Endeavor™

Instructions for use

For parents, caregivers and healthcare professionals

Digital therapeutic for pediatric Attention Deficit Hyperactivity Disorder (ADHD)

Caution: Contact your child's healthcare provider before using Endeavor. During the COVID-19 public health emergency, Endeavor is being made available without a prescription under FDA's emergency guidance for digital health devices.

REF This document is intended to support treatment version:
1.3

MANUFACTURER

Akili Interactive Labs, Inc.

125 Broad Street 4th Floor, Boston, MA 02110 USA

These Instructions for Use were last updated in June 2020

Part Number: 5014 Revision C

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Labels and Symbols

CAUTION: Pay special attention to the following details

Manufacturer

Reference Part Number

Consult Instructions for Use

We’re here to help.

Akili Assist is available for questions regarding the use of Endeavor and to offer technical assistance.

Available: Monday–Friday (excluding National Holidays)

Hours of Operation: 9:00 am – 5:00 pm Eastern time zone (EST/EDT)

Website: AkiliAssist.com

Phone: 1-844-AKILI-IQ (1-844-254-5447)

Cautions ⚠

During the public COVID-19 health emergency, Endeavor is being provided without a prescription. Please ensure you contact your child's physician before using Endeavor.

The Endeavor treatment is not intended to be used as a stand-alone therapeutic and is not a substitution for your child's medication.

For medical questions, please contact your child's healthcare provider. If you are experiencing a medical emergency, please dial 911.

If your child experiences frustration, emotional reaction, dizziness, nausea, headache, eye-strain, or joint pain while playing Endeavor pause the treatment. If the problem persists contact your child's healthcare provider. If your child experiences a seizure stop the treatment and contact your child's healthcare provider.

Please follow all of your mobile device manufacturer's instructions for the safe operation of your mobile device. For example, this may include appropriate volume settings, proper battery charging, not operating the device if damaged, and proper device disposal. Contact your mobile device manufacturer for any questions or concerns that pertain to your device.

Notes

Endeavor may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict use of a mobile device; parents should consult with their child's healthcare provider.

Endeavor

Indications for Use, Side Effects and Additional Resources

INDICATIONS FOR USE

Endeavor is a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined-type ADHD who have a demonstrated attention issue. Patients who engage with Endeavor demonstrate improvements in a digitally assessed measure, Tests of Variables of Attention (TOVA®), of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. Endeavor should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

SIDE EFFECTS

There were no serious adverse events seen in any clinical trials of Endeavor. Of 538 participants using Endeavor (AKL-T01) in clinical trials, 50 participants (9.3%) experienced treatment-related adverse events. Endeavor associated adverse events included frustration (6.1%), headache (1.3%), dizziness (0.6%), emotional reaction (0.4%), nausea (0.4%), and aggression (0.2%). All adverse events were generally transient. Only 3 events led to device discontinuation, and no participant reported lasting or irreversible effects after discontinuation.

NOTE: Endeavor was previously know as AKL-T01 during the clinical investigations.

Additional resources related to the treatment of ADHD can be found at:

CHADD®, Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD®)
www.chadd.org

The National Resource Center on ADHD
www.chadd.org/nrc

AAP, American Academy of Pediatrics, Healthy Children Parenting Website
www.healthychildren.org

AACAP, American Academy of Child and Adolescent Psychiatry, Family Resources
www.aacap.org

Core Technologies

Patented, proprietary mechanics designed to target key neurological attention processing systems

SELECTIVE STIMULUS MANAGEMENT

With neuroscience and technology as its foundation, the Selective Stimulus Management Engine (SSME™) is a proprietary & patented technology that is designed for the targeted activation of specific neural systems in the brain to treat diseases with associated cognitive dysfunction. The technology presents specific sensory stimuli and simultaneous motor challenges designed to target and activate the neural systems which play a key role in attention function.

The technology platform implements algorithms that adapt in both real-time and between treatment sessions to automatically adjust the difficulty level for a personalized treatment experience that is adapted to the needs of each individual patient. This enables second by second monitoring of patient progress completing the treatment sessions, and continuously challenges each patient to an optimized level, encouraging patients to improve their performance.

Product Description

Endeavor is a digital, non-drug treatment that is delivered through an action video game that was shown to improve attention function in children with ADHD.

The Endeavor treatment is used on a mobile device. See page 18 for compatible devices.

Endeavor is different from other action video games that a child might play because it was developed and programmed using scientific principles known to strengthen regions of the brain that regulate attention. The treatment programmed into the game was scientifically designed to challenge a child's attention during treatment, requiring attention and focus on multiple tasks at the same time.

Endeavor has been evaluated in over 600 children with ADHD across 5 clinical studies:

- A study of 348 children with ADHD, where Endeavor was used for a 4-week treatment period and showed improvements in attention measures and attention-related ADHD symptoms and behaviors.
- A study of 206 children with ADHD, where Endeavor was used for two 4-week periods and showed that an additional treatment period resulted in further improvements in attention-related ADHD symptoms and behaviors.
- Three separate studies of 40, 20 and 19 children with ADHD, where Endeavor was used for a 4-week treatment period and showed improvements in attention measures and attention-related ADHD symptoms.

Getting Started with Endeavor™

Endeavor is provided in **1-month treatment cycles**. At the end of each treatment cycle, your child may benefit from another 1-month treatment cycle. If your child has experienced any side effects from using Endeavor and if you have any questions about the benefit of continuing with Endeavor treatment, please contact your child's physician to discuss your child's experience and determine if additional treatment cycles are warranted. For additional treatment cycles please visit *getendeavor.com*.

Daily treatments with Endeavor last 25-30 minutes, and it is recommended that they are completed by your child without interruption. Try to ensure that your child has **30 minutes of uninterrupted time** to complete each daily treatment.

Be sure that the mobile **device is fully charged** before use and that the **device's audio system is functioning properly** and the **audio is set at an appropriate level**.

Minimize distractions for your child during each treatment with Endeavor. For example, consider taking him or her into a quiet room or using headphones, turning off other mobile devices and televisions, and removing siblings and pets.

In order to avoid numbness, stiffness or other discomforts, find a comfortable place where your child can use Endeavor daily, ideally **seated in an upright position** in a **well-lit room with minimal glare on the device**. It is best if the patient adjusts the field of view and avoids using the device too close to their eyes. It is recommended to turn on the blue light filter on the device if administered during nighttime, but also recommended not to play right before bedtime to avoid risk of potential reduction in sleep quality.

During a treatment cycle, be sure to let your child know that **it is OK to occasionally take a break** from treatment for a few minutes in order to avoid excess eye strain or fatigue.

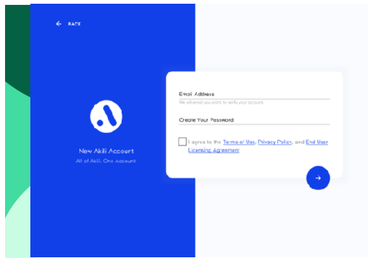
Encourage your child to give each treatment of Endeavor their **full attention and effort** to help ensure the positive treatment results.

Let your child know that by design, Endeavor will be **challenging** (and sometimes frustrating) to play.

It is recommended that the mobile device be stored **password protected** to reduce the risk of unauthorized access.

Ensure that the **treatment version downloaded on your device matches the version number on page 1 of this document.**

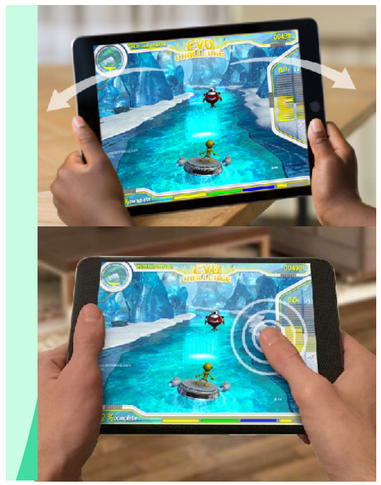
Operating Instructions



LAUNCH & LOGIN

Tap the application icon on the mobile device to start.

Select **Getting Started** and follow on-screen instructions to register your user account or log-in using your email address and password.



MANIPULATING THE DEVICE

Endeavor features 3 primary actions: 1) **Steering**, 2) **Tapping**, and 3) **Steering** and **Tapping** at the same time.

To **Steer**, your child should tilt the mobile device left and right.

To **Tap** on a target, your child should touch the mobile device screen using his or her thumb. This touch can be anywhere on the screen – it does not have to be directly on the target.

Encourage your child to hold the mobile device with both hands to help with **Steering** and **Tapping**.

Operating Instructions

PAUSE AND RESUME TREATMENT

Each daily treatment can be paused at any time by tapping the upper-left corner of the screen. Tap “Resume” to continue the treatment. *Note: There are built-in rest periods between sessions (on average every 4-5 minutes).*

COMPLETE TREATMENT AND/OR EXIT

When a daily treatment is completed, the Endeavor application can be closed on your device. After completing a full treatment cycle of Endeavor, the treatment will become automatically disabled. There is no need to remove the Endeavor treatment from your mobile device. Contact your physician with any questions regarding follow-up for your treatment plan.

Endeavor Daily Treatment

When using Endeavor, the goal is for your child to successfully **Steer** their character through a course while avoiding bumping into obstacles, and to **Tap the screen** to collect targets when they appear. Each course completed from start to finish is an individual **Mission**. A daily treatment session requires your child to complete 5 missions.

There are many separate **Worlds** to unlock and explore as your child progresses through treatment.

Endeavor is used for approximately 25-30 minutes a day, 5 days a week, over a 1-month treatment cycle.

Endeavor will display reminders if treatment days are missed as well as a notification when the treatment cycle is soon to expire.

Unlike an action video game, there is no way to "win" **Endeavor**. The goal of **Endeavor** treatment is to continuously challenge the child to get better. The game gets more difficult as the treatment progresses. Collecting rewards during daily missions indicates successful completion of a daily treatment.

Missions

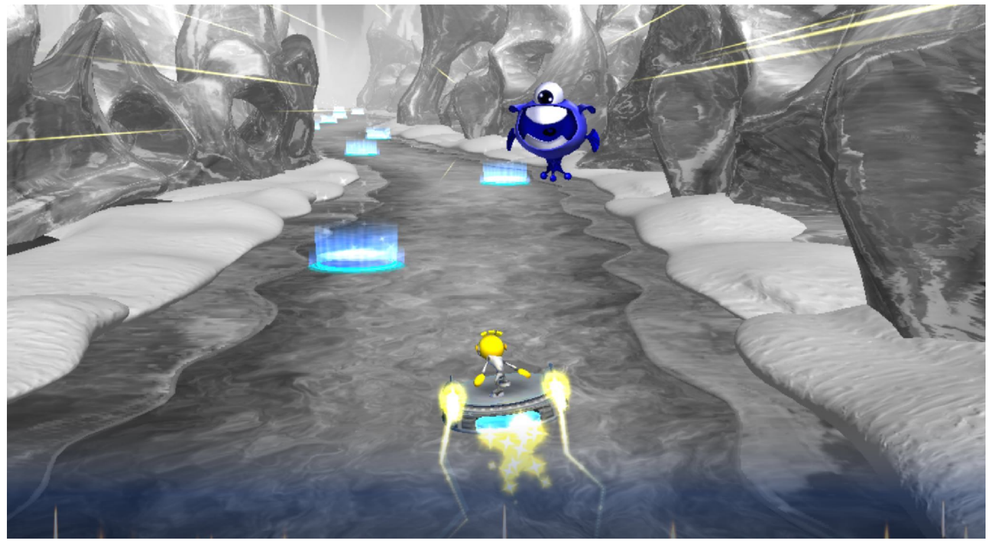
A daily treatment with Endeavor requires your child to complete 5 game missions. After completing the 5 missions, your child will no longer be able to play until the next day. This makes sure Endeavor is used in a manner consistent with the intended treatment schedule and prevents overuse.

During each mission, your child will steer his or her avatar through a course, moving through gates and/or avoiding obstacles, and tapping to collect targets when they appear. With successful tapping and steering, your child can earn rewards when they enter **The Zone**.

When the **The Zone** appears, Endeavor has recognized that your child has reached a new ability level in his or her mission.

The Zone stays open for a few seconds at a time, and the child can earn reward orbs. Reward orbs can be hard to get – and each one will be harder to get than the previous one.

After collecting 15 reward orbs a new World will be unlocked.



Treatment Screens

SUMMARY SCREEN

When your child finishes a mission, a summary screen will appear displaying the important goals, progress and rewards achieved.

STORE

Your child can use the rewards they have earned to unlock their desired costumes in the game store. As they progress they can choose the costume they like the best, or collect them all!

GALAXY MAP

This ‘main menu’ provides a visual of overall progress through the many environments across the Galaxy of Endeavor! From here, your child can equip new costumes for their character, view their active daily quests, and choose an environment in their current ‘world’ to play next!

Mobile Device Security

DEVICE SECURITY RECOMMENDATIONS

Endeavor software is designed with consideration of state-of-the-art cybersecurity measures. For your mobile device, the measures below are recommended to maximize overall cybersecurity:

Mobile device should be protected with a password or pin to reduce the risk of unauthorized access

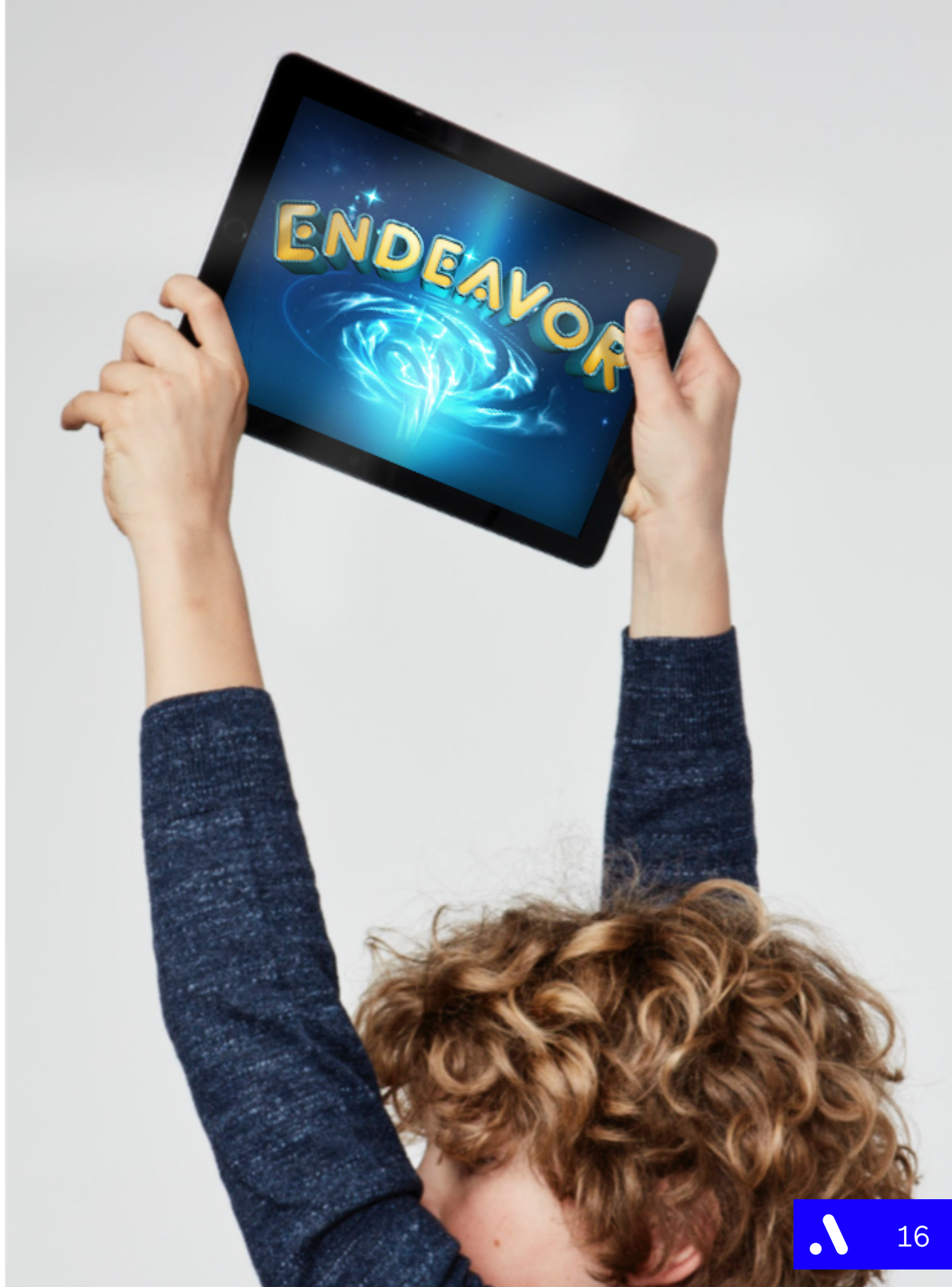
Mobile device should be in automatic lock mode after a period of inactivity

Avoid using untrusted WiFi networks

Mobile device security software should be installed to protect against malware and viruses

Mobile device operating system (OS) and Endeavor application should be updated to latest available

Mobile device should not be jailbroken to maintain device manufacturer restrictions



Troubleshooting

We’re here to help.
AkiliAssist.com

Q. The Endeavor application does not start properly.

Ensure that the mobile device is connected to WiFi.

Ensure that the mobile device meets the minimum specifications outlined in list of compatible devices section.

Ensure there is enough free storage space on your device to download and operate the application.

Q. My email / password / activation code is not accepted by the Endeavor Application.

Double-check you have entered the text correctly.

Ensure that the mobile device is connected to WiFi during login, account registration or activation.

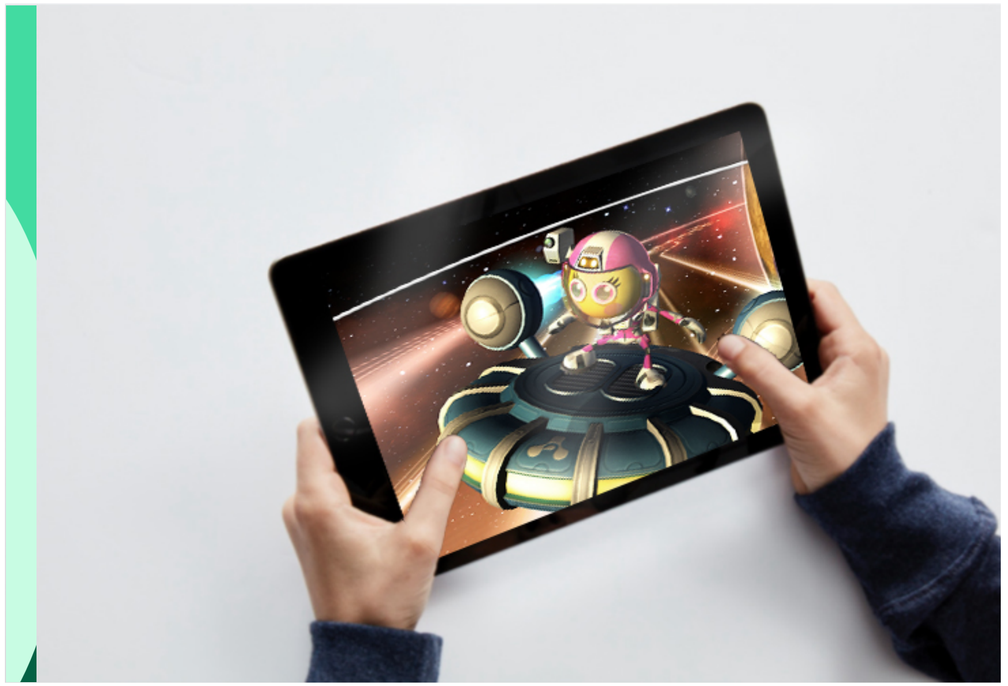
Q. I can’t play all 5 missions.

If played right around midnight in your local time, some of the sessions might count for next day’s gameplay (e.g. starting the gameplay at 11.50pm and finishing at 12.20am). This issue can be alleviated by playing all 5 missions in the same calendar day.

Q. The app unexpectedly quits, stops responding, or won’t open

Follow your device manufacturer instructions to force quit the app (then open it again), restart your device, check for system updates or reinstall the app, if necessary.

Compatible Devices



iOS DEVICE MINIMUM REQUIREMENTS

iOS version	**12.0**
Storage	**16 GB**
Chip	**1.3GHz dual-core with 64-bit architecture CPU**
Memory	**1 GB**
Network	**WiFi**

Some of the devices with the above minimum specifications are **iPad Mini 4**, **iPhone 7** & **later models**.

NOTE: Endeavor is not currently compatible with Android OS.

We’re here to help.

AkiliAssist.com

Clinical Research Behind Endeavor

For Physicians and Healthcare Professionals

NOTE: Endeavor was previously known as AKL-T01 during the clinical

Clinical Research Behind Endeavor (AKL-T01)

CLINICAL ENDPOINT ACRONYMS

ADHD-RS: ADHD Rating Scale (total scale)

ADHD-RS-Hyperactive: Hyperactive Sub-Scale of the the ADHD-RS

ADHD-RS-Inattentive: Inattentive Sub-Scale of the ADHD-RS

BRIEF: Behavior Rating Inventory of Executive Function

CGI-I: Clinical Global Impression - Improvement

IRS: ADHD Impairment Rating Scale

MFaCTS: Mathematic Fluency and Calculation Tests

TOSREC: Test of Silent Reading Efficiency and Comprehension

TOVA: Test of Variables of Attention

TOVA API: TOVA Attention Performance Index (also know as TOVA ACS: Attention Composite Score)

TOVA RT Mean H1: TOVA Reaction Time Mean (first half of the test)

TOVA RT Var: TOVA Reaction Time Variability (total test)

Clinical Research Behind Endeavor (AKL-T01)

INTRODUCTION

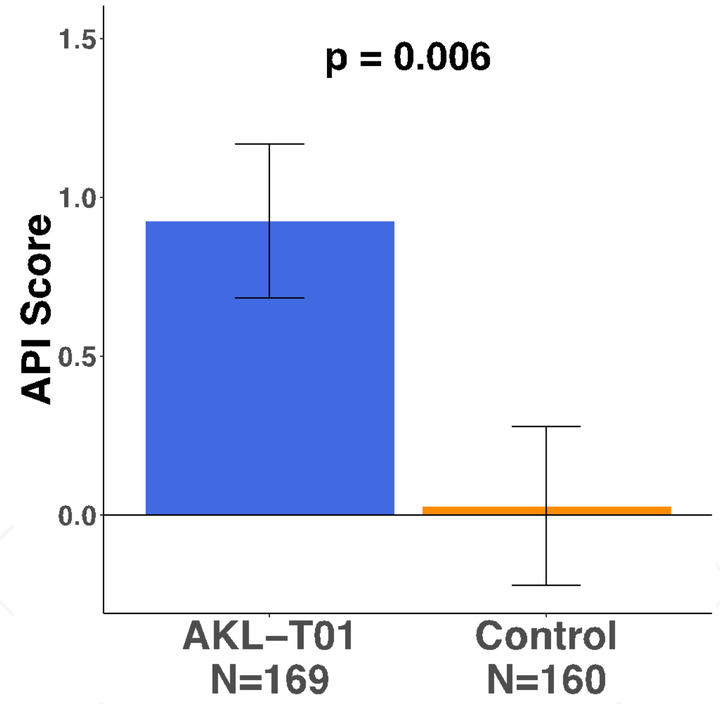
The Endeavor treatment (AKL-T01) has been studied in over 600 children with ADHD across 5 clinical studies. 3 studies in ADHD (STARS-ADHD, STARS-Adjunct and ADHD-POC) and 2 pilot studies in ADHD with different comorbidities (Sensory Processing Disorder and Autism Spectrum Disorder).

STARS-ADHD Pivotal Study[1]

Study Design: a randomized, double-blind, parallel-group, 4-week, controlled trial of AKL-T01 in children aged 8-12 years old with ADHD (not taking ADHD medications) and TOVA API baseline scores of ≤ –1·8, conducted at 20 sites in the USA. 348 subjects were randomly assigned to receive AKL-T01 (n=180) or control (n=168) for approximately 25 minutes per day, 5 days per week, for 4 weeks.

Objectives: The primary endpoint was mean change in TOVA API from pre- to post-intervention (baseline to 4 weeks). Secondary endpoints were mean changes in ADHD-RS (Total, Inattentive, Hyperactive), IRS, CGI-I, BRIEF (working memory, inhibit).

Results: The primary endpoint was achieved, mean change from baseline on the TOVA API was 0.93 in the AKL-T01 group versus 0.03 in the control group (p=0.006). The secondary endpoint within-group (baseline to post-treatment) changes were all significantly improved, and several mean changes numerically favored AKL-T01 over control (ADHD-RS Total, ADHD-RS Inattentive, IRS), however there was no statistically meaningful difference in a non-parametric analysis of the 7 secondary parental or clinical rating scales (Adjusted p=0.34 to 1.00). There were two notable responder analyses (56% of parents indicated the treatment improved their child's attention and 48% were shown to improve their ADHD-related impairment as reported in the IRS).



Safety and Compliance: There were no serious adverse events or discontinuations. Treatment-related adverse events were mild and included frustration (5 [3%] of 180), headache (3 [2%] of 180) and emotional reaction (2 [1%] of 180). Patient compliance was a mean of 83 (83%) of 100 expected sessions

[1] *Kollins et al, Lancet Digital Health, 2020*

Clinical Research (cont.)

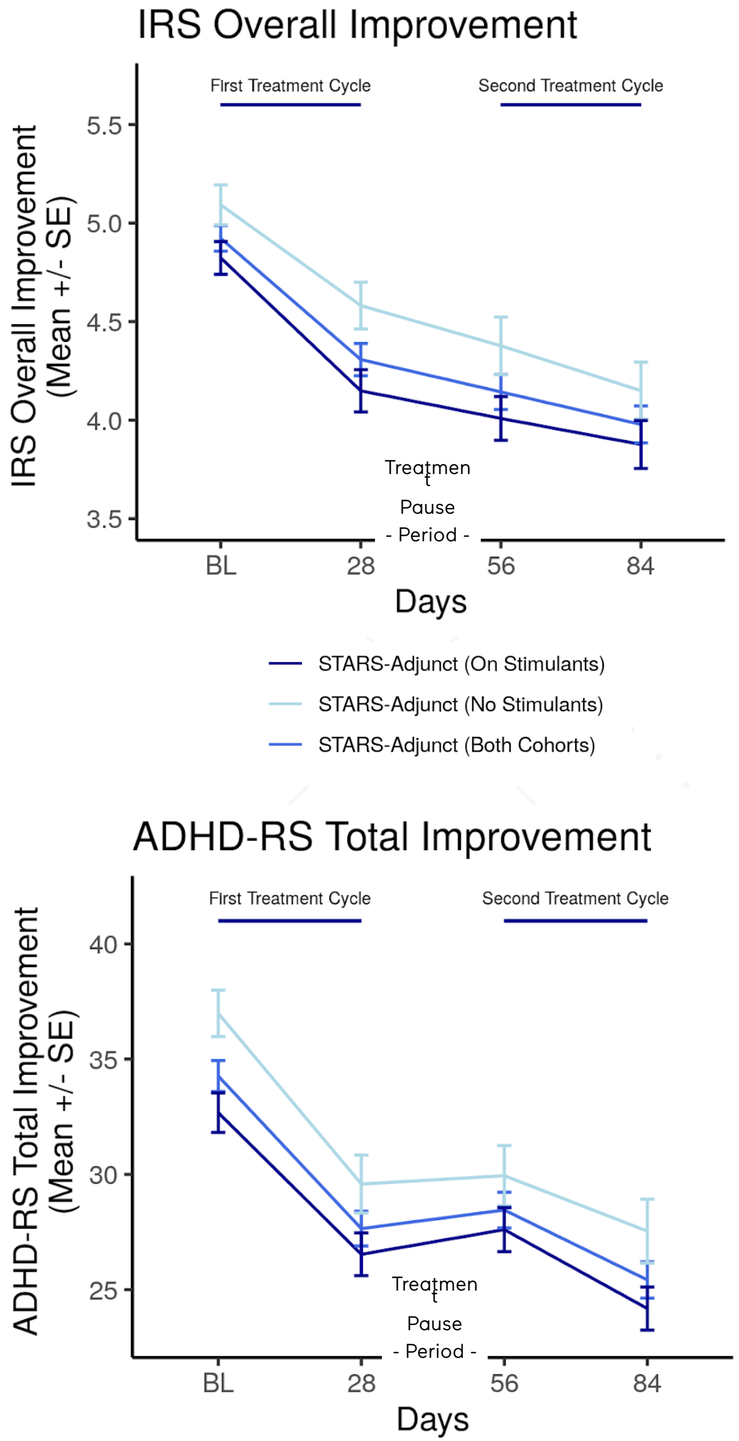
STARS-Adjunct Study[1]

Study design: a multicenter, 12-week, open-label study of Endeavor (AKL-T01) in 206 children aged 8-14 years with ADHD, consisting of 2 cohorts: 1) Subjects currently treated with ADHD medication (On Stimulants, n=130) and 2) Subjects not on any ADHD medication (No Stimulants, n=76). Subjects required an IRS score of ≥3 at baseline and both cohorts received AKL-T01 for approximately 25 minutes per day, 5 days per week, over two 4 week treatment periods, separated by a 4-week treatment pause. There was no digital control in this study.

Objectives: The primary endpoint was change from baseline to day 28 on the Impairment Rating Scale (IRS), a measurement of ADHD-specific impairment. Secondary measures included changes from baseline to day 28 and day 84 on ADHD symptoms (ADHD-RS), objective measures of attention (TOVA), CGI, academic performance measures of math and reading (MFaCTS, TOSREC) and measures of patient/parent preference and experience.

Results: After the first treatment month (day 28), IRS overall severity score was significantly improved for both the On Stimulants (-0.7, p<0.001) and No Stimulants (-0.5, p<0.001) cohorts compared to baseline. ADHD-RS (Total, Inattentive and Hyperactive subscales) and CGI-I were also significantly improved for both cohorts compared to baseline at day 28. IRS, ADHD-RS, and CGI-I all further improved with an additional treatment month (baseline to day 84). Objective attention (TOVA ACS/API) was correlated with academic performance measures (TOSREC and MFACTS) at each time point throughout the study and an improvement in objective attention was related to an improvement in both academic performance measures.

⚠ **Safety and Compliance:** 37 (18%) subjects experienced a device-related AE. The most common device-related AEs were frustration (27 [13.1%] of 206), headache (4 [1.9%] of 206), and irritability (3 [1.5%] of 206). All device-related AEs were either mild or moderate in severity. There were 3 discontinuations due to AEs (all frustration). No serious device-related AEs occurred during this study.



[1] *Data on File, Akili, 2020*

Clinical Research (cont.)

ADHD Proof of Concept Study[1]

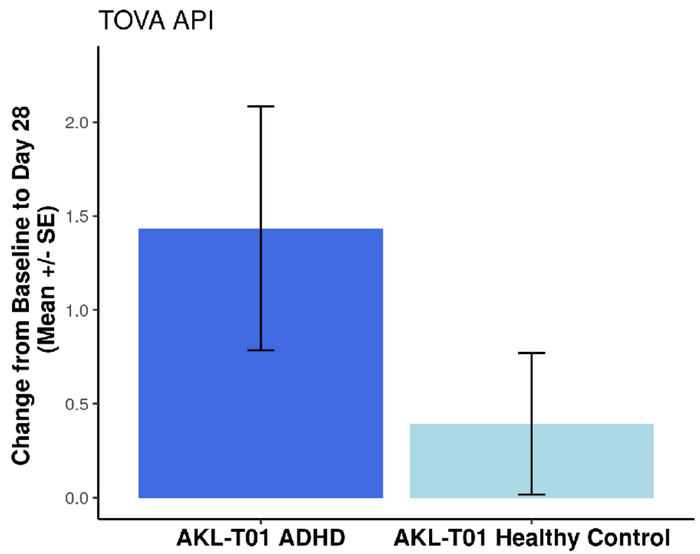
Study Design: A 4-week, open-label study of EndeavorRx (AKL-T01) in children aged 8-12 years old, comparing 40 children with ADHD to 40 neurotypical children (healthy controls). The ADHD group were required to have an in-clinic diagnosis of ADHD, not be taking ADHD medications and have an ADHD-RS total score of ≥24 at baseline (healthy controls were required to have an ADHD-RS ≤13). The study was conducted at 3 sites in the US.

Treatment: Subjects were instructed to complete approximately 25 minutes of AKL-T01 per day, 5 days per week for 4 weeks.

Objectives: to explore whether subjects demonstrated improvements in attention function, as measured by TOVA and other measures.

Results: Improvements were observed on TOVA API for the ADHD group (1.43 / SD=4.1) There was no significant change for the healthy control group (0.39 / SD=2.39)

Safety and Compliance: There were no treatment-related AEs. 84% of treatment sessions were completed.



[1] *Davis et al., PLOS One, 2018*

Clinical Research (cont.)

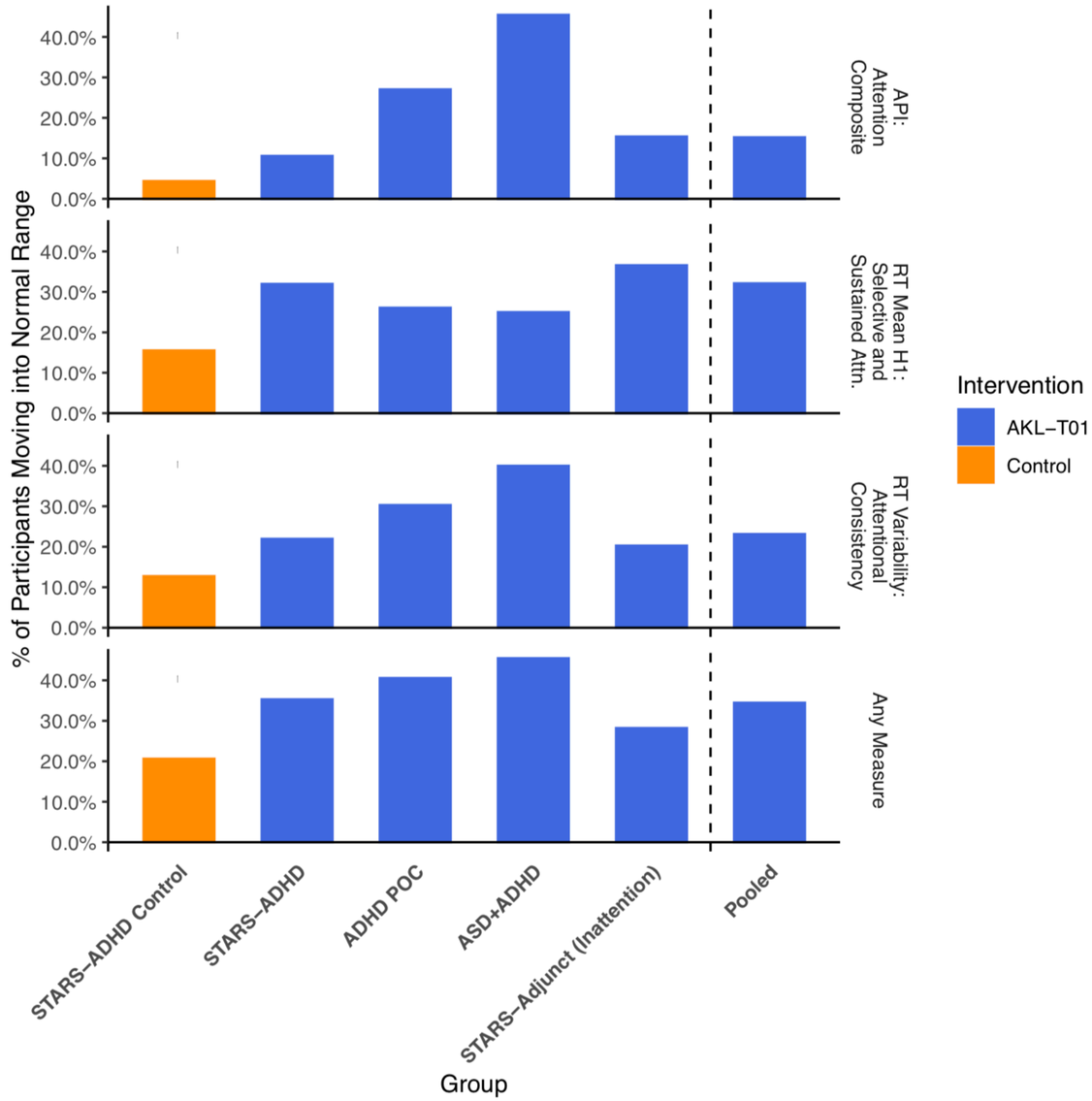
ADDITIONAL STUDIES

Sensory Processing Disorder (SPD)[1]: a pilot study of EndeavorRx (AKL-T01) in children ages 8-12 with SPD only (n=13), SPD+ADHD (n=20) and Healthy Controls (n=24). There was improvement in objective attention measures comparable to STARS-ADHD and the SPD+ADHD group showed a decrease in parent-reported ADHD-inattentive symptoms (-4.5 / SD=4.7).

Autism Spectrum Disorder (ASD)[2]: a randomized, double-blind, controlled study of EndeavorRx (AKL-T01) in 19 children ages 9-13 years old with ASD and comorbid ADHD, 11 randomized to AKL-T01 and 8 to digital control. AKL-T01 group improved in TOVA API (1.86 / SD=3.66) while the Control group worsened (-0.82 / SD=3.4). AKL-T01 group improved in ADHD symptoms (ADHD-RS-Total, -6.72 / SD=5.6). Both groups had high compliance with their intervention. There was one non-serious AE (decreased frustration tolerance) in the AKL-T01 group.

OBJECTIVE ATTENTION ACROSS STUDIES[3]

The percentage of children moving into the normative range on objective measures of attention (TOVA API, RT Mean H1 and RT Var) is between 10-45% across all clinical studies. Overall, 34.5% of children moved into the normative range on at least one of these objective measure of attention after 4 weeks of treatment with AKL-T01.



[1] *Anguerra et al., PLOS One, 2017*
[2] *Yerys et al., J Autism Dev Disord, 2019*
[3] *Data on File, Akili, 2020*

Clinical Research (cont.)

SIDE EFFECTS

There were no serious adverse events seen in any clinical trials of Endeavor. Of 538 participants using Endeavor (AKL-T01) in clinical trials, 50 participants (9.3%) experienced treatment-related adverse events. Endeavor associated adverse events included frustration (6.1%), headache (1.3%), dizziness (0.6%), emotional reaction (0.4%), nausea (0.4%), and aggression (0.2%). All adverse events were generally transient. Only 3 events led to device discontinuation, and no participant reported lasting or irreversible effects after discontinuation. 3 participants experienced treatment-related adverse events with the digital control, in studies where a control was used.

NOTES

Endeavor may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict use of a mobile device; parents should consult with their child's healthcare provider.

INDICATIONS FOR USE

Endeavor is a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined-type ADHD who have a demonstrated attention issue. Patients who engage with Endeavor demonstrate improvements in a digitally assessed measure, Tests of Variables of Attention (TOVA), of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. Endeavor should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.