasks • The task difficulty level was automatically optimized for each patient's level.	• A single task • A certain task difficulty level was set, and the level was not adjusted according to each patient's level. (The specifications as same as those of SDT-001 without the core mechanisms of SDT-001)
Packaging and labeling	SDT-001 and Sham were installed in iPad mini® in advance and then provided to the medical institutions. The labeling showing that it is a study device was displayed on the top screen of SDT-001/Sham.	

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Instructions for treatment	• Once SDT-001/Sham was started, the participant himself/herself had to go through with SDT-001/Sham. • As a rule, SDT-001/Sham was not to be suspended in the middle and was to be continued until the end of the 5th session for the day. • A place was to be maintained, where the participant could be concentrating on SDT-001/Sham comfortably while sitting in a good posture. However, it was not to be performed in front of the investigator (subinvestigator) and the study coordinator.
Manufacturer and supplier	Akili Interactive Labs, Inc. 125 Broad St., 4th Floor Boston, MA 02110, USA

*: There were three types of sessions: the analysis session, challenge session, and training session. Each session took about 5 minutes. Among these 3 types of sessions, a participant went through with 5 sessions as assigned every day.

2. Treatment procedures

The investigator (subinvestigator) or study coordinator assigned the code number and the password for each participant among those in the tables provided in advance. Participants used the study device according to the following procedures.

- Tap the icon of the application on iPad mini®.
- 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.
- After changed the password, follow the navigation and understand the procedures and precautions on the screen.
- After understood the procedures and precautions, start the first session.
- After finished all the 5 sessions assigned for the day, press the home button on iPad mini®.
- In the next day, tap the application icon and repeat the same procedures.

Participants were supposed to do two types of operations during the sessions, ie, steering (tilt the tablet to the left and right to drive and move the character along the path as specified on the screen) and tapping (touch anywhere on the screen when predefined object appeared on the screen).
There was no change in the treatment procedures.

Duration of treatment:

6 weeks

Assessment criteria:

1. Efficacy Assessment
   - Changes in the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment) from baseline to each time

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point of assessment

- 30% improvement rates (30% responder rates) in the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment) from baseline to the last assessment in the treatment period (Visit 5)
- Changes in the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (teacher's assessment) from baseline to each time point of assessment
- Change in the Test of Variables of Attention Attention Comparison Score (T.O.V.A. ACS) from baseline to the last assessment in the treatment period (Visit 5)
- A proportion of participants with T.O.V.A. ACS of ≥ 0 in the analysis set at the last assessment in the treatment period (Visit 5)
- Change in the impairment rating scale (IRS) from baseline to each time point of assessment
- Change in Behavior Rating Inventory of Executive Function (BRIEF) from baseline to each time point of assessment
- Change in Conners 3^{TM} for parents from baseline to the last assessment in the treatment period (Visit 5)
- Improvement rate in Clinical Global Impression–Improvement (CGI-I) at each time point of assessment (rate of participants assessed as "very much improved" or "much improved" in the analysis set)
- Improvement rate in the parent's global assessment (PGA) at each time point of assessment (rate of participants assessed as "very much improved" or "much improved" in the analysis set)
- Change in the Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales from baseline to each time point of assessment
- Change in the EuroQol Five-Dimensional Questionnaire, Youth Version (EQ-5D-Y) from baseline to each time point of assessment

2. Safety assessment

Adverse events (AEs), adverse device effects, device deficiencies, C-SSRS, and questionnaire about gaming addiction

Statistical methods:

1. Efficacy analyses

Efficacy analyses were performed on the FAS. The analyses of the ADHD-RS-IV total score, inattentive subscale score, hyperactivity/impulsivity subscale score (physician's assessment), and T.O.V.A. ACS were performed also in the PPS in the same way as the FAS.

Analysis of change from baseline

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- Descriptive statistics were calculated for each of the SDT-001 group, Sham group, and observation group.
- The following analyses were performed in the SDT-001 group and the Sham group.
    - For endpoints that were observed from Visit 2 to Visit 5, the between-group difference at each time point of assessment and its 95% confidence interval (CI) were calculated using a mixed-effects model repeated measures (MMRM) method. A model with unstructured covariance structure on error variance was applied to all available data obtained at each time point of assessment at Visits 3 to 5, using the change from the baseline as a response variable, the group, assessment time point, and interaction between the group and assessment time point as fixed effects, and baseline values, age group and presence/absence of history of drug therapy indicated for ADHD as covariates.
    - For the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment), and T.O.V.A. ACS, the analysis of covariance was performed for the changes at the last assessment in the treatment period (Visit 5) with missing data imputed by the last observation carried forward (LOCF), and between-group differences and 95% CIs were calculated. The covariates were the baseline values, age group, and presence/absence of history of drug therapy indicated for ADHD.
    - For the ADHD-RS-IV (teacher's assessment), Conners 3^{TM}, and BRIEF measured at Visit 2 and Visit 5, the analysis of covariance was performed using the baseline values, age group, and presence/absence of history of drug therapy indicated for ADHD as covariates, and between-group differences and 95% CIs at Visit 5 were calculated.

Analysis of improvement rate

- For the SDT-001 group, the Sham group, and the observation group, the number of participants with improvement and the rate in the analysis set were obtained by group.
- For the SDT-001 group and the Sham group, between-group differences were estimated by the Cochran-Mantel-Haenszel method stratified by the age group and the presence/absence of history of drug therapy indicated for ADHD, and the 95% CIs were calculated.

2. Safety analyses

Safety analyses were performed in the safety analysis set.

Reported AEs were coded to terms of the International Conference on Harmonisation (ICH) Medical

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Dictionary for Regulatory Activities (MedDRA) Version 23.0, and tabulated by System Organ Class (SOC) and Preferred Term (PT). AEs that occurred after enrollment in the treatment period were used for safety analyses.
The numbers of participants with AEs that occurred after enrollment in the treatment period and the incidences were summarized by group. Serious adverse events (SAEs) were similarly summarized.
Among the AEs that occurred after enrollment in the treatment period, the events assessed as related to the study device were regarded as adverse device effects, and similarly summarized.
For the summary of AEs that occurred after enrollment in the treatment period by system organ class and preferred term, the number and proportion of participants were presented for each group. Adverse device effects were analyzed in the same manner.
Device deficiencies were coded with the Medical Device Deficiency Terminology, and the numbers of deficiencies reported after enrollment in the treatment period were listed for each group.
For C-SSRS, the distribution of the presence or absence of suicidal ideation and suicidal behavior at each time point of assessment was summarized for each group.
For the questionnaire about gaming addiction, the results of the questionnaire at each evaluation time point were tabulated by group.

3. Other analyses

Subgroup analyses

For the following efficacy endpoints, subgroup analyses were performed by age group, sex, and ADHD disease type in addition to the presence/absence of history of pharmacotherapy indicated for ADHD.

- Changes in the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment) from baseline to the last assessment in the treatment period (Visit 5)
- 30% improvement rates (30% responder rates) in the ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment) from baseline to the last assessment in the treatment period (Visit 5)
- Change in T.O.V.A. ACS from baseline to the last assessment in the treatment period (Visit 5)
- A proportion of participants with T.O.V.A. ACS of ≥ 0 in the analysis set at the last assessment in the treatment period (Visit 5)

Also for the safety endpoints, subgroup analyses were performed by the presence/absence of history of pharmacotherapy indicated for ADHD.

Questionnaires about playing video games and about the security of blindness

The results of the questionnaires were tabulated for each group.

Questionnaire about the treatment after study

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The rates of answer "The participant would need to start pharmacotherapy (indicated for ADHD)" as the treatment policy after completion of the study were tabulated for each group.

Summary - conclusions

Efficacy results:

ADHD-RS-IV (physician's assessment)

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the total score from baseline were −3.3 (4.9), −2.3 (3.8) and −1.7 (4.2), respectively, at Visit 3; −5.7 (5.7), −4.6 (4.5) and −2.0 (5.0), respectively, at Visit 4; and −7.2 (6.3), −6.3 (6.2) and −2.5 (4.8), respectively, at Visit 5.
- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the inattentive subscale score from baseline were −2.2 (3.6), −1.5 (2.5) and −1.0 (2.9), respectively, at Visit 3; −3.6 (3.9), −3.0 (3.0) and −1.5 (3.4), respectively, at Visit 4; and −4.6 (4.2), −3.9 (4.2) and −1.7 (3.2), respectively, at Visit 5.
- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the hyperactivity/impulsivity subscale score from baseline were −1.1 (2.5), −0.7 (2.0) and −0.7 (2.6), respectively, at Visit 3; −2.0 (3.1), −1.6 (2.6) and −0.6 (2.9), respectively, at Visit 4; and −2.6 (3.5), −2.4 (3.0) and −0.8 (3.1), respectively, at Visit 5.
- In the SDT-001 group, the Sham group and the observation group, the 30% responder rates at Visit 5 were 35.5%, 28.6% and 15.6%, respectively, for the total score; 39.3%, 27.6% and 17.8%, respectively, for the inattentive subscale score; and 40.6%, 37.1% and 23.3%, respectively, for the hyperactivity/impulsivity subscale score.
- In the SDT-001 group and the Sham group, the total score, the inattentive subscale score and the hyperactivity/impulsivity subscale score decreased from baseline over time, indicating improving trends. Moreover, for all the scores, the mean changes from baseline at Visit 5 indicated greater improving trends in the SDT-001 group compared with in the Sham group. Nonetheless, the differences in the changes (least squares means) from baseline at Visit 5 between the SDT-001 group and the Sham group were −1.1 (95% CI = −2.7, 0.6; p = 0.2112) for the total score, −0.8 (95% CI = −1.9, 0.3; p = 0.1750) for the inattentive subscale score, and −0.3 (95% CI = −1.2, 0.5; p = 0.4199) for the hyperactivity/impulsivity subscale score, which were not statistically significant. For all the scores, the 30% responder rates at Visit 5 were numerically greater in the SDT-001 group than in the Sham group, however no statistically significant difference was indicated between the SDT-001 group and the Sham group.
- In the observation group, the total score, the inattentive subscale score and the hyperactivity/impulsivity subscale score at Visit 5 decreased from baseline, indicating improving

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trends.

ADHD-RS-IV (teacher's assessment)

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the total score from baseline at Visit 5 were −2.2 (5.0), −2.4 (5.7) and −0.6 (4.8), respectively.
- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the inattentive subscale score from baseline at Visit 5 were −1.1 (3.0), −1.5 (3.7) and −0.2 (3.4), respectively.
- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes in the hyperactivity/impulsivity subscale score from baseline at Visit 5 were −1.1 (2.9), −0.8 (2.8) and −0.4 (2.5), respectively.
- In the SDT-001 group and the Sham group, the total score, the inattentive subscale score and the hyperactivity/impulsivity subscale score at Visit 5 decreased from baseline, indicating improving trends. Nonetheless, the differences in the changes (least squares means) from baseline at Visit 5 between the SDT-001 group and the Sham group in the analysis of covariance were 0.0 (95% CI = −1.5, 1.4; p = 0.9667) for the total score, 0.4 (95% CI = −0.6, 1.3; p = 0.4435) for the inattentive subscale score, and −0.4 (95% CI = −1.2, 0.3; p = 0.2515) for the hyperactivity/impulsivity subscale score, which were not statistically significant.
- In the observation group, the total score, the inattentive subscale score and the hyperactivity/impulsivity subscale score at Visit 5 decreased from baseline, indicating improving trends.

T.O.V.A. ACS

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline were −0.04 (2.71), −1.15 (2.98) and −0.09 (2.30), respectively, at Visit 3; −0.13 (2.87), −1.40 (3.19) and −0.83 (2.89), respectively, at Visit 4; and −0.90 (3.59), −1.67 (3.73) and −0.85 (3.48), respectively, at Visit 5.
- In the SDT-001 group, the Sham group and the observation group, the proportions of participants with a T.O.V.A. ACS of ≥ 0 were 39.3%, 32.4% and 52.3%, respectively, at Visit 3; 40.6%, 28.2% and 35.6%, respectively, at Visit 4; and 34.0%, 31.4% and 35.6%, respectively, at Visit 5.
- In the SDT-001 group and the Sham group, the score decreased from baseline over time, indicating no improving trend. The proportions of participants with a T.O.V.A. ACS of ≥ 0 did not increase over time in the SDT-001 group and the Sham group, indicating no improving trend. For the

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T.O.V.A. ACS at Visit 5, the difference in the changes (least squares means) from baseline between the SDT-001 group and the Sham group was 0.80 (95% CI = −0.15, 1.74; p = 0.1003), which was not statistically significant.

- In the observation group, the score decreased from baseline over time, indicating no improving trend. The proportions of participants with a T.O.V.A. ACS of ≥ 0 did not increase over time, indicating no improving trend.

BRIEF

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline at Visit 5 were −0.7 (2.5), −0.3 (3.0) and −0.2 (2.7), respectively, for Monitor; −0.7 (2.3), −0.9 (2.0) and −0.5 (1.6), respectively, for Organization of Materials; −0.8 (3.9), −1.9 (4.3) and −0.6 (3.9), respectively, for Plan/Organize; −0.8 (3.5), −1.6 (3.5) and 0.2 (3.3), respectively, for Working Memory; −0.3 (2.9), −0.8 (2.4) and −0.3 (2.7), respectively, for Initiate; 0.4 (3.2), −0.3 (2.9) and 0.4 (3.1), respectively, for Emotional Control; −0.5 (2.4), 0.0 (2.5) and 0.4 (2.5), respectively, for Shift; −0.4 (2.9), −0.5 (2.7) and 0.0 (2.9), respectively, for Inhibit; −3.3 (11.9), −5.4 (12.4) and −1.3 (10.4), respectively, for Meta-Cognition; and −0.4 (6.4), −0.8 (6.5) and 0.7 (6.4), respectively, for Behavioral Regulation.
- In the SDT-001 group and the Sham group, the scores of Monitor, Organization of Materials, Plan/Organize, Working Memory, Initiate, Inhibit, Meta-Cognition and Behavioral Regulation decreased from baseline, indicating improving trends. For Emotional Control, the score decreased from baseline and an improving trend was indicated in the Sham group, however the score increased and no improving trend was indicated in the SDT-001 group. For Shift, the score did not change from baseline and no improving trend was indicated in the Sham group, however the score decreased and an improving trend was indicated in the SDT-001 group.
- In the observation group, the scores of Monitor, Organization of Materials, Plan/Organize, Initiate and Meta-Cognition decreased from baseline, indicating improving trends. For Working Memory, Emotional Control, Shift and Behavioral Regulation, the scores increased from baseline, indicating no improving trend. For Inhibit, the score did not change from baseline, indicating no improving trend.

Major variables of Conners 3^{TM} for parents

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline at Visit 5 were −3.3 (4.9), −2.7 (4.4) and −0.4 (4.1), respectively, for ADHD inattention; −2.9 (4.6), −3.2 (4.5) and −0.6 (3.7), respectively, for ADHD hyperactivity/impulsivity; −0.6 (2.8), −0.9 (2.7) and −0.4 (2.4), respectively, for conduct disorder;

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and −1.4 (3.4), −1.2 (3.4) and 0.0 (3.2), respectively, for oppositional defiant disorder.

- In the SDT-001 group and the Sham group, the scores of ADHD inattention, ADHD hyperactivity/impulsivity, conduct disorder and oppositional defiant disorder all decreased from baseline, indicating improving trends.
- In the observation group, the scores for ADHD inattention, ADHD hyperactivity/impulsivity and conduct disorder decreased from baseline, indicating improving trends. For oppositional defiant disorder, the score did not change from baseline, indicating no improving trend.

IRS

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline were −0.5 (1.0), −0.2 (1.2) and −0.1 (1.2), respectively, at Visit 3; −0.6 (1.2), −0.4 (1.2) and −0.2 (1.1), respectively, at Visit 4; and −0.9 (1.4), −0.7 (1.2) and −0.2 (1.1), respectively, at Visit 5.
- In the SDT-001 group and the Sham group, the score decreased from baseline over time, indicating improving trends.
- In the observation group, the score at Visit 5 decreased from baseline, indicating an improving trend.

CGI-I

- In the SDT-001 group, the Sham group and the observation group, the improvement rates (proportions of participants assessed as “very much improved” or “much improved”) were 11.1%, 2.8% and 2.3%, respectively, at Visit 3; 16.8%, 11.5% and 4.4%, respectively, at Visit 4; and 24.3%, 21.0% and 6.7%, respectively, at Visit 5.
- In the SDT-001 group and the Sham group, the improvement rates increased over time, indicating an improving trend. Moreover, the improvement rates in the SDT-001 group were always numerically greater than in the Sham group.
- In the observation group, the improvement rates increased over time, indicating an improving trend.

PGA

- In the SDT-001 group, the Sham group and the observation group, the improvement rates in the PGA (proportions of participants assessed as “very much improved” or “much improved”) were 6.5%, 3.8% and 2.3%, respectively, at Visit 3; 16.8%, 10.6% and 4.4%, respectively, at Visit 4; and 25.2%, 19.0% and 13.3%, respectively, at Visit 5.
- In the SDT-001 group and the Sham group, the improvement rates increased over time, indicating an

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improving trend. Moreover, the improvement rates in the PGA were always numerically greater in the SDT-001 group than in the Sham group.

- In the observation group, the improvement rates increased over time, indicating an improving trend.

PedsQL™ Generic Core Scales

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline were 2.44 (10.65), 1.92 (8.80) and 0.99 (8.97), respectively, at Visit 3; 3.89 (11.34), 3.70 (7.90) and 2.22 (7.69), respectively, at Visit 4; and 4.78 (12.21), 4.31 (8.95) and 3.45 (8.28), respectively, at Visit 5.
- In the SDT-001 group and the Sham group, the score increased from baseline over time, indicating improving trends.
- In the observation group, the score increased from baseline over time, indicating an improving trend.

EQ-5D-Y (visual analogue scale)

- In the SDT-001 group, the Sham group and the observation group, the means (standard deviations) of changes from baseline at Visit 5 were 3.1 (15.7), −0.6 (20.0) and −1.5 (24.8), respectively.
- The score at Visit 5 decreased from baseline and no improving trend was indicated in the Sham group, however, increased from baseline and an improving trend was indicated in the SDT-001 group.
- In the observation group, the score at Visit 5 decreased from baseline, indicating no improving trend.

Questionnaire for the security of blindness

- In the SDT-001 group and the Sham group, parents of 62/106 participants (58.5%) and 53/103 participants (51.5%), respectively, answered “I suppose the participant has used SDT-001”; as well as 53/79 participants (67.1%) and 50/80 participants (62.5%), respectively, answered “I suppose I have used SDT-001.” The results of the questionnaire did not show a difference between the SDT-001 group and the Sham group, indicating that the participants and/or their legally authorized representatives could not correctly identify which study device participant had used. Therefore, the blindness should have been maintained in this study.

Safety results:

- No participant died in the study.
- One non-fatal SAE (humerus fracture) occurred in 1 participant in the Sham group. The event was not related to the study device in the opinion of the investigator (subinvestigator). No non-fatal serious adverse device effect occurred.

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- There were 56 AEs in 38/108 participants (35.2%) in the SDT-001 group, 48 AEs in 35/107 participants (32.7%) in the Sham group and 12 AEs in 9/46 participants (19.6%) in the observation group. No AE led to discontinuation of the study device. The AEs that occurred in 3 or more participants in the SDT-001 group or the Sham group (the number of participants [incidence] in the SDT-001 group and the number of participants [incidence] in the Sham group) were nasopharyngitis (8/108 participants [7.4%] and 8/107 participants [7.5%]), headache (3/108 participants [2.8%] and 2/107 participants [1.9%]), somnolence (1/108 participants [0.9%] and 3/107 participants [2.8%]) and pyrexia (3/108 participants [2.8%] and 1/107 participants [0.9%]). In the observation group, no AE occurred in 3 or more participants.
- As AEs related to the study device (adverse device effects), 4 events occurred in 4/108 participants (3.7%) in the SDT-001 group and 5 events occurred in 4/107 participants (3.7%) in the Sham group. In the SDT-001 group, the adverse device effects were irritability, headache, tinnitus and nausea (each 1/108 participants [0.9%]). In the Sham group, the adverse device effects were somnolence (2/107 participants [1.9%]) and irritability, headache and asthenopia (each 1/107 participants [0.9%]).
- In the SDT-001 group and the Sham group, no severe AE occurred. As moderate AEs, 2 events (1 event each of oppositional defiant disorder and avulsion fracture) occurred in 2/108 participants (1.9%) in the SDT-001 group, and 3 events (1 event each of tooth fracture, humerus fracture and injury) occurred in 2/107 participants (1.9%) in the Sham group. The other AEs were all mild in severity. The moderate AEs were all not related to the study device in the opinion of the investigator (subinvestigator). The adverse device effects were all mild in severity.
- AEs with outcome of “not recovered/not resolved” occurred in 4/108 participants (3.7%) in the SDT-001 group (1 event each of oppositional defiant disorder, chalazion, rhinitis allergic and cough), 3/107 participants (2.8%) in the Sham group (1 event each of skin papilloma, asthma, eczema asteatotic and acne) and 0/46 participants (0%) in the observation group. AEs with outcome of “recovering/resolving” occurred in 5/108 participants (4.6%) in the SDT-001 group (1 event each of somnolence, eye pruritus, blepharospasm, rhinitis allergic, dental caries, hand fracture and avulsion fracture), 4/107 participants (3.7%) in the Sham group (1 event each of nasopharyngitis, rhinitis allergic, eczema and humerus fracture) and 1/46 participants (2.2%) in the observation group (1 event of seasonal allergy). Of all the other AEs, outcome was “recovered/resolved.” The AEs with outcome of “not recovered/not resolved” were all not related to the study device in the opinion of the investigator (subinvestigator). Of all the adverse device effects, outcome was “recovered/resolved.”
- For the questionnaire about gaming addiction, 28/108 participants (25.9%) and 26/106 participants (24.5%) in the SDT-001 group and the Sham group, respectively, at Visit 3 and 17/107 participants

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(15.9%) and 16/105 participants (15.2%) in the SDT-001 group and the Sham group, respectively, at Visit 5 answered "I want to use the study device for a longer time in a day." Moreover, 38/107 participants (35.5%) and 31/105 participants (29.5%) in the SDT-001 group and the Sham group, respectively, at Visit 5 and 33/103 participants (32.0%) and 28/101 participants (27.7%) in the SDT-001 group and the Sham group, respectively, at Visit 7 answered "I want to use the study device again." There was no event suggestive of gaming addiction.

Conclusions:

Efficacy results:

The ADHD-RS-IV total score, inattentive subscale score, and hyperactivity/impulsivity subscale score (physician's assessment) decreased from baseline over time to the last assessment (Visit 5) in the 6-week treatment period in both the SDT-001 group and the Sham group, indicating improving trends but no statistically significant difference between the SDT-001 group and the Sham group. Similarly, for all the endpoints (BRIEF, Conners 3TM for parents, IRS, CGI-I, PGA, PedsQLTM, and EQ-5D-Y) except T.O.V.A. ACS, the changes from baseline to the last assessment in the 6-week treatment period indicated improving trends in the SDT-001 group but no statistically significant difference between the SDT-001 group and the Sham group. Meanwhile, no improving trend was indicated for T.O.V.A. ACS in any of the SDT-001 group, the Sham group and the observation group, and there was no statistically significant difference between the SDT-001 group and the Sham group. The trends of the T.O.V.A. ACS were different from those of ADHD-RS-IV and other endpoints.

The above results suggest that SDT-001 may improve ADHD symptoms.

For the questionnaire for the security of blindness, the results did not show a difference between the SDT-001 group and the Sham group, indicating that the participants and/or their legally authorized representatives could not correctly identify which study device participant had used. Therefore, the blindness should have been maintained in this study.

Safety results:

There were 56 AEs in 38/108 participants (35.2%) in the SDT-001 group, 48 AEs in 35/107 participants (32.7%) in the Sham group and 12 AEs in 9/46 participants (19.6%) in the observation group. No AE led to discontinuation of the study device. As AEs related to the study device (adverse device effects), 4 events occurred in 4/108 participants (3.7%) in the SDT-001 group and 5 events occurred in 4/107 participants (3.7%) in the Sham group. There was no severe AE. As moderate AEs, 2 events (1 event each of oppositional defiant disorder and avulsion fracture) occurred in 2 participants in the SDT-001 group, and 3 events (1 event each of tooth fracture, humerus fracture and injury) occurred in 2 participants in the Sham group. For these events, the outcome was "recovered/resolved" for 2 events (1 event each of tooth fracture and injury), "recovering/resolving" for 2 events (1 event each of avulsion

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fracture and humerus fracture) and “not recovered/not resolved” for 1 event (oppositional defiant disorder). The other AEs and adverse device effects were all mild in severity. One non-fatal SAE (humerus fracture) occurred in 1 participant in the Sham group, which however was not related to the study device in the opinion of the investigator (subinvestigator).
The results of the questionnaire about gaming addiction showed no event suggestive of gaming addiction.
Based on the above results, there was no specific finding in terms of type, severity and outcome of AEs and adverse device effects, and no significant safety concern was suggested during and after use of this device.

In the statistical analysis plan, only comparison between the SDT-001 group and the Sham group was planned, and comparison between the SDT 001 group (or the Sham group) and the observation group was not planned. Evaluation of efficacy of SDT-001 compared to the observation group is described in the post-hoc analysis (Appendix 16.1.9).
In consideration of protocol deviation of this study etc., there was no impact of COVID-19 on the study.

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