MANUFACTURER
Akili Interactive Labs, Inc.
71 Commercial St.
Mailbox 312
Boston, MA 02109 USA

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Part Number: 5015 Revision K

REF

EndeavorOTC®

Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder

INSTRUCTIONS FOR USE

REVISION K

CONTENTS

3 Labels and Symbols
4 Customer Support
5 Instructions for Use
6 Important Reminders
7 Compatible Devices
8 Product Description & Core Technology
9 Getting Started with EndeavorOTC
10 Operating Instructions
11 EndeavorOTC Daily Treatment
12 Daily Mission Minutes
13 The Main Hub Interface
14 Treatment User Interface
15 Clinical Research

Labels and Symbols

CAUTION: Pay special attention to the following details

Manufacturer

Reference Part Number

Lot Number

Consult Instructions for Use

Customer Support

We're here to help.

Ensuring your satisfaction with our products is our priority.

For answers to common questions related to purchases, treatment recommendations, technical issues, or general information check out our **Frequently Asked Questions**.

For anything else please email us at

support@endeavorotc.com

Instructions For Use

CAUTIONS

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.

If you experience frustration, emotional reaction, dizziness, nausea, headache, eye-strain, or joint pain while playing EndeavorOTC, pause the treatment. If the problem persists contact your health care provider. If you experiences a seizure stop the treatment and contact your health care provider.

EndeavorOTC may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict use of a mobile device; patients should consult with their health care provider. This device is not for persons who have a comorbid psychiatric condition in addition to ADHD. When using this device it is recommended that you seek care from a medical health care provider in conjunction with its use.

EndeavorOTC is not a substitute for your medication.

EndeavorOTC is only intended for those who have been diagnosed by a licensed health care provider with inattentive or combined type ADHD.

For additional resources relating to ADHD treatment, or if your ADHD symptoms and/or impairments are not improving, contact your healthcare provider. If you are experiencing a medical emergency, please dial 911.

The single arm study used to support the EndeavorOTC did not include a sham control group and it is therefore possible that observed effects were due to bias or placebo effects. Akili has conducted and published additional studies that support the lack of a placebo effect on the TOVA[1,2]. Patients and health care providers should consider the totality of the clinical evidence in light of this before using this product.

INDICATIONS FOR USE

EndeavorOTC is an over the counter digital therapeutic indicated to improve attention function as measured by computer-based testing in patients 18 and older with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorOTC demonstrate improvements in a digitally assessed measure, Test of Variables of Attention (TOVA®) of sustained and selective attention and may not display benefits in typical behavioral symptoms such as hyperactivity. EndeavorOTC is not intended to be a replacement for any form of treatment and should be used 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

No serious adverse events have been reported in any of our clinical studies. Of 221 participants in the trial supporting the technology behind EndeavorOTC receiving the intervention, 11 participants (5%) experienced treatment-related adverse events (probable, likely). Associated adverse events included nausea (4 participants [1.8%]), headache (3 participants [1.4%]), frustration tolerance decreased (2 participants [0.9%]), arthritis, dizziness, fatigue, and somnolence (1 participant each [0.5%]). All adverse events were generally transient, and no subject reported lasting or irreversible effects after discontinuation.

NOTE: EndeavorOTC and EndeavorRx were previously known as AKL-T01 during the clinical investigations.

[1] Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7

[2] Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125

Important Reminders for this Over-The-Counter Product

- This product is intended to be used by adults aged 18 years and above with ADHD
- You should not use this product instead of seeking care from a healthcare professional - if you need help finding an appropriate healthcare provider or need other information about ADHD, please see resource links at the bottom of this page
- This product is not intended to be a substitute for other forms of ADHD management. You should not make adjustments to your treatment without consulting your healthcare provider
- Recommended treatment regimen is 25 minutes a day, at least 5 days a week, for 6 weeks
- Use of the product other than described above or less than the recommended treatment regimen may yield different results than expected or described elsewhere in this product label

Endeavor OTC

Attention Deficit Disorder Association: ADHD testing, provider directory, resources, support, and support groups https://add.org/
Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD): Education, resources, support & ADHD specialists https://chadd.org/for-adults/overview/
Duke Center for Girls and Women with ADHD: Education, resources, support, and support groups for girls and women with ADHD https://adhdgirlsandwomen.org/
ZocDoc ADHD Provider Search: Provider directory https://www.zocdoc.com/procedure/hyperactive-disorder-add-adhd-179

Compatible Devices

ANDROID DEVICE MINIMUM SPECIFICATIONS

Android™ OS version	11.0
Storage	32 GB of storage space
Memory	3 GB of RAM
Network Infrastructure	WiFi
Example Devices	**Samsung Galaxy S10™, Samsung Tab A8, and similar or later models.**

iOS DEVICE MINIMUM SPECIFICATIONS

iOS™ version	15.0	iPadOS® version	15.0
Storage	16 GB of storage space		
Memory	2 GB of RAM		
Network Infrastructure	WiFi		
Example Devices	**iPad® Mini 5, iPhone® 11 and later models.**		

For more information on device compatibility, please visit the EndeavorOTC.com FAQ. Refer to the section *Technical* > *"What devices are compatible with EndeavorOTC?"*

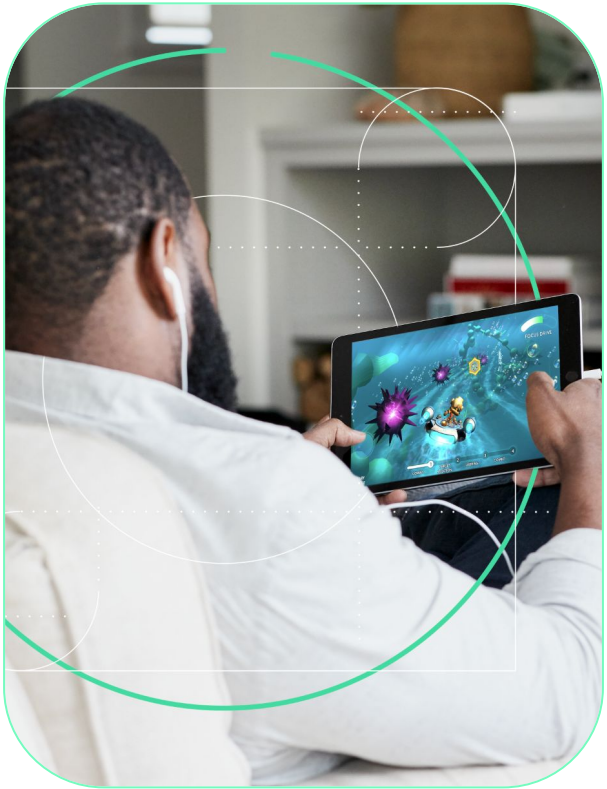
To easily determine if your device is compatible, download EndeavorOTC from your app store and open it. If you cannot find it in your app store, your device may not be compatible.

Please configure the mobile device with the device manufacturer's security suggestions.

Product Description & Core Technology

EndeavorOTC is…

- a digital, non-drug treatment delivered through an action video game that was shown to improve attention function as measured by computer-based testing in adults with ADHD.
- a treatment used on a mobile device. See page 7 for compatible devices.
- different from other action video games that you might play. The treatment programmed into the game was designed to challenge attentional control during gameplay, requiring focus and flexibility to manage multiple tasks at the same time.



Patented, proprietary technology designed to target key neural attentional control systems in the brain.

SELECTIVE STIMULUS MANAGEMENT

The Selective Stimulus Management Engine (SSME™) is a proprietary & patented technology that presents specific sensory stimuli and simultaneous motor challenges designed to target key neural systems in the brain related to attentional control.

SSME implements specific closed-loop algorithms that adapt real-time and between treatment sessions to automatically adjust the difficulty level for a personalized treatment experience. The algorithms enable second by second monitoring of patient progress, and continuously challenge each patient to an optimized level, encouraging them to improve their performance.

Getting Started with EndeavorOTC

RECOMMENDATIONS BEFORE YOU START TREATMENT

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

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**.

GETTING STARTED WITH TREATMENT

For best results, we recommend playing the treatment approximately 25 minutes a day, 5 days a week. Our clinical study showed that the best results come with this routine for 6 weeks. Playing less than the recommended treatment regimen may not result in the same full benefit. To assist in understanding daily progress, the app displays a 25 minute countdown timer on the home screen that resets at the start of each treatment day. The 25 minutes only counts gameplay time, referred to as Mission Minutes, and does not include extra time you may spend in the game browsing non-mission areas like the Costume Store and the Collection.

Try to fit EndeavorOTC into your routine and make it a habit. You can make use of reminders in the game or any other tools you use for managing your schedule.

Minimize distractions during each treatment with EndeavorOTC. We recommend turning off device reminders and notifications, using EndeavorOTC in a quiet room with headphones, and turning off other mobile devices and televisions. Find a comfortable place where you can use EndeavorOTC 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.

Understand that by design, EndeavorOTC will be **challenging** (and sometimes frustrating) to play. Try and give each treatment of EndeavorOTC your full attention and effort to help ensure the best treatment results.

During a treatment session **it is OK to occasionally take a break** from treatment for a few minutes if needed, for example to avoid excess eye strain or fatigue.

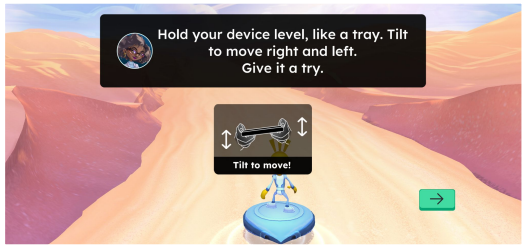
Operating Instructions

LAUNCH & LOGIN

Tap the application icon on the mobile device to start. If you already have an existing Akili account, tap the **"Log In"** button and log in with your existing Akili Account using your email address and password. At this point you will be granted access to treatment if you have an active subscription. If you do not have an active auto-renewing subscription you will be prompted to purchase one after login.

If you do not have an Akili account, tap the button on the initial screen to get started, create an Akili Account, and sign up for an auto-renewing subscription.

To open the EndeavorOTC product label, tap the "Product Label" link found in corner of the screen. Here you can find helpful information like the app version number and a link to the EndeavorOTC Instructions for Use.



MANIPULATING THE DEVICE

EndeavorOTC features 3 primary actions: 1) **Navigating**, 2) **Tapping**, and 3) **Navigating** and **Tapping** at the same time (multitasking).

To **Navigate**, tilt the mobile device left and right. Try to hold the mobile device with both hands to help with the navigation and tapping.

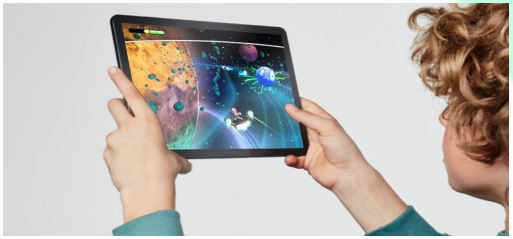
To **Tap** on a target, touch either the right or left half of the mobile device screen using your thumb. This touch can be anywhere on the right or left side of the screen – it does not have to be directly on the flying target nor the thumbpad icons.

EndeavorOTC Daily Treatment

When using EndeavorOTC, the goal is to successfully **Navigate** the character through a course while driving over Power Zones or avoiding obstacles, and **Tap** the right or left sides of the screen to collect only the correct targets when they appear while ignoring all other targets. At the beginning of the **Mission**, you will be shown multiple targets and asked to collect only specific types of targets - for example, you may be shown red, green, and blue targets and will be asked to only tap the red targets.

Each course completed from start to finish is an individual **Mission**, and time spent within those Missions are known as **Mission Minutes**. The technology behind EndeavorOTC has been shown to benefit those who play up to 25 minutes a day. For this reason, we've included a 25 **Mission Minute** countdown in the treatment intended to help you maximize your time.

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



Playing **EndeavorOTC** can fit into your daily routine. The more you play, the better your results.

Using the treatment at least 5 days a week for six weeks can improve your attention and other functions that make up your ability to focus. At six weeks, we recommend a short recovery period to evaluate your progress and prepare for the next dose, as the treatment is intentionally challenging. Then, resume treatment for another six weeks to further enhance your progress.

Unlike a video game, there is no way to "win" EndeavorOTC. The treatment continuously adjusts to maintain a consistent level of difficulty relative to how well you are managing each challenge. As long as you are using the product consistently and trying your best, you are engaging with the treatment as intended.

Daily Mission Minutes

The technology behind EndeavorOTC has been shown to benefit those who use the treatment up to 25 minutes a day. For this reason, we've included a 25 **Mission Minute** countdown in the experience, intended to help you maximize your time. **Mission Minutes** can be tracked on the Main Hub screen. When **Mission Minutes** reach zero you will receive an in-app reward for your efforts and be reminded to take a break until the next day, consistent with the intended treatment.

During each **Mission**, you will **Navigate** your character through a course, moving through gates and/or avoiding obstacles, and **Tap** to collect targets when they appear. With successful tapping and navigating, you can collect **Guides** and earn rewards.

The hover pod's capture ray will automatically lock on when you get close to the **Guide**. If you remain locked on for a few seconds, you will capture the **Guide** and earn a **Gem**. **Gems** can be hard to get – and each one will be harder to get than the previous one.

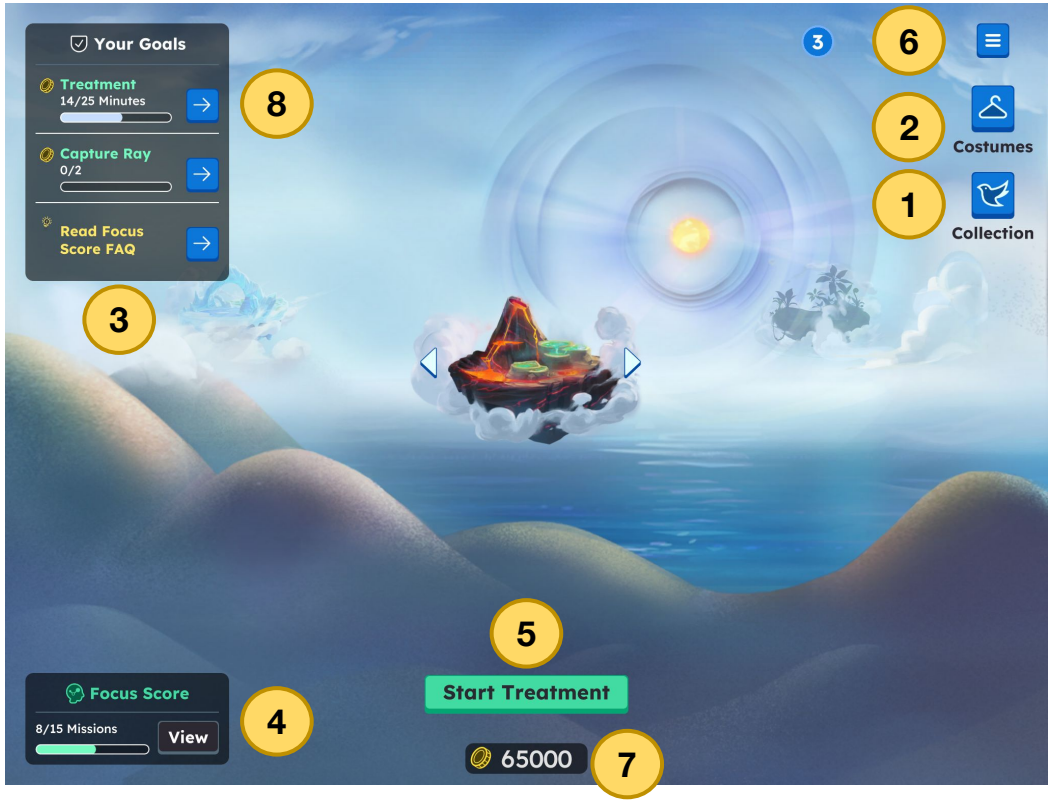
When the hover pod locks on to a **Guide** and captures it, EndeavorOTC has recognized that you have reached a new ability level in your play.

After collecting 15 **Gems** a new **World** will be unlocked.

EndeavorOTC was designed to, on average, take around 4 weeks to unlock all worlds, but actual speed of progression may vary across users. Independent of your progress, it is important that you engage regularly with the treatment.

Once all worlds are unlocked, you can revisit your favorite **World** to play and beat your previous scores. In addition, you can continue to complete **Goals**, unlock costumes, and view your **Collection**.

The Main Hub Interface



1. **Collection:** As you progress you will collect different Guides. View them in the Collection area.
2. **Costumes:** Spend your earned Coins to unlock your desired costumes. As you progress you can choose the costume you like best, or collect them all!
3. **Goals:** View and complete available Goals to earn more rewards.
4. **Focus Score™:** View your Focus Score. A new one unlocks every 15 Missions, learn more here.
5. **Start Treatment:** Begin your treatment by flying down into the selected planet and choosing the area you want to complete a Mission or Challenge in.
6. **User Info and Settings:** View your Level, return to the Dashboard, or replay the Tutorial. The Settings menu to adjust vibration, volume and sound levels is available here as well.
7. **Coin Count:** Amount of Coins collected available to spend on Costumes.
8. **Mission Minutes:** A Treatment Goal that displays the amount of Mission Minutes remaining out of the recommended 25 minutes for the day.

Treatment User Interface

PAUSE AND RESUME MISSION

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 missions.*

SETTINGS MENU

The Settings Menu is available on the Main Hub in the bottom left. It allows you to toggle Music and Sound Effects off and on, contact Customer Support, and access Licence, Terms of Use and Privacy information. Vibration can also be toggled off and on if your device supports it.

EXIT AND END TREATMENT

When a daily session is completed, the EndeavorOTC application can be closed on your device.
After your treatment subscription to EndeavorOTC expires, the treatment will become automatically disabled.

Please contact your health care provider to discuss your experience and the best treatment plan for you.

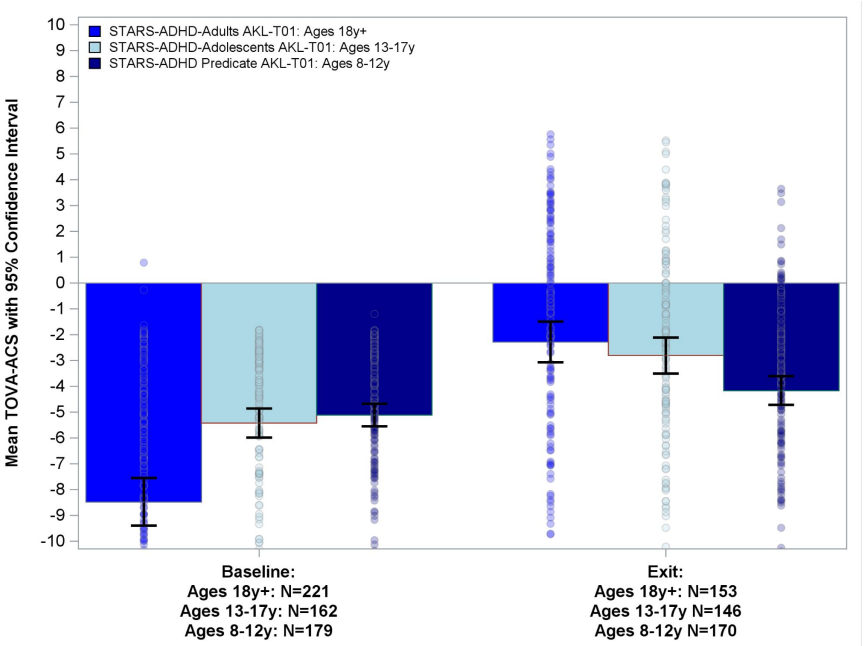
Clinical Research

The proprietary technology (AKL-T01) underlying EndeavorOTC and EndeavorRx has been supported by a study of of 221 adults with ADHD[1] (either on or off ADHD medication), where AKL-T01 was used for a 6-week treatment period.

Study Design: An open label single arm 6 week trial of AKL-T01 in adults. 18 years and older, with ADHD, primarily inattentive or combined-type ADHD (either on or off ADHD medication) with a TOVA ACS baseline score ≤ -1.8, conducted at 14 sites in the USA. For inclusion in this study, a diagnosis of ADHD was determined using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as confirmed by Mini International Neuropsychiatric Interview (MINI) for ADHD adults version 7.0.2. The 221 participants were asked to engage with the treatment for approximately 25 minutes per day, 5 days per week, for 6 weeks.

Objectives: The primary endpoint was mean change in TOVA ACS from pre- to post-intervention (baseline to 6 weeks). Secondary endpoints were mean changes in ADHD-RS (Total score and Inattentive subscore). Exploratory endpoints were Adult ADHD Quality of Life Scale (AAQoL) total score, AAQoL Life Productivity Subscore, CAARS-S:S and TOVA results other than the API.

Results: The primary endpoint was achieved; mean change from baseline on the TOVA ACS was 6.46 (p≤0.0001). For the ADHD-RS, clinically meaningful improvement based on literature is estimated as 10 point difference or a 30% change in Total Score.[2] In the present study, the ADHD-RS total score improved by a mean of 8.3 points (SD: 7.74) compared to an improvement of 6.2 in the predicate study. Additionally, the ADHD-RS inattentive score improved by 5.1 points (SD: 4.78), compared to an improvement of 3.6 in the predicate study. Comparisons of the magnitude of effect in the present study versus the predicate study should take into account that the present study was a single-arm study versus a randomized, parallel group study for the predicate. In addition, 32.7% of all participants in the present study demonstrated improvement in ADHD-RS Total Scores of 30% or greater. An 8-point improvement on the validated AAQoL is considered to be a clinically meaningful change.[3] In the current study, 45.8% of participants exhibited improvement on the AAQoL of 8 points or more, although in this single-arm study, it is possible that improvements were due to expectancy effects.



Markers represent individual subject values. Two participants in STARS-ADHD-Adults were enrolled that did not meet inclusions criteria of baseline TOVA-ACS ≤ -1.8 and were reported as protocol violations. TOVA-ACS scores below zero suggest performance similar to individuals with ADHD.[4]

Endeavor OTC

[1] *ADHD diagnosis in the clinical study was determined in a similar manner as was done in the predicate study of EndeavorRx; some non-serious comorbid psychiatric conditions were also allowed in both studies and did not impact the outcomes.* [2] *Zhang et al. 2005,* [3] *Goodman et al. 2010,* [4] *TOVA Clinical Manual 2020, p. 32 of 78:* https://files.tovatest.com/documentation/9/Clinical%20Manual.pdf

Clinical Research (Continued)

Participant Disposition: All 221 participants who were enrolled in the adult study were included in the Safety population (also known as ITT or intent to treat population, is all subjects enrolled in the study), and 153 participants were included in the Efficacy Population (also known as the mITT or modified intent to treat population, is all enrolled subjects with drop outs excluded). Safety population is all participants who were exposed to AKL-T01 intervention. Efficacy population is all participants who took the AKL-T01 intervention home and completed both baseline and day 42 exit visit assessments (including TOVA).

Seventy-five participants (33.9%) discontinued the study: the most common reason for study discontinuation was withdrawal by participant*. Three (1.7%) participants discontinued the study due to adverse events (1 headache, 2 nausea).

**Reasons for withdrawal by participants include the following: experiencing technical bugs or technical issues; game took too much time away from school, work, or other activities; did not like AKL-T01; did not want to complete the on-site study activities any further.*

Safety and Compliance: See page 5, Side Effects

Important notes:

This single arm study did not include a sham control group and it is therefore possible that observed effects were due to bias or placebo effects. Users should consider the totality of the clinical evidence in light of this before using the product. Akili has conducted and published additional studies that support the lack of a placebo effect on the TOVA.[5,6] Patients and health care providers should consider the totality of the clinical evidence in light of this before using this product. Some persons with known comorbid psychiatric conditions were excluded from this study and therefore the risk profile for persons with comorbid psychiatric conditions is not fully known.

[5] *Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7*

[6] *Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125*

Clinical Research (Continued)

Clinical Study Design Comparison

	Subject Device K233496	Predicate Device DEN200026	Comparison describing differences and a rationale why it is acceptable
	STARS-Adult Study (ages 18+)	**STARS Study (ages 8-12)**	
Population	Verified ADHD diagnosis with impaired attention; on or off medication	Verified ADHD diagnosis with impaired attention; medication exclusionary	SIMILAR - the adult study allowed for medication as long as use was stable for ≥4 weeks prior to study enrollment and throughout the study. A prior study demonstrated benefits of intervention on the pediatric population with ADHD both on and off medication.
Study Design	Single arm, open-label, adaptive design	Randomized clinical trial	DIFFERENT - Presence of attentional improvement from treatment compared to those on active control was established in the STARS study. The adult study investigated the magnitude of improvement and safety in the new age range. The Adult study used an adaptive design based on the total information as measured by the standard error of the primary endpoint which would allow the trial to be stopped prior to recruitment of the 325 participants derived from the sample size calculations. The adaptive design accounts for the uncertainty regarding whether the variation in TOVA-ACS mean change differed between the adult and pediatric ADHD populations. The safety and effectiveness of the exact same device was established in an RCT De Novo in a younger population. The primary endpoint used in the current study was identical to the original STARS RCT. Based on the predicate RCT, the primary outcome measure TOVA demonstrates less susceptibility to placebo effect in the randomized, controlled trial utilized for the de novo. Another consideration for the single arm design is that the TOVA-ACS is less susceptible to placebo effects when measuring attentional control processes within the context of ADHD, as supported by the predicate RCT and multiple published studies in the literature.[1,2,3]
Intervention	EndeavorRx (AKL-T01)	EndeavorRx (AKL-T01) EVO: Words (Active control)	SIMILAR - All use the same active intervention, minor differences in software. The adult study is a single arm study that did not require the use of an active control. AKL-T01 is a low-risk device, and the STARS predicate study was an RCT that already showed the effectiveness of AKL-T01 against an active control. Therefore, comparison of the device's effectiveness to active control was not part of the study design rationale.

[1] Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125

[2] Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7

[3] Murray DW, Childress A, Giblin J, Williamson D, Armstrong R, Starr HL. Effects of OROS methylphenidate on academic, behavioral, and cognitive tasks in children 9 to 12 years of age with attention-deficit/hyperactivity disorder. Clin Pediatr (Phila). 2011;50(4):308-320. doi:10.1177/0009922810394832

Clinical Research (Continued)

	Subject Device K233496	Predicate Device DEN200026	Comparison describing differences and a rationale why it is acceptable
	STARS-Adult Study (ages 18+)	**STARS Study (ages 8-12)**	
Treatment regimen	25 minutes/day for 5 days/week	25 minutes per day, 5 days per week	SIMILAR
Participant Duration	Approximately 6 weeks on treatment	Approximately 4 weeks on treatment	DIFFERENT - In Adults, treatment duration was adjusted to match duration used in past adult studies using a similar SSME™-driven product.
Diagnosis of ADHD	Yes - Diagnosis of ADHD combined or inattentive type, required according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as confirmed by Mini International Neuropsychiatric Interview (MINI) for Attention – Deficit / Hyperactivity Disorders Studies (Adult) 7.0.2	Yes - Confirmed ADHD diagnosis, any presentation, required at Screening based on DSM-V criteria and established via the MINI-KID administered by a trained clinician	SIMILAR - An age-appropriate version of the MINI was used in the adult study.
Sites	Multi-site: 14 sites across the US (a mix of institutional sites and private practice centers)	Multi-site: 20 sites across the US (a mix of institutional sites and private practice centers)	SIMILAR
Enrollment	223 enrolled	348 enrolled	SIMILAR - in Adults, enrollment stopped early for reasons unrelated to safety or efficacy prior to reaching the prespecified enrollment numbers (N=325).
Stably on or off ADHD medications	Stably on or off stimulant medication (≥4 weeks) allowed Stably on or off non- stimulant medication (≥4 weeks) allowed	Stimulant medication use not allowed Use of non-stimulant ADHD medication not allowed	DIFFERENT - Another published study[1] demonstrated ADHD improvement occurred similarly in patients both stably on and off ADHD medications. This criterion was adopted into the adult study design to better simulate real-world user base. The adult study allowed non-stimulant medication use as long as stability 4- weeks before and after study enrollment is maintained to better represent the diversity of patients who may use the device and to generalize to real-world user base.

[1] Kollins, S.H., Childress, A, Heusser, AC and Lutz, J. (2021). Effectiveness of a digital therapeutic as adjunct to treatment with medication in pediatric ADHD. npj Digit. Med. 4, 58. https://doi.org/10.1038/s41746-021-00429-0

Clinical Research (Continued)

	Subject Device K233496	**Predicate Device DEN200026**	**Comparison describing differences and a rationale why it is acceptable**
	STARS-Adult Study (ages 18+)	**STARS Study (ages 8-12)**	
Stably on or off nonpharmacological treatments	Stably on or off nonpharmacological treatments (≥4 weeks) allowed	Stably on or off nonpharmacological treatments (≥4 weeks) allowed	SIMILAR
Absence/Presence of comorbid psychiatric diagnosis and/or treatments that may confound study	Presence of comorbid psychiatric diagnosis and/or treatments that may confound study not allowed	Presence of comorbid psychiatric diagnosis and/or treatments that may confound study not allowed	SIMILAR
Absence/Presence of conditions that would prevent the proper use of the investigational product	Presence of conditions that would prevent the proper use of the investigational product not allowed	Presence of conditions that would prevent the proper use of the investigational product not allowed	SIMILAR
Primary Outcome Measure	Change in TOVA attention comparison score (ACS) from pre- to post-intervention	Change in TOVA attention performance index (API, also known as TOVA-ACS) from pre- to post-intervention	SIMILAR
Secondary Outcome Measures	Mean changes in: • ADHD-Rating Scale-IV (ADHD-RS) Inattention Subscale Score • ADHD-RS Total Scale Scores	Mean changes in: • ADHD-RS Total Score • ADHD-RS Inattention Subscale Score • ADHD-RS Hyperactivity Subscale • Behavior Rating Inventory of Executive Function (BRIEF) Working Memory percentile • BRIEF Inhibit percentile • Impairment Rating Scale (IRS) • Clinical Global Impression (CGI)	DIFFERENT –The predicate device used the Impairment Rating Scale (IRS) and the Clinical Global Impressions Scale (CGI) to assess functional impairment, but since the IRS is a parent reported measure and the CGI was not sensitive to treatment effects in the predicate study, neither was used in the subject study, which used the Adult ADHD Quality of Life (AAQoL) Scale as a measure of ADHD impairment in adults. Both studies had ADHD-RS as secondary measures. Whereas the STARS study listed multiple secondary measures, the adult study focused on ADHD-RS as the secondary measure, which the predicate study showed to be sensitive to the AKL-T01 treatment.

Clinical Research (Continued)

Comparison of Clinical Study Outcomes

Outcome Measure	Clinical Study for EndeavorOTC (K233496)	Clinical Studies used to support EndeavorRx (DEN200026)	Differences
	Adults (ages 18+)	STARS (ages 8-12)	
1. pre-post change score on TOVA ACS (Positive change indicates improvement)	6.46	0.93	Adults show nearly 6 times the improvement in TOVA-ACS than in STARS. Although the magnitude of benefit is different between EndeavorOTC and the predicate device, both devices show improvement in TOVA-ACS Score.
2. pre-post change score on ADHD-RS Inattention subscale (Negative change indicates improvement)	-5.1	-3.6	Greater mean change than STARS. Although the magnitude of benefit is different between EndeavorOTC and the predicate device, both devices show improvement in ADHD-RS Inattentive Scale Score, which did not reach a clinically meaningful threshold. Clinically meaningful improvement based on literature for the ADHD-RS is estimated at 10-point difference.[1]
3. pre-post change score on ADHD-RS Total Score (Negative change indicates improvement)	-8.3	-6.2	SIMILAR - Greater or comparable mean change to STARS.

Endeavor OTC

[1] Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. Int J Methods Psychiatr Res. 2005;14(4):186-201. doi:10.1002/mpr.7

Clinical Study (Continued)

Table of Modified Intent-to-Treat (mITT) and Intent-to-Treat (ITT) Analysis with Multiple Imputation (MI) of the Primary Efficacy Endpoint – TOVA-ACS Change from Baseline to Exit

Analysis	Baseline TOVA-ACS	Exit TOVA-ACS	Change from Baseline
STARS ITT Population			
n	179	170	169
Mean (SD)	-5.11 (0.22)	-4.16 (0.28)	0.93 (0.24)
95% CI			0.45, 1.40
p-value[1]			0.0002
Adult Efficacy Population (mITT)			
n	153	153	153
Mean (SE)	-8.739 (0.6089)	-2.279 (0.3978)	6.460 (0.5621)
95% CI			5.349, 7.570
p-value[1]			<0.0001
Adult Safety Population (ITT with MI[2])			
n	221	221	221
Mean (SE)	-8.644 (0.5249)	-2.489 (0.4542)	6.155 (0.5698)
95% CI			5.037, 7.273
p-value[1]			<0.0001

Study results were based on a modified intent-to-treat (mITT, also known as Efficacy population, is all enrolled subjects with drop outs excluded) population. This population included all enrolled participants with sufficient data at baseline and exit to calculate change scores (N=153) instead of the intent-to-treat (ITT, also known as Safety Population, is all subjects enrolled in the study) population (N=221).

A sensitivity analysis using multiple imputation (MI) was performed to assess the impact of missing exit data in the ITT population. Change in TOVA-ACS was generally similar in the ITT population after imputation, with a mean [95% CI] of 6.144 [5.037, 7.273] as compared with the mITT population 6.460 [5.349, 7.570].

Abbreviations: CI = confidence interval; FCS = fully conditional specification; ITT = intent-to-treat, also known as Safety Population, is all subjects enrolled in the study; mITT = modified intent-to-treat, also known as Efficacy Population, is all enrolled subjects with drop outs excluded; MI = multiple imputation; SE = standard error

[1] From a one-sample t-test of change greater than zero. Positive changes indicate improvement.

[2] Multiple imputation for participants with missing data at Day 42 was performed using FCS with 100 imputations and included covariates age, sex, race, ethnicity, education plan, age of ADHD symptom onset, concomitant stimulant use, treatment exposure defined as number of non-practice missions completed, and baseline TOVA-ACS value. Estimates of mean and standard error at baseline, exit and change from baseline were calculated for each imputation and combined using PROC MIANALYZE in SAS version 9.4.

Clinical Research (Continued)

The predicate device used for this 510(k) submission (DEN200026) was studied using secondary outcome measures that were different from the current device. The table below describes the differences in outcome measures and their comparability.

Comparison of secondary and exploratory measures in STARS-Pediatric (Predicate) and STARS-Adult (Subject)			
Domain of interest	*STARS-Pediatric Outcome (DEN200026)*	*STARS-Adult outcome (K233496)*	*Comparability/Rationale for difference*
Clinician assessed ADHD symptoms	ADHD Rating Scale (ADHD-RS) - Total Score and Inattentive scales	ADHD Rating Scale (ADHD-RS) - Total Score and Inattentive scales	No difference across studies - same measure used
Patient reported ADHD symptoms		Conners Adult ADHD Rating Scale (CAARS) - Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/ Emotional Lability, Problems with Self Concept, ADHD Index scales	The reliability of self-reported ADHD symptoms in children and adolescents is not high. However, the CAARS is a well-validated and psychometrically sound scale for assessing patient reported ADHD symptoms and functioning[1,2] and was therefore used to assess this domain in the current study
Functional Impairment	Impairment Rating Scale (IRS)	Adult ADHD Quality of Life Scale (AAQoL) - Total score and Life Productivity subscale	
	Clinical Global Impressions-Improvement Scale (CGI-I)		
Parent Reported Executive Functioning	Behavior Rating Inventory of Executive Functioning		

[1] Conners C, Erhardt D, Sparrow E. Conners' Adult ADHD Rating Scales (CAARS): Technical Manual. Multi-Health Systems, North Tonawanda, NY; 1999.
[2] Erhardt, D., Epstein, J. N., Conners, C. K., Parker, J. D. A., & Sitarenios, G. Self-ratings of ADHD symptoms in auts II: Reliability, validity, and diagnostic sensitivity. *J. Atten. Disord., 1999;3(3):153-158.*

Clinical Research (Continued)

Comparison of Clinical Study Safety Outcomes

Safety outcomes for participants who received AKL-T01 in STARS-Adults (Safety Population[1]) and STARS-ADHD (DEN200026) studies

ADEs by Preferred Term n (%)	All Studies N = 401	Adults (K233496) N = 221	STARS-ADHD (DEN200026) N = 180
Any ADE	23 (5.74%)	11 (5.0%)	12 (6.7%)
Frustration tolerance decreased	7 (1.75%)	2 (0.9%)	5 (2.8%)
Headache	6 (1.5%)	3 (1.4%)	3 (1.7%)
Nausea	5 (1.25%)	4 (1.8%)	1 (0.6%)
Dizziness	2 (0.5%)	1 (0.5%)	1 (0.6%)
Emotional disorder	2 (0.5%)	0 (0%)	2 (1.1%)
Aggression	1 (0.25%)	0 (0%)	1 (0.6%)
Fatigue	1 (0.25%)	1 (0.5%)	0 (0%)
Somnolence	1 (0.25%)	1 (0.5%)	0 (0%)
Arthritis	1 (0.25%)	1 (0.5%)	0 (0%)

[1] Safety Population, also known as ITT or intent to treat population, is all subjects enrolled in the study.

Compared to STARS study, fewer participants in the Adult study experienced treatment-emergent adverse device effects (TE-ADE) overall. The only ADE where adults reported higher incidence at greater than 1% was nausea. All other incidences (fatigue, somnolence, and arthritis) remain low at <1%. Therefore, both EndeavorOTC and the predicate device are both safe for their intended use.

Clinical Research (Continued)

Benefit-Risk Profile:

No serious adverse events were reported. Of the 221 subjects who received AKL-T01 in the adult study supporting EndeavorOTC authorization for ages 18 years and above, 11 (5.0%) subjects experienced 13 treatment-emergent adverse device events (TE-ADE). Reports include 4 (1.8%) nausea, 3 (1.4%) headaches, 2 (0.9%) decreased frustration tolerance, and 1 each (0.5%) of arthritis, dizziness, fatigue, and somnolence. Three TE-ADEs (somnolence, fatigue, and arthritis) were considered unanticipated, and 3 TE-ADEs (1 occurrence of headache and 2 occurrences of nausea) resulted in study treatment discontinuation. All TE-ADEs were either mild or moderate in severity, and all were considered related to the study treatment.

There were no serious adverse device events. All adverse events were resolved by the end of treatment.

EndeavorOTC showed a general improvement in attention associated with ADHD. The totality of the evidence demonstrated clinical benefit in attention, as measured by the TOVA in the adult population (18+ years) with ADHD with a demonstrated attention issue. Improvements in ADHD inattentive symptoms were comparable or greater than the improvements in ADHD inattentive symptoms seen in the pediatric population from the predicate studies. As noted, the risks associated with EndeavorOTC are minimal.

For EndeavorOTC, the AE rates were low, in mild-moderate severity range. There were no SAEs, and all TE-ADEs were resolved by the end of the clinical trial. Given the favorable safety profile, even small benefits in inattentive ADHD symptoms would justify use of the product.

The benefits of the EndeavorOTC have been found to outweigh the individual risks. After evaluating all benefits, risks and applicable considerations, it has been determined that the overall residual risk of the EndeavorOTC is acceptable, and the product is considered safe for use by the intended user within the intended use environment.