Instructions for Use

Revision U

For parents, caregivers and licensed health care providers

℞ Only

Prescription-only digital therapeutic for pediatric Attention Deficit Hyperactivity Disorder (ADHD)

Caution: Federal law restricts this device to sale by or on the order of a licensed health care provider.

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

These Instructions for Use were last updated in Jan 2024

REF Part Number: 5011 Revision U

CONTENTS

Labels and Symbols

CAUTION: Pay special attention to the following details

℞ Only

Prescription Medical Device. Federal law restricts this device to sale by or on the order of a licensed health care provider.

Manufacturer

Reference Part Number

Lot Number

Catalog Number

Consult Instructions for Use

Obelis S.A.
Bd. Général Wahis 53
B-1030 Brussels, Belgium

EndeavorRx®

We're here to help.

Check out our FAQ for answers to frequently asked questions:

endeavorrx.com/faq/

Akili Assist® is available for questions regarding the use of EndeavorRx (prescriptions, health insurance reimbursement, technical assistance, feedback, and so on).

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

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

℞

Federal law restricts this device to sale by or on the order of a licensed health care provider. EndeavorRx should only be used by the patient for whom the prescription was written. For medical questions, please contact your child's health care provider. If you are experiencing a medical emergency, please dial 911. The restriction to sale by or on the order of a licensed health care provider includes those who are licensed by the law of the State in which they practice to use, or order the use of, this device in accordance with the indications for use.

NOTES

EndeavorRx 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 health care provider.

INDICATIONS FOR USE

EndeavorRx is a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8-17 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx 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. EndeavorRx 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 ⚠

No serious adverse events were reported. Of 342 participants who received AKL-T01 in the two clinical trials supporting EndeavorRx authorization for age ranges 8-17, 17 participants (4.97%) experienced treatment-related adverse events (TE-ADE) (possible, probable, likely). TE-ADEs reported at greater than 1% across the studies include: frustration tolerance decreased (2.34%) and headache (1.17%). Other adverse events occurred less than 1% and included dizziness, emotional disorder, nausea, and aggression. All adverse events were transient and no events led to device discontinuation. Across other studies in children and adolescents with ADHD, rates of adverse events were similarly low (<10%) and no Serious Adverse Events have been reported. All reported adverse events across all clinical trials resolved at the end of treatment. Users should consider the totality of evidence presented along with their health care provider when considering incorporating AKL-T01 into their treatment plan.

NOTE: EndeavorRx was previously known as AKL-T01 during the clinical investigations.

EndeavorRx®

Compatible Devices

ANDROID DEVICE MINIMUM SPECIFICATIONS

Android™ OS version	9.0
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.**		

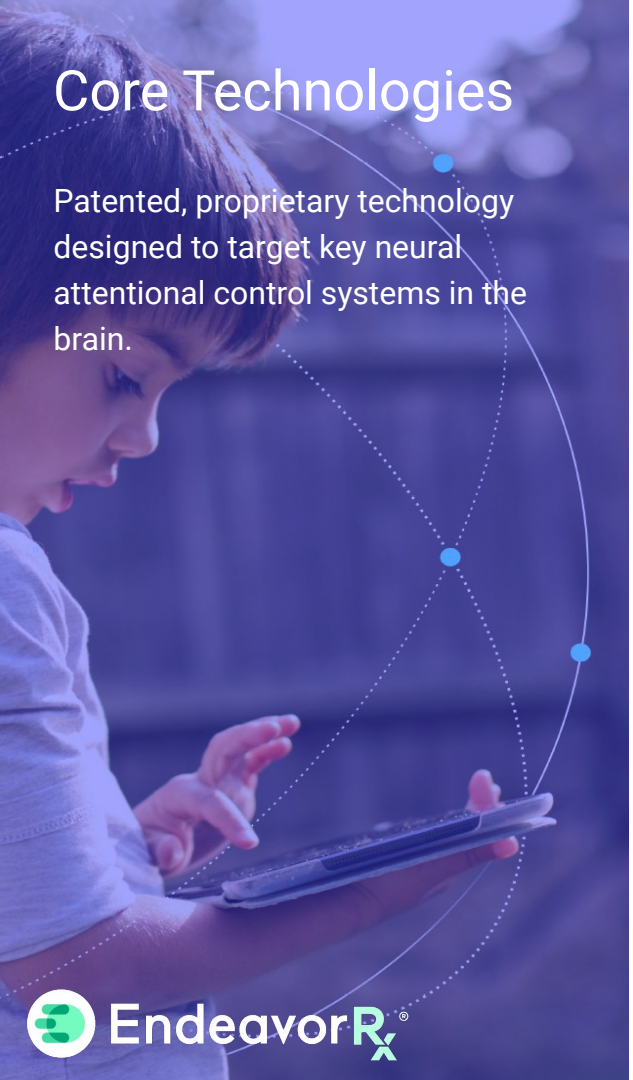
For more information on device compatibility, please visit the EndeavorRx.com FAQ.

Refer to the section *Technical > "What devices are compatible with EndeavorRx?"*

If you cannot find EndeavorRx in your app store, your device may not be compatible.

We're here to help.

AkiliAssist.com



Core Technologies

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.

Product Description

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

EndeavorRx treatment is used on a mobile device. See page 7 for compatible devices.

EndeavorRx is different from other action video games that a child might play. The treatment programmed into the game was designed to challenge a child's attentional control during gameplay, requiring focus and flexibility to manage multiple tasks at the same time.

2 clinical studies in over 500 children with ADHD, and 1 clinical study in over 150 adolescents with ADHD, have been conducted to support EndeavorRx authorization:

- A study of 348 children with ADHD (not receiving ADHD medication) and a separate study of 146 adolescents with ADHD (stably on or off ADHD medication), where EndeavorRx was used for a 4-week treatment period and showed improvements in attention function (as measured by computer-based testing) and attention-related ADHD symptoms and impairments.
- A study of 206 children with ADHD (on stimulant medication or not receiving any ADHD medication), where EndeavorRx was used for a 4-week period, followed by a treatment pause of one month and a subsequent second 4-week treatment period. Improvements in attention-related ADHD symptoms and impairments were similar in magnitude to those seen in other studies and further improved with the second treatment period in children on or off ADHD medication.
- A study of 162 adolescents with ADHD (on stimulant medication or not receiving any ADHD medication), where EndeavorRx was used for a 4-week period, showed improvements in attention, ADHD-related symptoms, and functioning.

NOTE: EndeavorRx was previously known as AKL-T01 during the clinical investigations. AKL-T02, while retaining the same user interface and SSME therapeutic engine as AKL-T01, has adapted gameplay difficulty intended to increase user engagement in an autism spectrum disorder population.

Getting Started with EndeavorRx

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

The recommended prescribed play time for all patients is approximately 25 minutes a day, 5 days a week, for 4 consecutive weeks. To assist your child, 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 your child may spend in the game browsing non-mission areas like the Costume Store and the Space Farm.

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

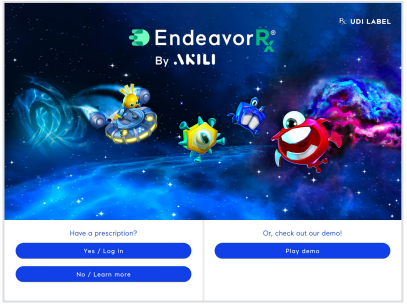
Minimize distractions for your child during each treatment with EndeavorRx. We recommend turning off device reminders and notifications, using EndeavorRx in a quiet room with headphones, and turning off other mobile devices and televisions. Find a comfortable place where your child can use EndeavorRx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

Regularly discuss the treatment experience with your child and let your child know that by design, EndeavorRx will be **challenging** (and sometimes frustrating) to play. Encourage your child to give each treatment of EndeavorRx their full attention and effort to help ensure the best treatment results.

During a treatment session, be sure to let your child know that **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.

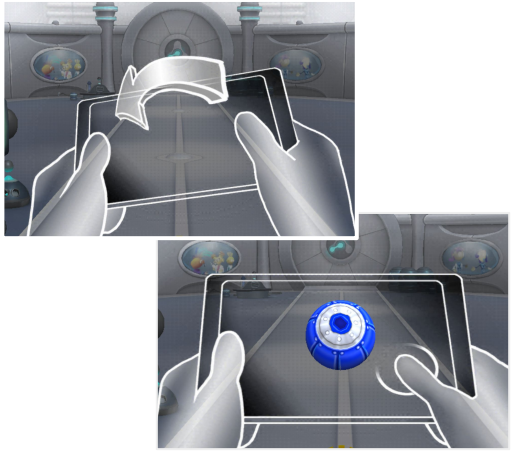
Operating Instructions



LAUNCH & LOGIN

Tap the application icon on the mobile device to start. Tap the "**Yes / Log In**" button and log in with your existing Akili Account using your email address and password. To register for a new Akili Account, check your activation code email for the create account link.

To open the EndeavorRx product label, tap the “Rx UDI Label” button found in the upper right corner of the screen. Here you can find helpful information like the app version number and a link to the EndeavorRx Instructions for Use.



MANIPULATING THE DEVICE

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

To **Steer**, your child should tilt the mobile device left and right. Encourage your child to hold the mobile device with both hands to help with the steering and tapping.

To **Tap** on a target, your child should touch the right half of the mobile device screen using their thumb. This touch can be anywhere on the right side of the screen – it does not have to be directly on the flying target nor the “target” button.

In addition to the primary actions above, your child will be able to unlock **Boosts** through the course of play. Equipped **Boosts** can be activated by tapping the left side of the screen and have a variety of effects in the racing experience.

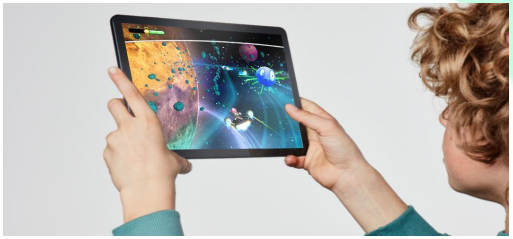
EndeavorRx®

EndeavorRx Daily Treatment

When using EndeavorRx, the goal is for your child to successfully **Steer** their character through a course while driving over power zones or avoiding obstacles, and **Tap** the right side of the screen to collect only the correct targets when they appear while ignoring all other targets. At the beginning of the **Mission**, your child will be shown multiple targets and asked to collect only specific types of targets - for example, they 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**. A daily treatment session requires your child to complete approximately 25 minutes of **Mission** gameplay. Your child will know they are done each day when their **Mission Minutes** timer on the Galaxy Map screen reaches zero.

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

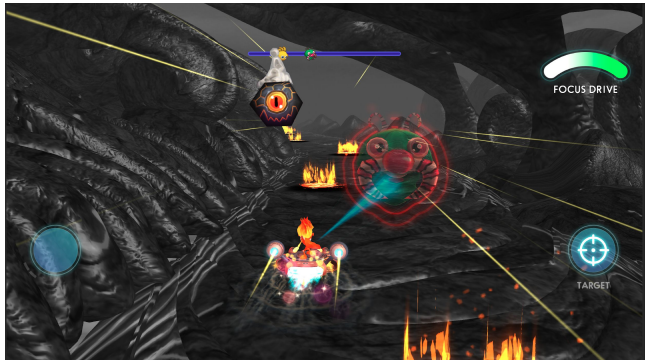


EndeavorRx is recommended to be used for approximately 25 minutes a day, 5 days a week, over initially at least 4 consecutive weeks, or as recommended by your child's health care provider.

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

Unlike an action video game, there is no way to "win" EndeavorRx. The game continuously challenges the child by adjusting the gameplay to maintain a consistent level of difficulty relative to how well they are playing the game. As long as the child is playing consistently and trying their best, the child is engaging with the treatment as intended.

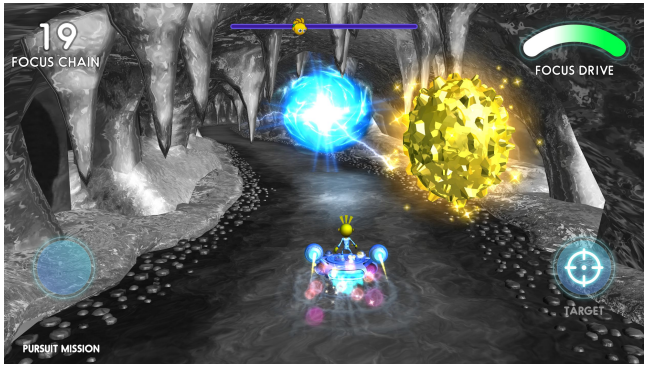
Missions



A daily treatment with EndeavorRx requires your child to complete approximately 25 minutes of play within the race-like portions of the app (also known as **Missions**). **Mission Minutes** can be tracked on the Galaxy Map screen. When **Mission Minutes** reach zero your child will receive an in-game reward for their efforts, and will no longer be able to participate in new Missions until the next day. This makes sure EndeavorRx is used in a manner consistent with the intended treatment schedule and prevents overuse.

During each **Mission**, your child will **Steer** their character through a course, moving through gates and/or avoiding obstacles, and **Tap** to collect targets when they appear. With successful tapping and steering, your child can catch **Mystic Creatures** and earn rewards.

The hover pod's capture ray will automatically lock on when your child gets close to the **Mystic Creature**. If your child remains locked on for a few seconds, they will capture the creature and earn a **Mystic Gem**. **Mystic 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 creature and captures it, EndeavorRx has recognized that your child has reached a new ability level in their play.

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

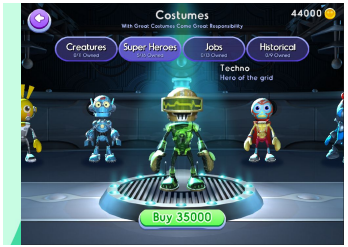
EndeavorRx was designed to, on average, take around 4 weeks to unlock all worlds, but actual speed of progression may vary across children. Independent of your child's progress, it is important that your child engages regularly with the treatment.

Once all worlds are unlocked, your child can revisit their favorite **World** to play and beat their previous scores. In addition, they can continue to complete **Quests**, unlock costumes, and upgrade their **Space Farm**.

Game User Interface

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

The **"main menu"** provides a visual representation of overall progress through the many environments across the **Galaxy** of EndeavorRx! From here, your child can access the costume store, visit their **Space Farm**, view their **Quests**, and choose an environment in their current **World** to play next! In the bottom-right of this screen your child can see how many **Mission Minutes** they have left to play for the day.

Game User Interface (cont.)

SPACE FARM

As your child plays, they will capture different kinds of **Mystic Creatures**. Captured creatures live in the **Space Farm** and each kind of creature gets its own special dwelling. These dwellings generate **Boosts** that your child can use during gameplay. Your child can upgrade a **Mystic Creature's** dwelling by collecting more of that creature. Build better dwellings to get better **Boosts**!

BOOST EQUIP SCREEN

Prior to each **Pursuit Mission**, your child will be able to equip a **Boost** to help them in their race. They have a limit on how many they can bring with them based on their **Player Level**, and can only equip from their current inventory of **Boosts**. New **Boosts** are generated each day after the first **Mission**!

Pausing and Exiting Treatment

PAUSE AND RESUME TREATMENT

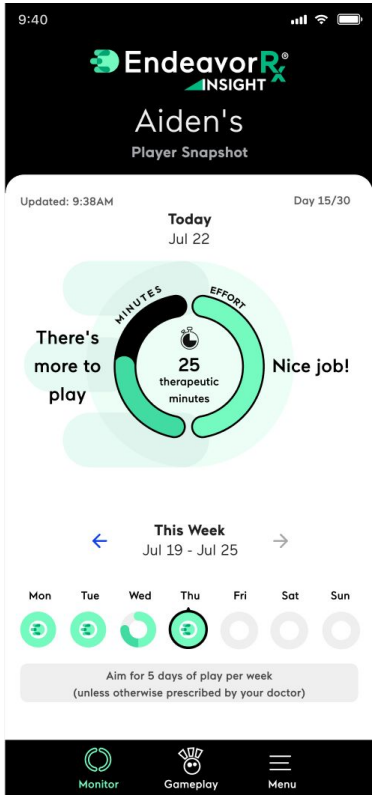
Each daily treatment can be paused at any time by tapping the upper-left corner of the screen.
Tap **"Resume"** to continue the treatment. *Note: There are built-in rest periods between missions.*

EXIT AND END TREATMENT

When a daily session is completed, the EndeavorRx application can be closed on your child's device.
After completing a treatment period of EndeavorRx, the treatment will become automatically disabled. EndeavorRx will display notifications when the treatment is soon to expire.

Please contact your child's health care provider to discuss your child's experience and the best treatment plan for your family.

Tools for Caregivers



EndeavorRx Insight®

The EndeavorRx system uses a proprietary algorithm to provide caregivers insights into how their child is performing during their treatment.

EndeavorRx analyzes if your child is playing using the correct rules and the level of effort they are applying to completing each mission. For a review of gameplay rules, refer to the section EndeavorRx Daily Treatment. These analyses are available in EndeavorRx Insight, a companion app for caregivers. To calculate and display this information, the EndeavorRx treatment app and EndeavorRx Insight app must both be connected to the internet. EndeavorRx Insight is available on the Apple App Store® and on Google Play™.

Mobile Device Security

DEVICE SECURITY RECOMMENDATIONS

EndeavorRx software incorporates state of the art security features in order to protect the data of users. Users should configure the mobile device they're using to play EndeavorRx with the following security settings in order to maximize their security.

Configure the mobile device with a strong passcode, pin code, Face ID, or Touch ID.

Configure the mobile device to automatically lock after a period of inactivity.

Configure the mobile device with USB Restricted Mode enabled.

Configure the mobile device with two-factor authentication enabled.

Configure the mobile device to show notifications only when the device is unlocked.

Only connect the device to secure wireless networks with a passcode and encryption.

Configure the mobile device backup with encryption enabled.

Keep the mobile device operating system and EndeavorRx application up to date with the latest available versions.

In order to maintain manufacturer security protections do not jailbreak or root the device.

Troubleshooting

We're here to help.
AkiliAssist.com

Q. The EndeavorRx 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 the 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 EndeavorRx 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 of my Mission Minutes.

If played right around midnight in your local time, some of the Mission Minutes might count for next day's gameplay (for example, starting the gameplay at 11.57pm and finishing at 12.03am). This issue can be alleviated by playing all missions in the same calendar day.

Q. The application unexpectedly quits, stops responding, or won't open.

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

Q. The application keeps getting interrupted by notifications.

Follow your device manufacturer instructions to turn off or modify notifications prior to playing EndeavorRx.

Clinical Research

For Licensed Health Care Providers

Note: EndeavorRx was previously known as AKL-T01 during the clinical investigations. AKL-T02, while retaining the same user interface and SSME therapeutic engine as AKL-T01, has adapted gameplay difficulty intended to increase user engagement in an autism spectrum disorder population.

Clinical Research

CLINICAL ENDPOINT ACRONYMS

ADHD-RS: ADHD Rating Scale (total score)

ADHD-RS-Hyperactive: ADHD-RS hyperactivity-impulsivity subscale

ADHD-RS-Inattentive: ADHD-RS inattention subscale

BRIEF: Behavior Rating Inventory of Executive Function

CGI-I: Clinical Global Impression - Improvement

IRS: Impairment Rating Scale to measure ADHD-related impairment

TOVA: Test of Variables of Attention

TOVA API: TOVA Attention Performance Index (also known as TOVA ACS: Attention Comparison 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

INTRODUCTION

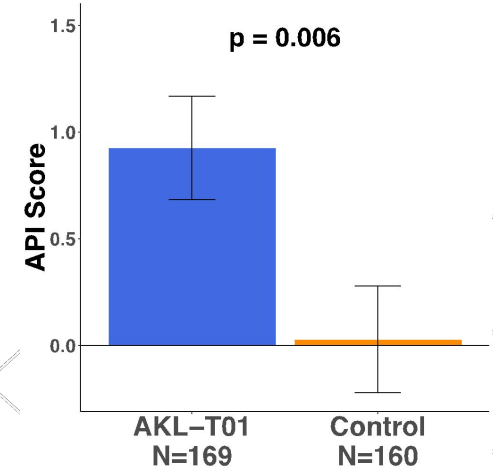
The two primary studies supporting clearance of the device include a randomized, controlled trial of AKL-T01 in 348 children aged 8-12 with ADHD and a demonstrated attention deficit; and a second, single-arm trial of 162 adolescents aged 13-17 with ADHD and a demonstrated attentional deficit. Four additional studies including over 350 participants have also evaluated the effectiveness and safety of AKL-T01 and have been published.[1,2,3,4]

STARS-ADHD Pivotal Study[5]

Study Design: a randomized, double-blind, parallel-group, 4-week, controlled trial of EndeavorRx (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 EndeavorRx 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 played (SD, 29.2 sessions).

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[1] *Kollins et al., 2021,* [2] *Davis et al., 2018,* [3] *Yerys et al., 2019* [4] *Anguera et al., 2017* [5] *Kollins et al,, 2020*

Clinical Research (cont.)

STARS-Adolescent Study[1]

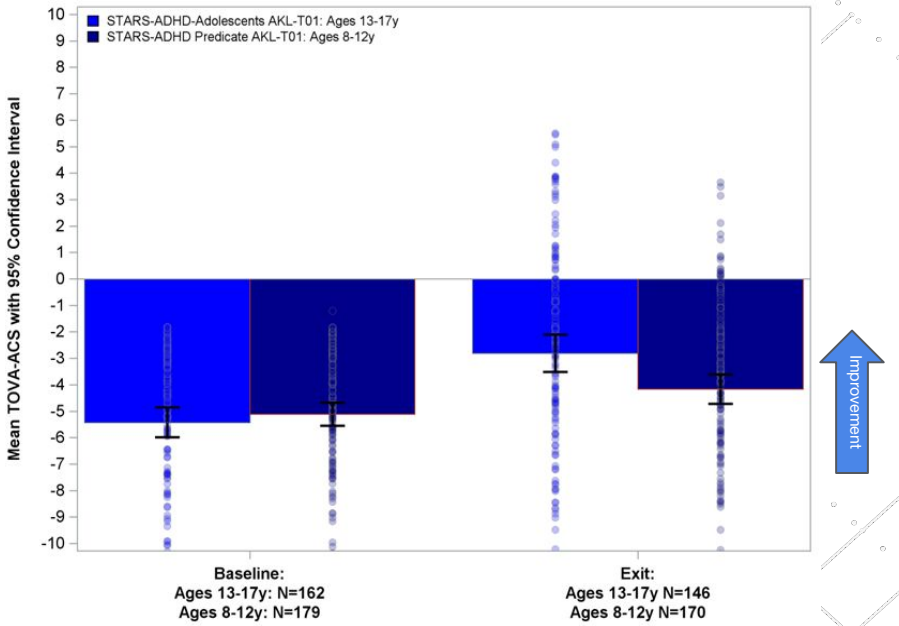
Study design: A multicenter, 4-week, open-label study of EndeavorRx (AKL-T01) in 162 children aged 13-17 years diagnosed with ADHD conducted at 14 sites in the USA. Subjects required a TOVA API score of ≤ −1.8 at baseline and to be stably on or off ADHD medication. Eligible participants received EndeavorRx for approximately 25 minutes per day, 5 days per week, over 4 weeks. There was no digital control in this study.

Objectives: The primary endpoint was change from baseline to day 28 on the TOVA ACS. The secondary measures were changes from baseline to day 28 on ADHD symptoms (ADHD-RS) inattention and total scale scores.

Results: TOVA ACS score was significantly improved at Day 28 compared to baseline. For the ADHD-RS, clinically meaningful improvement based on literature is estimated as 10 point difference[2] or a 30% change in Total Score.[3] In this study, ADHD-RS inattentive score improved by 3.0 (SD: 5.38) compared to an improvement of 3.6 in the predicate study. In the present study, the ADHD-RS total score improved by a mean of 4.6 points (SD: 8.14) compared to an improvement of 6.2 in the predicate study. Twenty-seven percent of participants in the STARS-Adolescent study exhibited a change in ADHD-RS total score of ≥30% from Baseline to Day 28, compared to 24% in the predicate study .

Safety and Compliance: Four (2.5%) participants experienced a device-related adverse event (AE). The most common device-related AEs were frustration (3 [1.9%] of 162) and headache (1 [0.6%] of 162). 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.

NOTE: This single arm study did not include a sham control group and it is therefore possible that a placebo effect may have impacted the study results by inflating the effect of the EndeavorRx device. The study had sufficient statistical power to detect a significant effect of treatment compared to a similarly sized control group with placebo response of up to a 1.7-point improvement in TOVA-ACS. Patients and health care providers should consider the totality of the clinical evidence in light of this before using this product.



Markers represent individual subject values. TOVA-ACS scores below zero suggest performance similar to individuals with ADHD.[4]

[1] *Under review;* [2]*Nasser et al., 2021,* [3] *Zhang et al. 2005*
[4] *TOVA Clinical Manual 2020, p. 32 of 78: https://files.tovatest.com/documentation/9/Clinical%20Manual.pdf*

Clinical Research

Comparisons of Clinical Studies

Study Design	Adolescents (ages 13-17)	STARS (ages 8-12)	Comparison
Study design	Single-arm, open-label	Randomized clinical trial	**Different** - the adolescent study intended for evaluation of substantial equivalence via comparison of results to the STARS AKL-T01 group. The company made a decision not to include a control/sham arm as part of this study for following reasons: 1) the safety and efficacy of the product was already established in a randomized controlled trial in the younger population; 2) the primary endpoint used in STARS-Adolescent was identical to the original STARS RCT; 3) based on the predicate RCT and multiple published studies of ADHD children and adolescents in the literature, the primary outcome measure demonstrates little to no placebo effects in randomized, controlled trials; 4) AKL-T01 is a low-risk device; 5) the predicate study (STARS) was an RCT using the same device 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.
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	162 enrolled	348 enrolled	Similar - the larger N in STARS study takes into account two arms. Sample size in adolescent study was determined by power calculations.
Intervention	EndeavorRx (AKL-T01)	EndeavorRx (AKL-T01) EVO: Words (Active control)	Similar - the adolescent 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 predicate study (STARS) 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.
Treatment regimen	25 minutes per day (equivalent to 6-8 missions), 5 days per week for 4 weeks	25 minutes of AKL-T01 or active control per day, 5 days per week for 4 weeks	Similar
Participant Duration	Approximately 4 weeks on treatment	Approximately 4 weeks on treatment	Same

Clinical Research (cont.)

Table of Complete Case Analysis (CCA) and Intent-to-Treat (ITT) Analysis with Multiple Imputation (MI) of the Primary Efficacy Endpoint – TOVA-ACS Change from Baseline to Day 28

Analysis	Baseline TOVA-ACS	Exit (Day 28) 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
Adolescent Efficacy Population (CCA)			
n	146	146	146
Mean (SE)	-5.447 (0.3106)	-2.808 (0.3546)	2.639 (0.3144)
95% CI			2.018, 3.261
p-value[1]			<0.0001
Adolescent Safety Population (ITT with MI[2])			
n	162	162	162
Mean (SE)	-5.421 (0.2870)	-2.784 (0.3486)	2.637 (0.3147)
95% CI			2.020, 3.253
p-value			<0.0001

Abbreviations: CCA = complete case analysis; ITT = intent-to-treat, MI = multiple imputation; MCAR = missing completely at random; MAR = missing at random; FCS = fully conditional specification

[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 28 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, Day 28 and change from baseline were calculated for each imputation and combined using PROC MIANALYZE in SAS version 9.4.

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Clinical Research (cont.)

IMPROVEMENTS IN ATTENTION ACROSS STUDIES

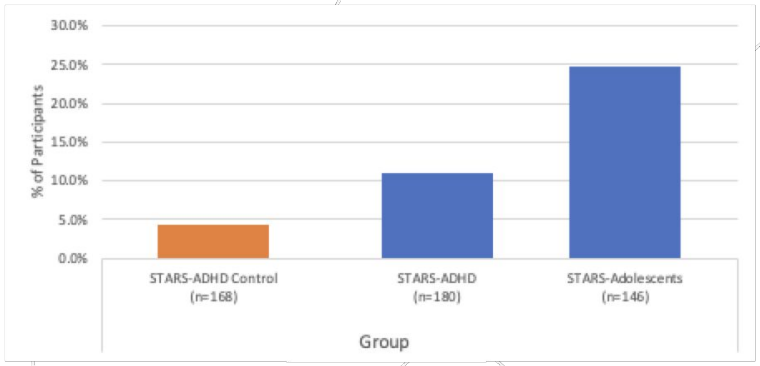
A responder analysis was conducted on key cognitive measures of attention. A comparison of the participants on EndeavorRx (AKL-T01) therapeutic software versus an *active* control from the STARS-ADHD study in participants aged 8-12 years are shown here. The active control group were instructed to play a non-therapeutic word-based game for 25 minutes per day, 5 times a week for 4 weeks.

Responder Endpoints:

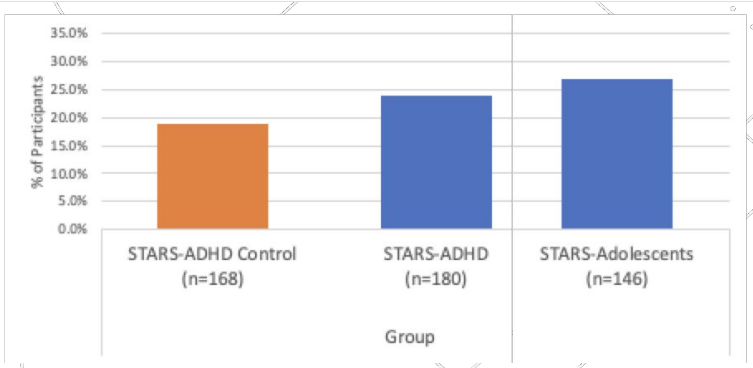
- **TOVA-ACS** - a TOVA-ACS score above zero indicate performance like the normative sample[1]
- **ADHD-RS** - a 30% improvement in ADHD-RS total score is generally accepted as clinically significant improvement[2]

The percentage of participants moving into the normative range on key measures of attention after 4 weeks of EndeavorRx use is between 11-33% across the large multi-site clinical studies. Whereas the active control group (8-12 years) from the STARS-ADHD study had only 4.4% of responders on an objective measure of attention, TOVA-ACS, the STARS and Adolescent trial cohorts had 11% and 24.7% responders, respectively, at the end of the 4 weeks. Whereas the active control group had 18.9% of responders on the subjective ADHD-RS assessment, the STARS and Adolescent cohorts had 24% and 27% responders, respectively, at the end of the 4 weeks. The observed responder rates for both TOVA and ADHD-RS were similar to other studies that have been conducted using AKL-T01.[3]

Across Studies Comparison of Participants Moving into the Normal Range on TOVA-ACS (>0) After 4 Weeks of AKL-T01 Use



Across Studies Comparison of Participants Experiencing Greater than 30% Improvement on ADHD-RS After 4 Weeks of AKL-T01 Use



[1] *Greenberg et al. 2007,* [2] *Zhang et al. 2005,* [3] *Kollins et al., 2021*

Clinical Research (cont.)

SIDE EFFECTS

No serious adverse events were reported. Of 342 participants who received AKL-T01 in the two clinical trials supporting EndeavorRx authorization for age ranges 8-17, 17 participants (4.97%) experienced treatment-related adverse events (TE-ADE) (possible, probable, likely). TE-ADEs reported at greater than 1% across the studies include: frustration tolerance decreased (2.34%) and headache (1.17%). Other adverse events occurred less than 1% and included dizziness, emotional disorder, nausea, and aggression. All adverse events were transient and no events led to device discontinuation. Across other studies in children and adolescents with ADHD, rates of adverse events were similarly low (<10%) and no Serious Adverse Events have been reported. All reported adverse events across all clinical trials resolved at the end of treatment. Users should consider the totality of evidence presented along with their health care provider when considering incorporating AKL-T01 into their treatment plan.

NOTE

EndeavorRx 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 health care provider.

INDICATIONS FOR USE

EndeavorRx is a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8-17 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx 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. EndeavorRx 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.

BENEFIT-RISK PROFILE

No serious adverse events were reported. Of 342 participants who received AKL-T01 in the two clinical trials supporting EndeavorRx authorization for age ranges 8-17, 17 participants (4.97%) experienced treatment-related adverse events (TE-ADE) (possible, probable, likely). TE-ADEs reported at greater than 1% across the studies include: frustration tolerance decreased (2.34%) and headache (1.17%). Other adverse events occurred less than 1% and included dizziness, emotional disorder, nausea, and aggression. All adverse events were transient and no events led to device discontinuation. All adverse events resolved by the end of treatment.

EndeavorRx showed a general improvement in attention as well as areas of improvement in other symptoms associated with ADHD. The totality of the evidence demonstrated clinical benefit in attention, as measured by the TOVA, as well as other assessments of symptoms and functioning in children with ADHD with a demonstrated attention issue. Improvements in ADHD symptoms and impairment favored EndeavorRx over control, including rates of participants exhibiting clinically meaningful symptom reductions. As noted, the risks associated with EndeavorRx are minimal.

For EndeavorRx, the AE rates were extremely low, in mild-moderate severity range. There were no SAEs, and all AEs were resolved. Given the favorable safety profile, even small benefit would justify use of the product.

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Clinical Research (cont.)

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