A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial

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Summary

Background Attention-deficit hyperactivity disorder (ADHD) is a common paediatric neurodevelopmental disorder with substantial effect on families and society. Alternatives to traditional care, including novel digital therapeutics, have shown promise to remediate cognitive deficits associated with this disorder and may address barriers to standard therapies, such as pharmacological interventions and behavioural therapy. AKL-T01 is an investigational digital therapeutic designed to target attention and cognitive control delivered through a video game-like interface via at-home play for 25 min per day, 5 days per week for 4 weeks. This study aimed to assess whether AKL-T01 improved attentional performance in paediatric patients with ADHD.

Methods The Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) was a randomised, double-blind, parallel-group, controlled trial of paediatric patients (aged 8–12 years, without disorder-related medications) with confirmed ADHD and Test of Variables of Attention (TOVA) Attention Performance Index (API) scores of –1·8 and below done by 20 research institutions in the USA. Patients were randomly assigned 1:1 to AKL-T01 or a digital control intervention. The primary outcome was mean change in TOVA API from pre-intervention to post-intervention. Safety, tolerability, and compliance were also assessed. Analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02674633 and is completed.

Findings Between July 15, 2016, and Nov 30, 2017, 857 patients were evaluated and 348 were randomly assigned to receive AKL-T01 or control. Among patients who received AKL-T01 (n=180 [52%]; mean [SD] age, 9·7 [1·3] years) or control (n=168 [48%]; mean [SD] age, 9·6 [1·3] years), the non-parametric estimate of the population median change from baseline TOVA API was 0·88 (95% CI 0·24–1·49; p=0·0060). The mean (SD) change from baseline on the TOVA API was 0·93 (3·15) in the AKL-T01 group and 0·03 (3·16) in the control group. There were no serious adverse events or discontinuations. Treatment-related adverse events were mild and included frustration (5 [3%] of 180) and headache (3 [2%] of 180). Patient compliance was a mean of 83 (83%) of 100 expected sessions played (SD, 29·2 sessions).

Interpretation Although future research is needed for this digital intervention, this study provides evidence that AKL-T01 might be used to improve objectively measured inattention in paediatric patients with ADHD, while presenting minimal adverse events.

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder of persistent impaired attention, hyperactivity, and impulsivity that negatively affects daily functioning and quality of life. ADHD is one of the most commonly diagnosed paediatric mental health disorders, with a prevalence estimated to be 5% worldwide,[1] and exerts a substantial burden on families and society.[2]

Front-line intervention for ADHD includes pharmacological and non-pharmacological interventions, which have shown short-term efficacy.[3–5] Existing treatments have side-effects that limit their acceptability,[6] are only effective when administered, and may not be as effective for reducing daily impairments versus ADHD symptoms.[7] Pharmacotherapy may not be suitable for some patients due to caregiver preferences or concerns about abuse, misuse, and diversion. Barriers to access also limit the use of behavioural interventions, given a shortage of properly trained paediatric mental health specialists[8] and variability in insurance coverage for such services.[9,10] Indeed, studies in both the USA and the UK have found that most children with paediatric mental health needs do not have proper access to services.[11,12]

Digital therapeutics for ADHD may address these limitations with improved access, minimal side-effects, and low potential for abuse. Numerous studies and meta-analyses on digital interventions targeting specific cognitive functions have attempted to assess the magnitude of efficacy for children and adolescents with ADHD. In general, the quality of the studies is low, and many do not include a control group.[3] Reported effect

Research in context

Evidence before this study

We searched PubMed with the search terms "ADHD," "cognitive/digital training/therapeutic," "children/pediatric," and "clinical trial" between Jan 1, 2010, and July 31, 2019. We found that few digital interventions were available before 2010. We also examined review articles and meta-analyses between Jan 1, 2010, and July 31, 2019. Although we did not limit the search to English language publications, we were not able to review non-English language publications, however, no relevant trial seemed to be available in a non-English language journal. Several digitally based interventions for attention deficit hyperactivity disorder (ADHD) were identified. Many trials focused on training working memory, and fewer on targeted attention and cognitive control specifically. Further, many of the studies contained methodological limitations, including inadequate control conditions or masking, or both, no random assignment to intervention conditions, small sample size, and no safety or adverse event assessments. Many studies used outcome measures similar to the training tasks and did not use US Food and Drug Administration-approved cognitive outcomes or those commonly used in clinical settings. Indeed, meta-analyses on cognitive training for children with ADHD confirm that most current studies have inadequate methodology and cannot definitively evaluate the efficacy and clinical relevance of such treatments. The most comprehensive review of these studies to date concluded that digital interventions cannot be recommended on the basis of the current body of evidence.

Added value of this study

In this randomised controlled trial, AKL-T01 (an investigational digital therapeutic) increased attentional functioning in an objective measure of attention to a significant degree in paediatric patients with ADHD, as well as patient-reported and parent-reported attentional functioning. Across several secondary outcomes, including parent and clinician ratings of ADHD symptoms and functional impairment, AKL-T01 significantly improved outcomes from pre-intervention to post-intervention, but not to a significantly greater degree than the control condition. This trial represents one of a small number of randomised controlled trials for digital interventions for paediatric patients with ADHD. The methods were modelled after randomised controlled trials for other treatment modalities (ie, pharmaceutical trials) and represent a model approach for evaluating the effects of a digital intervention.

Implications of all the available evidence

This study shows that a digital intervention can significantly increase attentional functioning of children with ADHD. Future trials are warranted to examine the durability and time course of this novel intervention, as well as the appropriate dose that might provide optimal benefit. In addition, studies to better characterise the clinical significance of objective attention measures versus subjective symptom ratings are needed. These findings have implications for clinical practice, as AKL-T01 is a safe and easy-to-access intervention that could address various intervention needs for paediatric patients with ADHD and without comorbid conditions (ie, attention deficits), but cannot replace current standard of care.

sizes are generally small but differ widely with respect to interventions and study designs.[13] In addition, a recent meta-review concluded that a range of digital interventions, including working memory training and neurofeedback, could not be recommended for treatment of ADHD owing to inconsistent findings and generally minimal effects on outcomes provided by independent unmasked observers.[14] Nevertheless, meta-analyses conclude that interventions more broadly targeting cognitive functions generally show larger effects.

ADHD has numerous well characterised but heterogeneous neurobiological substrates underlying cognitive impairments that can serve as targets for intervention development.[15] For example, impairments related to attention and cognitive control are associated with lower activation of frontal, frontoparietal, and ventral attention networks.[16] Research on video games and game-based interventions that may alter brain structures and function, suggest that targeted digital interventions—based on current models of cognitive function and which leverage video game design to engage patients over time—are promising.[17] Anguera and colleagues[18] described a game-like intervention developed to engage the cognitive control and attention systems in older adults. The digital intervention improved cognitive performance and these changes were associated with functional electroencephalogram (EEG) changes in the prefrontal cortex.This intervention specifically targeted the management of cognitive interference, which occurs when two or more tasks compete for cognitive and attentional resources. The cognitive control and attention systems evaluated in these studies are similar to the deficits observed in paediatric patients with ADHD.[18,19] This overlap informed the development of a novel digital therapeutic, AKL-T01 (Akili Interactive Labs, Boston, MA, USA), which was developed to engage paediatric users through video game graphics and reward loops and to use real-time adaptive mechanisms that continuously personalise intervention difficulty on the basis of the user's ability and progression. Specifically, AKL-T01 targets attentional control to manage competing tasks and to efficiently (flexibly) shift attention between tasks. Further, divided and selective attention systems are required to process several tasks simultaneously. In an

unmasked, proof-of-concept study, a prototype version of AKL-T01 showed improvements in attention, inhibition, and working memory in paediatric patients with ADHD but not in patients without ADHD.[20]

The primary objective of the present trial was to evaluate the efficacy and tolerability of AKL-T01 in paediatric patients with ADHD.

Methods

Study design

STARS-ADHD was a randomised, double-blind, parallel-group, controlled trial done at 20 research institutions (appendix p 3) in the USA from July 15, 2016, to Nov 30, 2017. During the screening phase (days –28 to –7), patients were evaluated for eligibility. Children treated with medication for ADHD discontinued medication to at least 3 days before baseline. At baseline (day 0), additional eligibility criteria were assessed. The study was done in accordance with the International Conference on Harmonisation Regulations, and was approved by each site's institutional review board (Copernicus Group [14 sites], Duke University Health System, Cincinnati Children's Hospital Medical Center, University of California Davis, University of California San Francisco, Johns Hopkins Medical Center, and Western Institutional Review Board).

Participants

Eligible patients were aged 8–12 years with a confirmed diagnosis of ADHD as per the *Diagnostic and Statistical Manual of Mental Disorders* (5th edn) criteria and confirmed via the Mini International Neuropsychiatric Interview for Children and Adolescents Kid Screen at screening. Other key inclusion criteria included baseline scores on the ADHD Rating Scale-IV (ADHD-RS-IV) of 28 and above, the Test of Variables of Attention (TOVA) Attention Performance Index (API) –1·8 and below, indicating cognitive deficits in the attention domain, and a baseline intelligence quotient of 80 and above. Key exclusion criteria were significant comorbid psychiatric diagnoses and use of ADHD medications that could not be discontinued. Parents provided written informed consent with patient assent at screening–baseline. Complete inclusion and exclusion criteria are described in the appendix (p 2).

Children who recently used or were currently using stimulants were eligible, provided they were not optimally managed and willing to washout between 7 and 3 days before baseline. This group was of particular interest because parents and children would have recent experience with some form of pharmacological intervention. As such, randomisation was stratified by medication status at screening (see below).

To minimise bias, parents and patients were informed that the study was evaluating the effect of two different investigational interventions for ADHD. Previous market research with expert interviews in a sample of 59 children and parents was done to evaluate expectation of benefit of both interventions. The results suggested parents had a similar expectation of benefit from both AKL-T01 and our control condition (see appendix p 4). Parents and patients were discouraged from discussing their randomised intervention with anyone other than an unmasked study coordinator. Investigators and other masked site staff were not permitted access to source documents or case report forms.

Randomisation and masking

Eligible patients were randomly assigned 1:1 to receive AKL-T01 or a control. The randomisation scheme was generated by Duke Clinical Research Institute statistics by means of validated computer software-generated pseudorandom numbers. Randomisation was stratified by stimulant medication status at screening. Each site had unmasked staff who enrolled patients through the clinical data management system, obtained the randomised intervention, and trained patients on the assigned device. Devices were provided to the unmasked site staff by Akili (Akili Interactive Labs, Boston, MA, USA) along with the list that linked the device serial number to intervention; Akili was masked as to which patient received which device until after database lock. Parents, patients, and investigators completing outcome measure assessments were masked to intervention allocation (appendix p 4).

See Online for appendix

Procedures

Eligible patients were instructed to use their randomised intervention for about 10 min while the unmasked coordinator monitored the session to ensure patients could follow the rules of their assigned intervention.

Study interventions were administered by means of an iPad mini 2 tablet (Apple, USA). iPads either had AKL-T01 or the control preloaded, and patients accessed their randomised intervention with a unique username and password.

AKL-T01 is an investigational digital therapeutic that uses a proprietary algorithm designed to improve attention and related cognitive control processes, by training interference management at an adaptive and personalised high degree of difficulty. Interference is instantiated through a video game-like interface displaying two tasks that are to be done in parallel (multitasking): a perceptual discrimination targeting task in which users respond to the instructed stimulus targets and ignore the stimulus distractors (similar to a Go–No-Go task) and a sensory motor navigation task in which users continuously adjust their location to interact with or avoid positional targets. Performance in each task is assessed during single and interference (multitask) conditions. On the basis of the individual's performance, the interference training is adapted in real time, by means of a staircasing algorithm methodology. This tailors the training specifically to each individual's performance level to

achieve a consistent and optimal challenge at a predefined level of difficulty that is challenging but also tolerable. Further, on the basis of difference between single-task and interference performance, the user advances by reducing interference costs (closes the performance gap between interference and single-task conditions, at a specified level). Progress is signalled by earning rewards and unlocking new environments. As the user proceeds through the intervention and the different environments, periodic recalibration occurs to maintain an optimal difficulty level. AKL-T01 is presented in the video.

See Online for video

The control was designed to match AKL-T01 on expectancy, engagement, and time on task in the form of a challenging and engaging digital word game, targeting cognitive domains not targeted by the AKL-T01 intervention and not primarily associated with ADHD.[21] The user was instructed to find and connect letters on a grid to spell words; points are awarded on the basis of number of words formed, word length, and the use of unusual letters. There is progression in difficulty to maintain engagement and expectation of benefit from patients and their caregivers. During the intervention period (days 1–28), patients were instructed to use AKL-T01 or the control at home for 5 sessions per day (total time on task about 25 min), 5 days per week, for 4 weeks or the control for 25 min per day, 5 days per week, for 4 weeks. Compliance was monitored electronically by unmasked study co-ordinators, who notified parents by email if the intervention was not administered over a 48-h period. AKL-T01 and the control also generated automatic reminders. Additional information regarding the protocol may be found in the appendix (pp 6–7). The post-intervention visit was scheduled on day 28. Patients were reassessed for attentional functioning, ADHD symptoms, and impairment.

Outcomes

The primary outcome measure was the mean change in the TOVA API from pre-intervention to post-intervention. The TOVA is a validated, computerised, continuous performance test that objectively measures attention and inhibitory control, normalised by age and sex.[22] TOVA has been cleared by the US Food and Drug Administration (FDA) to facilitate assessment of attention deficits and to evaluate the effects of interventions in ADHD.

TOVA presents targets and non-targets as squares that either appear at the top or bottom of the screen. The task takes 21·6 min and consists of two halves: the first half has a target-to-non-target ratio of 1:3·5 (similar to sustained attention tests); the second half has a target-to-non-target ratio of 3·5:1, thus requiring more inhibitory control. TOVA calculates a wide range of outcome measures that assess processes known to be disrupted in patients with ADHD, such as response time variability (attention consistency), ex-Gaussian tau (attentional lapses), and response time (processing speed).[22,23] The TOVA API is a composite score of the sum of three scores: reaction time (RT) mean Half-1 (highly infrequent targets), RT variability total (both halves), and d-prime Half-2 (highly frequent targets).[22,23]

Secondary efficacy endpoints were between-group comparisons of pre-intervention and post-intervention change in scores on the Impairment Rating Scale (IRS), ADHD-RS-IV (Total [ADHD-RS-T], Inattentive [ADHD-R-I], Hyperactive/Impulsive [ADHD-RS-H] subscales), Clinical Global Impressions—Improvement (CGI-I), and the Behavior Rating Inventory of Executive Function (BRIEF; Parent Inhibit, Working Memory subscales, and Metacognition Index [post hoc]). Descriptions of each of the measures are provided in the appendix (pp 4–5).

We further analysed patient-reported and parent-reported perceived benefits related to attention improvements in real life (post hoc), assessed during a structured exit questionnaire asking whether the intervention helped their or their child's attention in real life, with yes or no responses.

During the intervention period, caregivers spontaneously reported adverse events by phone to masked investigators; any adverse events spontaneously reported during study visits were captured. Details about use, performance, and compliance with intervention were automatically recorded by the study devices and uploaded to central servers when the iPads were connected to wireless internet.

The proportions of responders at the end of treatment phase for primary and secondary endpoints were prespecified on the basis of previous studies,[20,24] and clinical meaningfulness for these analyses was defined as: API improvement greater than 1·4 points, and post-test API score 0 or more (normative range), ADHD-RS improvement of 2 points or more, CGI-I post-score of 1 (very much improved) or 2 or less (very much or much improved), and any improvement in IRS. Additional post-hoc responder definitions were also examined: ADHD-RS total score change 30% or more, and percentage of participants who scored in the normative range for TOVA standard score measures (>85, per the TOVA Clinical Manual).[22] In post-hoc analyses, intervention effects in the subgroup of children who washed out of ADHD medication after screening (n=20) and children who had discontinued medication before but within 30 days of screening (n=45) were explored.

Statistical analysis

A prespecified analysis plan governed all analyses, unless identified as post hoc. Power analyses determined that a sample size of 150 patients per intervention group would be sufficient to detect an effect size of 0·40 with 90% or more power on a two-tailed, between-patients *t* test and α criterion of 0·05.

A single interim analysis for sample-size re-estimation was prespecified to occur after half of the initial sample size was collected, and done by separate unmasked statistical staff in order to minimise any bias in the conduct of the study. If the conditional power of the interim sample indicated the need for a larger final sample, the estimated

sample size required would have been communicated to the sponsor and investigators, up to a maximum of 1000 total participants. The α criterion for the final analysis of the primary outcome was reduced by means of the O'Brien-Fleming alpha-spending method to 0·0412. Since the interim analysis only looked at the primary outcome, and analysis of the secondary outcomes was gated by success of the primary outcome, no α adjustment for the secondary outcomes was necessary. The interim analysis was done at n=75/75 (AKL-T01/control).

All outcomes were analysed in all randomly assigned patients by means of an intention-to-treat methodology. Safety data are presented for the population of patients that received AKL-T01 or control for at-home intervention. For the safety analysis, patients who received an intervention inconsistent with their original randomly assigned group (n=1 for AKL-T01 and n=1 for control) were recategorised to the intervention received.

The primary endpoint (change in TOVA API) was analysed by means of a Wilcoxon rank-sum test owing to evidence of non-normality. The α criterion for the final analysis was adjusted for the interim analysis sample-size re-estimation by means of the O'Brien-Fleming alpha-spending function, and the interim and post-interim cohorts were tested separately, with the results combined via the Cui-Hung-Wang method.[25] If the combined p value was less than the adjusted criterion, the primary endpoint was considered successful. The α criterion for the primary endpoint significance was 0·041.

Key secondary endpoints (IRS, ADHD-RS, CGI-I, and BRIEF-Parent) were analysed by Wilcoxon rank-sum tests due to evidence of non-normality. The between-group difference for the primary endpoint was calculated by means of the Hodges-Lehmann estimate of location shift to coincide with the use of a Wilcoxon test. Type I error was controlled with a resampling bootstrap method to adjust p values due to correlated endpoints. Secondary endpoints were not adjusted for sample-size re-estimation. If the adjusted p value was less than 0·050, the endpoint was considered significant. Responder analyses used χ^2 tests to compare AKL-T01 and control for the primary and secondary endpoints. To summarise findings across a range of outcomes, odds ratios and CIs were calculated to compare the efficacy of AKL-T01 versus control.

Prespecified sensitivity analyses of the primary and key secondary endpoints were designed to assess the effects of: cohort, site, age, sex, missing data (if >10% of outcome data were missing), and parent expectancy (secondary endpoints only). For the primary and key secondary endpoints, post-hoc non-parametric analyses for within-group changes (pre-intervention *vs* post-intervention) were done by means of the Wilcoxon signed-rank test (SAS version 9.4).

Descriptive statistics summarised patient demographics, protocol deviations, intervention compliance, intervention-related adverse events, and qualitative survey results. Compliance with intervention was defined as the percentage of instructed sessions use completed during the intervention period or the percentage of instructed use time for the control (as the control did not follow a five-sessions-a-day format).

Post-hoc *t* tests for between-group and within-group changes were done on the primary and key secondary endpoints to assess sensitivity of results to statistical methodology. All such tests were in agreement with corresponding non-parametric Wilcoxon tests with respect to significance for all results reported.

A post-hoc Fisher's exact test was done to compare the percentage of patients–parents in the two groups who indicated real-life improvements related to attention on the exit questionnaire (yes or no response).

Protocol amendments

Three versions of the protocol were used throughout the study. Under the first version (version 1.0, dated Nov 17, 2015), no participants were enrolled. Under the second version (version 1.01, dated April 6, 2016), 43 participants were enrolled. Under the third version (version 1.02, dated July 25, 2016), 305 participants were enrolled. Details regarding all of the changes made for each of these amendments are found in the appendix (pp 6–7). One exclusion criterion was added to version 1.01 that disallowed participation for children who had previously been in a study with AKL-T01. Version 1.01 also added a requirement that participants be able to spell at least two words during the EVO: Words assessment at baseline. Version 1.02 added a requirement that sites document a discussion with participants and caregivers regarding intended and unintended use of the devices.

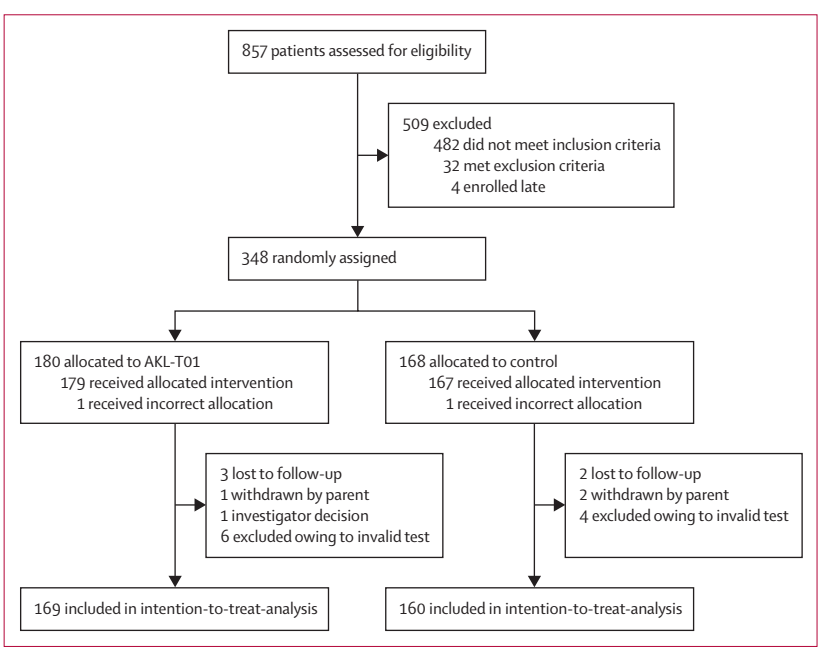


Figure 1: **Trial profile**
Detailed information on inclusion and exclusion criteria can be found in the appendix (p 2). AKL-T01=an investigational digital therapeutic.

	AKL-T01 (n=180)	Control (n=168)
Age, years	9·7 (1·3)	9·6 (1·3)
Male	125 (69%)	123 (73%)
Female	55 (31%)	45 (27%)
Baseline score		
Test of Variables of Attention—Attention Performance Index*	−5·1 (3·0)	−4·9 (3·1)
Impairment Rating Scale	5·5 (1·1)	5·5 (1·2)
ADHD-Rating Scale	39·0 (6·8)	38·3 (6·6)
ADHD-Rating Scale—Inattentive	21·9 (3·5)	21·6 (3·7)
ADHD-Rating Scale—Hyperactivity	17·1 (6·0)	16·7 (5·4)
Clinical Global Impressions—Severity†	4·5 (0·7)	4·6 (0·6)

Data are n (%) or mean (SD). AKL-T01=an investigational digital therapeutic. *n=179 for AKL-T01. †Assessed only at baseline.

Table 1: **Baseline characteristics**

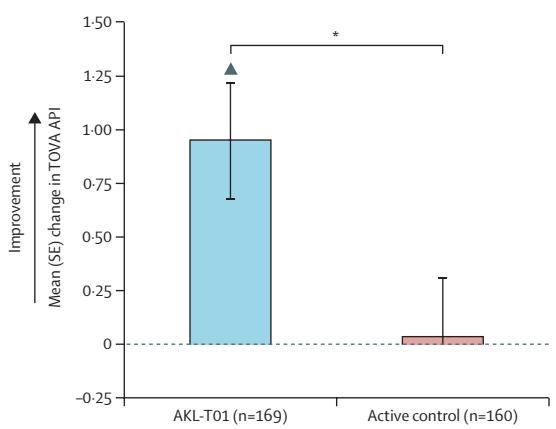


Figure 2: **Primary endpoint: TOVA API mean (SE) change pre-intervention to post-intervention in the intention-to-treat population**
*Adjusted p<0·050; prespecified Wilcoxon rank-sum test. Triangle represents median change, pre-intervention to post-intervention.

	AKL-T01	Control	χ^2 test	p
Test of Variables of Attention—Attention Performance Index (type A: improvement >1·4 points)	79/169 (47%)	51/160 (32%)	7·60	0·0058
Attention Performance Index (type B: post-intervention score ≥0)	18/170 (11%)	7/160 (4%)	4·54	0·033
ADHD-Rating Scale (improvement ≥2 points from pre-intervention to post-intervention)	128/173 (74%)	119/164 (73%)	0·088	0·77
ADHD-Rating Scale (≥30% reduction)*	42/173 (24%)	31/164 (19%)	1·43	0·23
Impairment Rating Scale	82/171 (48%)	60/161 (37%)	3·87	0·049
Clinical Global Impressions (≤2 at post-intervention)	29/175 (17%)	26/164 (16%)	0·032	0·86
Clinical Global Impressions (1 at post-intervention)	1/175 (1%)	1/164 (1%)	0·0021	0·96

Data are n/N (%) unless otherwise indicated. AKL-T01=an investigational digital therapeutic. *Post-hoc analysis. ADHD=Attention-deficit hyperactivity disorder. AKL-T01=an investigational digital therapeutic.

Table 2: **Clinical responder analysis intention-to-treat population**

Other changes included more details on device management and inventory procedures, updates to the statistical analysis section, requirements that unmasking events be captured in the study database, and a requirement that the same clinician rater complete assessments at pre-study and post-study timepoints. These changes are not expected to have any effect on study outcomes. VeraSci Trials (formerly NeuroCog Trials) reviewed data for select cognitive and clinical measures to determine quality and consistency within and between measures. This trial is registered with ClinicalTrials.gov, NCT02674633.

Role of the funding source

The funder had a role in study conception and design, confirming data and statistical analyses, and conducting the study. All authors had full access to all the data in the study and were involved in data interpretation and writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of 857 children screened for eligibility, 348 patients were randomly assigned to receive AKL-T01 (n=180) or control (n=168) between July 15, 2016, and Nov 30, 2017 (figure 1 and appendix p 3). Demographic and clinical characteristics at baseline are shown in table 1.

The mean number of sessions completed by patients in the AKL-T01 group was 83·2 out of 100 sessions (83% instructed use; SD=29·2 sessions). Patients in the control group used their intervention 480·7 min of 500 min (96% instructed use).

There was a significant difference between intervention groups on the primary efficacy endpoint (adjusted p=0·0060); non-parametric estimate of the population median change (Hodges-Lehmann estimate) was 0·88 (95% CI 0·24–1·49). The mean (SD) change from baseline on the TOVA API was 0·93 (3·15) in the AKL-T01 group and 0·03 (3·16) in the control group (figure 2). There were no intervention-group differences for secondary measures: IRS, ADHD-RS, ADHD-RS-I, ADHD-RS-H, BRIEF-Parent Inhibit and Working Memory and Metacognition (post hoc) from pre-intervention to post-intervention or mean CGI-I score at post-intervention (appendix pp 4–5).

Sensitivity analyses showed no evidence that site, baseline TOVA API, age, or sex attenuated the intervention effect. Because missing data did not exceed the prespecified limit, sensitivity analyses for missing data were not done. Sensitivity to parent expectancy was not evaluated owing to lack of significant differences between groups on the secondary endpoints.

In post-hoc within-group analyses, change in TOVA API score from pre-intervention to post-intervention significantly improved with AKL-T01 (p<0·0001) but not with control (p=0·67). Both AKL-T01 and patients in the control group showed significant within-group improvements in all secondary endpoints (appendix pp 4–5).

Additional exploratory post-hoc analyses were done to better interpret the change in objective measures of attention. The Standard Score transformations of TOVA components related to attention were analysed for between-group differences: significant between-group effects in favour of AKL-T01 were found for RT mean Half-1 (p<0·0003), RT variability total (p=0·019), and ex-Gaussian tau (p=0·0014).

Responder analyses showed that AKL-T01 resulted in TOVA API score improvements of greater than 1·4 points in 79 (47%) of 169 patients versus 51 (32%) of 160 controls (p=0·0058; table 2). AKL-T01 versus control was also associated with the movement of more patients into the normative ranges across different measures of attention on TOVA: API of 0 and above in 18 (11%) of 170 versus 7 (4%) of 160, RT mean Half-1 in 32% versus 16%, and RT variability total in 22% versus 13% (p values API p=0·033, RT mean Half-1 p=0·0043, RT variability total p=0·030). Overall, AKL-T01 versus controls moved significantly more patients into the normative range in at least one objective measure of attention (36% *vs* 21%, p=0·0027). IRS responder rates were significantly higher after AKL-T01 versus control (82 [48%] of 171 *vs* 60 [37%] of 161, p=0·049). Remaining responder comparisons did not differentiate between groups.

The percentage of patients reporting an improvement in attention on the exit questionnaire for AKL-T01 versus control (126 [73%] of 172 *vs* 107 [66%] of 162) was not significant ($\chi^2(1)=2·054$, p=0·15). However, the percentage of parents reporting improvements in their child's attention was significantly higher for AKL-T01 versus control (97 [56%] of 173 *vs* 71 [44%] of 162, $\chi^2(1)=5·015$, p=0·025). Comparisons of the efficacy of AKL-T01 versus control across a range of outcomes are summarised in figure 3.

In post-hoc analyses of patients who discontinued stimulant medication, within 30 to 3 days before the start of the study (washout group), AKL-T01 significantly differentiated from control on most secondary efficacy endpoints including ADHD-RS (p=0·0092), ADHD-RS-I (p=0·0083), and CGI-I (p=0·012). The difference between medication washout groups on the IRS was not significant (p=0·065; figure 4).

The proportion of patients reporting any intervention-related adverse events was 12 (7%) of 180 with AKL-T01 and 3 (2%) of 168 with control (table 3). There were no serious intervention-related AEs or discontinuations due to AEs in either group. The most common intervention-related AEs associated with AKL-T01 were frustration (5 [3%] of 180) and headache (3 [2%] of 180).

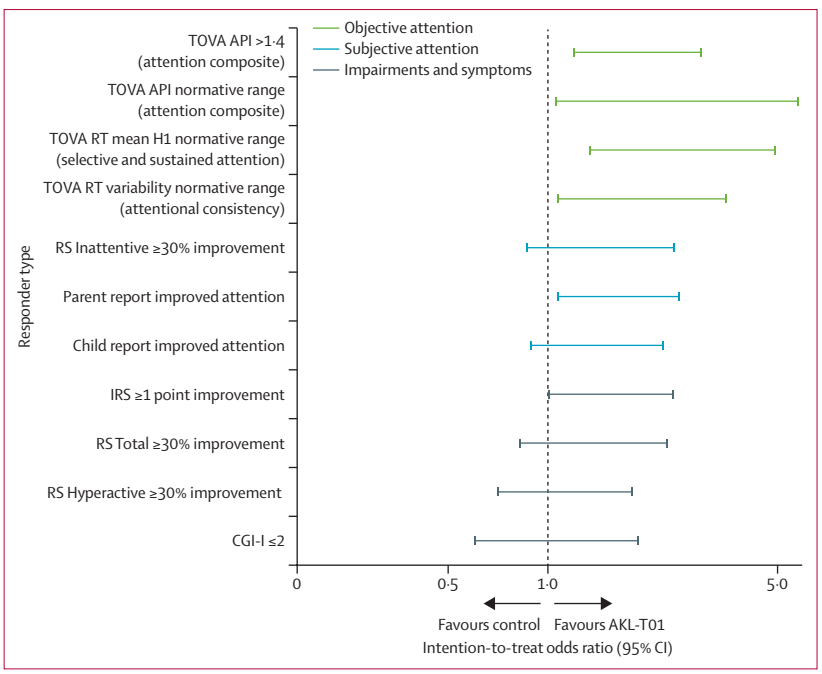


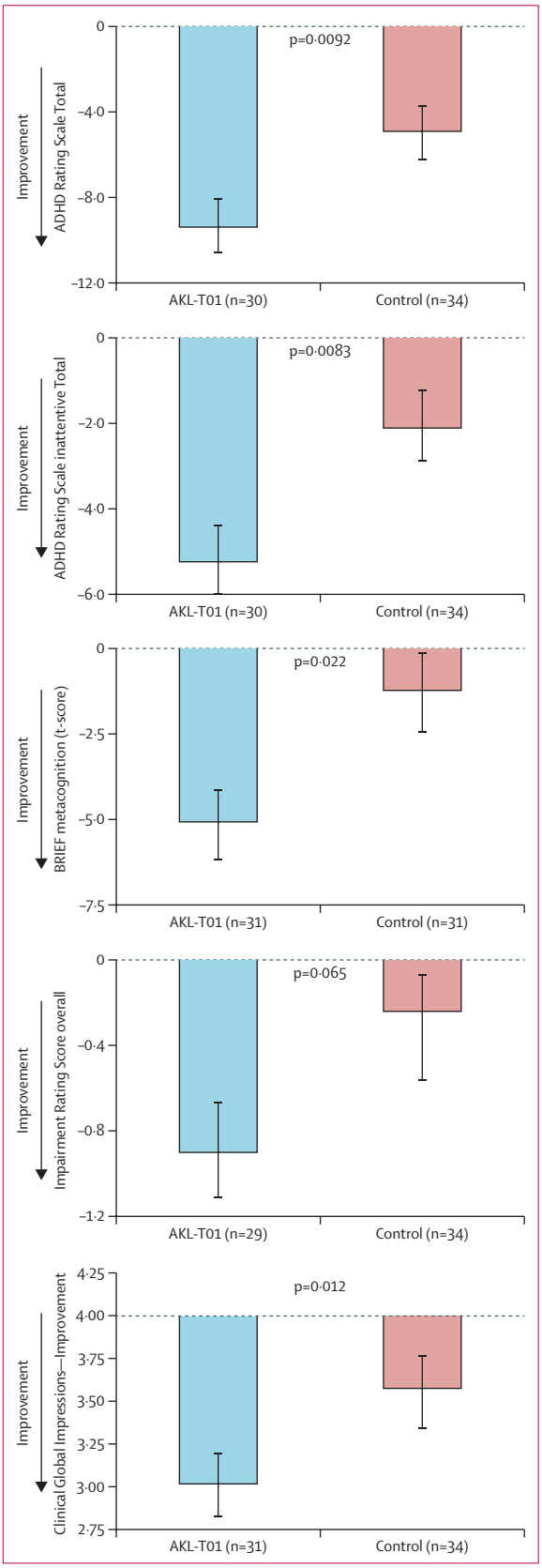
Figure 3: **STARS-ADHD intention-to-treat responder forest plot**
Odds ratio of 1·0 indicates that participants do not respond more to AKL-T01 than control. CIs in which the lower bound does not cross 1·0 are significant. API=Attention Performance Index. CGI-I= Clinical Global Impressions-Improvement. IRS=Impairment Rating Scale. RT mean H1=Reaction Time Mean during First Half of the TOVA. RS Inattentive=ADHD Rating Scale—Inattentive. RS Hyperactive= ADHD Rating Scale—Hyperactivity. ADHD=Attention-deficit hyperactivity disorder. TOVA=Test of Variables of Attention. AKL-T01=an investigational digital therapeutic.

Discussion

In this randomised controlled clinical trial of a digital intervention for ADHD, the active intervention AKL-T01 significantly improved performance on the primary outcome measure—an objective measure of attention (TOVA API) in paediatric patients with ADHD compared with the control condition. Across a range of secondary outcomes, including parent and clinician ratings of ADHD symptoms and functional impairment, the effects of AKL-T01 from pre-intervention to post-intervention were not different from the control condition. Additional attention-related measures from TOVA, including mean reaction time during infrequent target stimuli, and response variability (ie, total RT variability and ex-Gaussian tau) showed significantly greater improvements in the AKL-T01 group. Globally, parent-reported improvement of attention, as assessed by the exit survey, was higher in the AKL-T01 group compared with controls. A prespecified subgroup of patients who washed out of medications showed significant between-group effects on several secondary endpoints, including ADHD symptoms.

Both interventions were very well tolerated; only 12 (7%) of 180 and 3 (2%) of 168 patients in the AKL-T01 and control groups had intervention-related AEs, respectively. All AEs associated with AKL-T01 were classified as mild or moderate in severity and resolved after study discontinuation.

The current study findings of improved attention (via TOVA API) following treatment with AKL-T01 are consistent with benefits reported in previous uncontrolled studies.[18,20] As a digital therapeutic, AKL-T01 could



theoretically address several challenges faced by existing interventions. First, its risk–benefit profile is favourable, as only 12 (7%) of 180 patients assigned to AKL-T01 had AEs, compared with rates of 40–60% in trials of commonly used stimulant medications.[26] Therefore, AKL-T01 could be added to standard of care without substantial additional safety concerns. Second, the digital nature of this intervention could reduce barriers to access that are inherent in other forms of behavioural or non-pharmacological interventions.[27] Digital interventions have been cited as possible ways to improve otherwise poor access to mental health services.[14]

The primary outcome measure for this trial—the TOVA API—differs from most pharmacological efficacy trials for ADHD, which typically use parent-rated or clinician-rated symptom measures. The selection of the TOVA was based on several factors. First, because AKL-T01 was designed specifically to target cognitive control and attention, we sought an outcome that would most precisely and validly index these processes. The TOVA is an FDA-cleared device[23] for the objective assessment of attention and inhibitory control as part of an ADHD diagnosis or for monitoring intervention outcomes and has been widely used in both clinical practice and research studies. Second, the TOVA measures cognitive functions that are relevant to the clinical presentation of ADHD,[28] and attention performance metrics such as RT mean, RT variability, and ex-Gaussian tau are well characterised indicators of attention-relevant cognitive processes, and are associated with clinically relevant outcomes including academic behaviour[29] and inattention and social problems.[30]

Finally, the TOVA setting has been described as mimicking "one component of the classroom situation in which children are required to remain seated and engaged in a tedious, repetitive task,"[31] suggesting ecological validity of the TOVA test for real-world settings in which children with ADHD often struggle.[31] Traditional, symptom-based measures were included as secondary measures. We also selected the IRS as a targeted measure of ADHD-related impairment because, as noted previously, attentional processes are specifically linked to relevant clinical outcomes and symptom-based measures (eg, ADHD-RS) and do not always correlate highly with measures of functional impairment.[5] For example, in a paediatric stimulant medication trial, greater than 40% of patients who showed a positive response on the primary outcome measure (>30% reduction on the ADHD-RS) failed to show significant functional improvement on a validated measure of impairment.[7] It has also been reported that across four large-scale ADHD research samples, the average correlation between symptoms and

Figure 4: **Medication washout subpopulation, subjective measures**
ADHD=attention-deficit hyperactivity disorder. BRIEF=Behavior Rating Inventory of Executive Function.

impairment accounted for less than 10% of variance.[31] In the current trial, despite there being few group differences on the ADHD-RS, significantly more children in the AKL-T01 group were responders on the IRS, suggesting that this intervention, like other non-pharmacological interventions, may differentially affect impairment versus symptoms.

In post-hoc analysis, children with a recent history of pharmacological intervention exhibited significant AKL-T01-related improvements in a range of symptom-based outcomes, including ADHD-RS. This finding could be related to biological factors associated with a recent pharmacological intervention, or psychological factors such as parents being more attuned to symptom changes in children recently treated with medication. Further studies are warranted to explore the potential effects of AKL-T01 in this important subgroup.

In the current study, there were no differences between AKL-T01 and the control condition on secondary measures, and several factors might explain these findings. First, it is possible that parent or clinician-reported outcomes (ie, ADHD-RS) are not sensitive to the effects of AKL-T01. In other words, the shown effects of the intervention on attentional processes may not be as readily observable by parents and clinicians. The clinical implications of this possibility will be important to explore in future studies. Second, expectations of efficacy have been shown to moderate intervention effects in general, and also for digital interventions.[32] In our study, parents of patients in both groups believed that their child received a novel intervention for ADHD; thus, the expectation of intervention effect can be assumed for both interventions, and may partially explain improvements in both groups. This design feature is different from most pharmacological studies in which patients and their caregivers are aware of a non-active, placebo condition. Finally, specific mechanisms common to AKL-T01 and the control condition may have resulted in improvements in both groups. Both interventions required continued perseverance, sometimes in the face of failure, and may have trained coping and reappraisal skills or even increased the sense of self-efficacy and mastery.[33] Thus any intervention that requires the patient to engage in a regular, structured setting that may include repeated failure or repetitiveness can be seen as a potential intervention for ADHD.

The current study has several important limitations. First, the inclusion criteria required that patients have a TOVA API up to –1·8, thus showing an objective baseline deficit in attentional function. This resulted in a substantial number of patients with a clinical ADHD diagnosis being excluded from the trial. Second, children could not be taking medication for ADHD during the trial and could not have significant psychiatric comorbidity. Therefore, it is unclear if these findings will generalise to the broader population of patients with ADHD who have comorbid conditions or patients taking medication.

	AKL-T01 (n=180)	Active control (n=168)
Patients experiencing intervention-emergent adverse events	12 (7%)	3 (2%)
Frustration	5 (3%)	0
Headache	3 (2%)	2 (1%)
Emotional reaction	2 (1%)	1 (1%)
Dizziness	1 (1%)	0
Nausea	1 (1%)	0
Aggression	1 (1%)	0

Data are n (%). AKL-T01=an investigational digital therapeutic.

Table 3: **Summary of intervention-emergent adverse events (intention-to-treat population)**

Third, the study evaluated a 28-day intervention period with approximately 25-min daily sessions; it is unclear if the benefits in attentional functioning might have been observed with a different regimen. The current study represents a single intervention of 1-month duration, which is quite short. Additional studies with longer intervention periods are needed. An ongoing study (ClinicalTrials.gov identifier: NCT03649074) is examining longer intervention periods (repeat intervention for a total of 2 months) and durability of effects 1 month after the intervention. In addition, that study is investigating whether the intervention has effects in children currently treated with stimulant medication, which will help address questions of generalisability. Fourth, power analyses were calculated for our primary outcome to power our trial, but no power calculations were done for any of our secondary outcomes or post-hoc analyses. Fifth, the study did not collect data (eg, EEG) that would offer mechanistic explanation for the findings. The foundational study from which the intervention was developed reported that effects of the AKL-T01 prototype were mediated by EEG changes. Since EEG data were not collected in this study, conclusions cannot be drawn about the neural mechanisms that might underlie intervention effects. Given these limitations, the transfer of benefit of the AKL-T01 intervention to real-world settings and the full clinical meaningfulness of the findings, as well as the mechanisms underlying these effects, should be explored in further studies.

Despite these limitations, the current trial had several features that strengthen confidence in the results. Diagnostic methods modelled after pharmacological randomised controlled trials were used to establish eligibility for the study. Considerable steps were taken to minimise potential biases or differences in the expectation of benefit between AKL-T01 and control. These included having masked raters and clear procedures for minimising discussion between parents and study staff about intervention assignment, and instructing parents and children in both groups who believed that they were receiving an investigational intervention for ADHD.

The STARS-ADHD trial represented a randomised controlled trial for the evaluation of a digital intervention to improve objectively measured attention in children with ADHD. It showed that compared to the control condition, AKL-T01 significantly improved objective measures of attention, as measured by the TOVA. AKL-T01 also showed effects that were not different from the control condition, including the ADHD-RS. The intervention was well tolerated, and this risk–benefit ratio suggests that AKL-T01 could be a novel addition to the range of intervention options for ADHD. The digital nature of the intervention could help to increase access for populations who might not otherwise be able to find non-pharmacological interventions. Various additional questions remain to be answered regarding the full clinical meaningfulness of the findings, the effect of different dosing schedules, and which patients might benefit the most from this type of intervention. Given these limitations, the results of the current trial are not sufficient to suggest that AKL-T01 should be used as an alternative to established and recommended treatments for ADHD.

Contributors

SHK, RLF, RSEK, AJC, and SVF had a role in the concept and design. SHK, DJD, EC, JL, RLF, RSEK, JNE, and AJC had a role in acquisition, analysis, or interpretation of data. SHK, DJD, EC, JL, RSEK, RLF, and JNE drafted the manuscript. SHK, DJD, EC, JL, RLF, RSEK, JNE, AJC, and SVF critically revised the manuscript. DJD and RSEK did the critical analysis. SHK and RSEK obtained funding. DJD, EC, and RSEK provided administrative, technical and material support. SHK, DJD, RSEK, and JNE supervised.

Declaration of interests

SHK is a consultant, principal investigator and owns stock options for Akili Interactive Labs and received research support or consulting fees from Arbor, Bose, Ironshore, Jazz, KemPharm, Neos, Otsuka, Rhodes, Shire, Sunovion, and Tris. JL, DJD, and EC are employed by Akili Interactive Labs and may own stock options. EC is a patent holder (WO/2018/027080) for Processor Implemented Systems and Methods for Measuring Cognitive Abilities. RLF receives or has received research support, acted as a consultant or served on a speaker's bureau for Acadia, Aevi, Akili, Alcobra, Allergan, Amerex, American Academy of Child & Adolescent Psychiatry, American Psychiatric Press, Arbor, Bracket, Daiichi-Sankyo, Epharma SolutionfMRIs, Forest, Genentech, Insys, Ironshore, KemPharm, Luminopia, Lundbeck, Merck, the US National Institutes of Health, Neurim, Noven, Nuvelution, Otsuka, Patient-Centered Outcomes Research Institute, Pfizer, Physicians Postgraduate Press, Receptor Life Sciences, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, Teva, TouchPoint, Tris, and Validus. RSEK is a consultant for Akili Interactive Labs and has received research support or consulting fees from Aeglea, Akebia, Akili Interactive Labs, Alkermes, Allergan, ArmaGen, Astellas, Avanir, AviNeuro/ChemRar, Axovant, Blood Alcohol Content Testing Battery, Biogen, Boehringer Ingelheim, Cerecor, CoMentis, Critical Path Institute, Forum Pharmaceuticals, Gammon Howard & Zeszotarski, Global Medical Education, GW Pharmaceuticals, Intracellular Therapeutics, Janssen, Kempharm, Lundbeck, Lysogene, Matrics Battery, MedScape, Mentis Cura, Merck, Merrakris Therapeutics, Minerva Neurosciences, Mitsubishi, Montana State University, Monteris, Moscow Research Institute of Psychiatry, National Institute of Mental Health, Neuralstem, Neuronix, Novartis, NY State Office of Mental Health, Orygen, Otsuka, Paradigm Testing, Percept Solutions, Pfizer, Pharm-Olam, Regenix Bio, Reviva, Roche, Sangamo, Sanofi, SOBI, Sengenix, Six Degrees Medical, Sunovion, Takeda, Targacept, Teague Rotenstreich Stanaland Fox & Holt, Thrombosis Research Institute, University of Moscow, University of Southern California, University of Texas Southwest Medical Center, Virtual Reality Functional Capacity Assessment Tool, VeraSci, WebMD, and Wilson Therapeutics and is owner of VeraSci, which provided support for this trial. JNE is a consultant for Akili Interactive Labs and receives grant support, research support, or royalties from Akili Interactive Labs, the American Academy of Pediatrics, American Board of Pediatrics, IXICO, Multi-Health Systems, and mehealth for ADHD. AJC has received research support, honoraria, or consulting fees from Akili Interactive Labs, Arbor, Ironshore, Neos, Otsuka, Purdue Canada, Shire, Sunovion, Supernus, and Trisand is a member of the Neuroscience Education Institute Board. SVF reports income, potential income, travel expenses, continuing education support, or research support from Akili Interactive Labs, Arbor, Enzymotec, Genomind, Ironshore, Otsuka, Shire–Takeda, Sunovion, and Supernus and a US patent (US20130217707 A1) for the use of sodium–hydrogen exchange inhibitors in the treatment of ADHD.

Data sharing

The STARS-ADHD Investigators agree to share de-identified individual participant data, the study protocol, and the statistical analysis plan with academic researchers 6 months after publication, and following completion of a Data Use Agreement. Proposals should be directed to medinfo@akiliinteractive.com.

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