EndeavorRx™

Instructions for use

For parents, caregivers and healthcare professionals

℞ Only

Prescription-only digital therapeutic

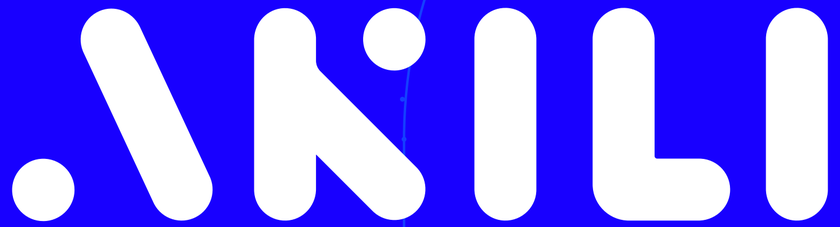
for pediatric Attention Deficit Hyperactivity Disorder (ADHD)

Caution: Federal law restricts this device to sale by or on the order of a physician.

This document is intended to support treatment version:

1.5.2

AKILI



MANUFACTURER

Akili Interactive Labs, Inc.

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

These Instructions for Use were last updated in October 2020

REF Part Number: 5011 Revision F

CONTENTS

Labels and Symbols

CAUTION: Pay special attention to the following details

Perception Medical Device. Federal law restricts the sale of this device to or on the order of a physician

Manufacturer

Reference Part Number

Lot Number

Catalog Number

Consult Instructions for Use

We’re here to help.

Akili Assist is available for questions regarding the use of EndeavorRx (prescriptions, health insurance reimbursement, technical assistance, complaints, etc.).

Available: Monday–Friday (excluding National Holidays)

Website: AkiliAssist.com

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

Fax: 1-866-565-4633

Hours of Operation: See Our Website AkiliAssist.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 healthcare provider. If your child experiences a seizure stop the treatment and contact your child's healthcare provider.

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

℞ ONLY

Federal law restricts this device to sale by or on the order of a physician. EndeavorRx should only be used by the patient for whom the prescription was written. For medical questions, please contact your child's healthcare provider. If you are experiencing a medical emergency, please dial 911.

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 healthcare provider.

INDICATIONS FOR USE

EndeavorRx 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 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 ⚠

There were no serious adverse events. Of 538 participants using EndeavorRx (AKL-T01), 50 participants (9.3%) experienced treatment-related adverse events (probable, likely), and three participants experienced treatment-related adverse events with the digital control, in studies where a control was used. EndeavorRx 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 subject reported lasting or irreversible effects after discontinuation.

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

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 17 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.

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

- A study of 348 children with ADHD (not receiving 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.
- Three separate studies of 40, 20 and 19 children with ADHD, where EndeavorRx was used for a 4-week treatment period and showed improvements in attention measures and attention-related ADHD symptoms.

EndeavorRx™

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.

Ensure that the numbers of the **treatment version downloaded (Ver. X.X.X) on your device match the version numbers (X.X.X) on page 1 of this document.**

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

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

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. For example, consider taking him or her into a quiet room or using 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**.

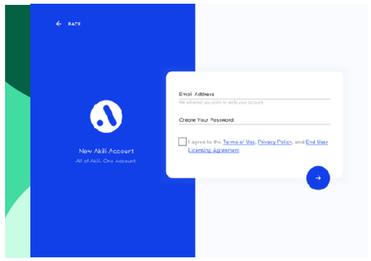
It is best if the patient adjusts the field of view and avoids using the device too close to their eyes. It is recommended to turn on the blue light filter on the device if administered during nighttime, but also recommended not to play right before bedtime to avoid risk of potential reduction in sleep quality.

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

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.

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.

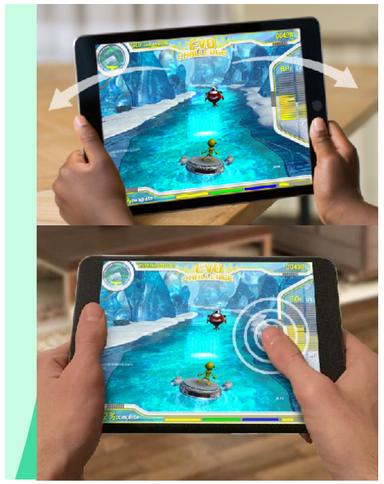
Operating Instructions



LAUNCH & LOGIN

Tap the application icon on the mobile device to start.

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

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.

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**.

EndeavorRx Daily Treatment

When using EndeavorRx, the goal is for your child to successfully **Navigate** 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.

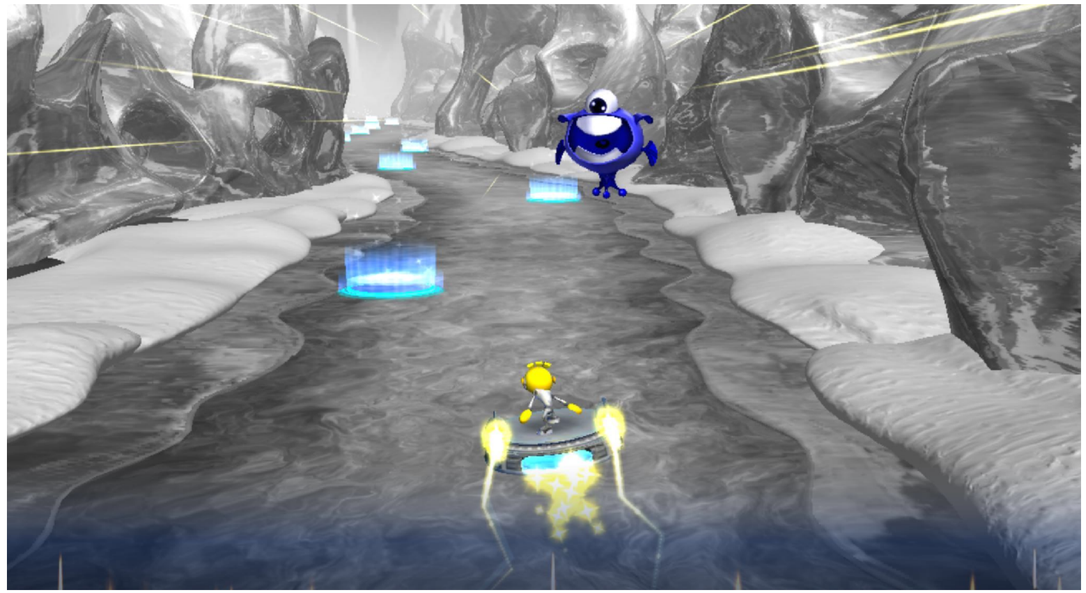
There are many separate **Worlds** to unlock and explore as your child progresses through treatment.

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 algorithm continues to challenge the child at a specific and consistent level of difficulty throughout the game, in addition, the multitasking rules get more complex as the game progresses through the 4 Worlds. As long as the child is playing consistently and trying her/his best, the child is engaging with the treatment as intended.

Missions



A daily treatment with EndeavorRx 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 EndeavorRx is used in a manner consistent with the intended treatment schedule and prevents overuse.

During each mission, your child will Navigate his or her character 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, EndeavorRx 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.

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. We recommend playing the 5 missions daily (approximately 25 minutes), 5 days a week, for at least 4 weeks or as recommended by your child's health care provider.

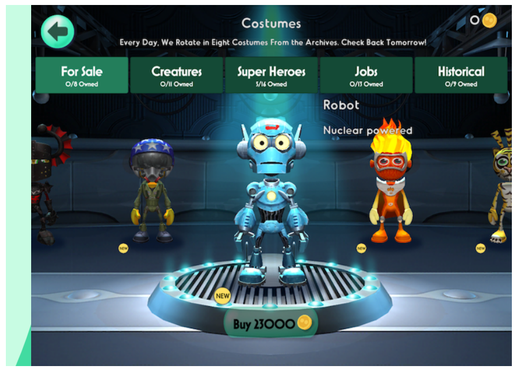
Once all worlds are unlocked, a child can revisit their favorite world to play and beat their previous scores, and there are new daily Quests to complete and costumes to unlock.

EndeavorRx™

Treatment Screens

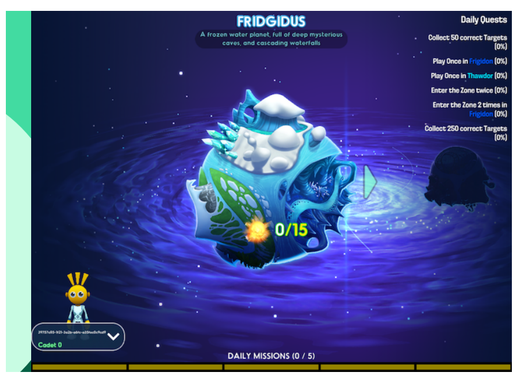
SUMMARY SCREEN

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 EndeavorRx! 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!

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 (on average every 4-5 minutes).*

EXIT AND END TREATMENT

When a daily session is completed, the EndeavorRx application can be closed on your 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 healthcare professional to discuss your child’s experience and the best treatment plan for your family.

Mobile Device Security

DEVICE SECURITY RECOMMENDATIONS

EndeavorRx 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 stored password / pin-protected to reduce the risk of unauthorized access

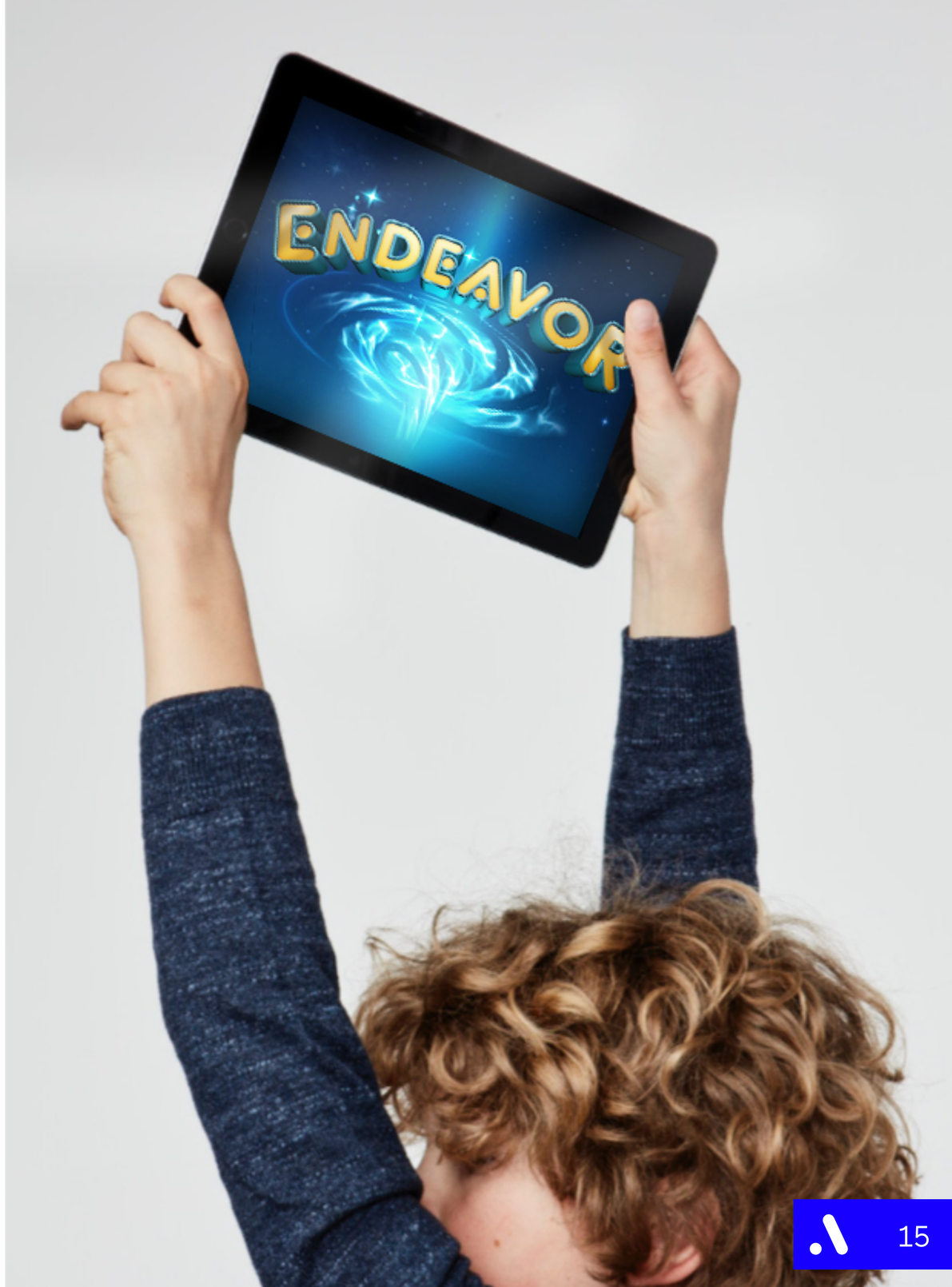
Mobile device should be in automatic lock mode after a period of inactivity

Avoid using untrusted WiFi networks

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

Mobile device operating system (OS) and EndeavorRx 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 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.

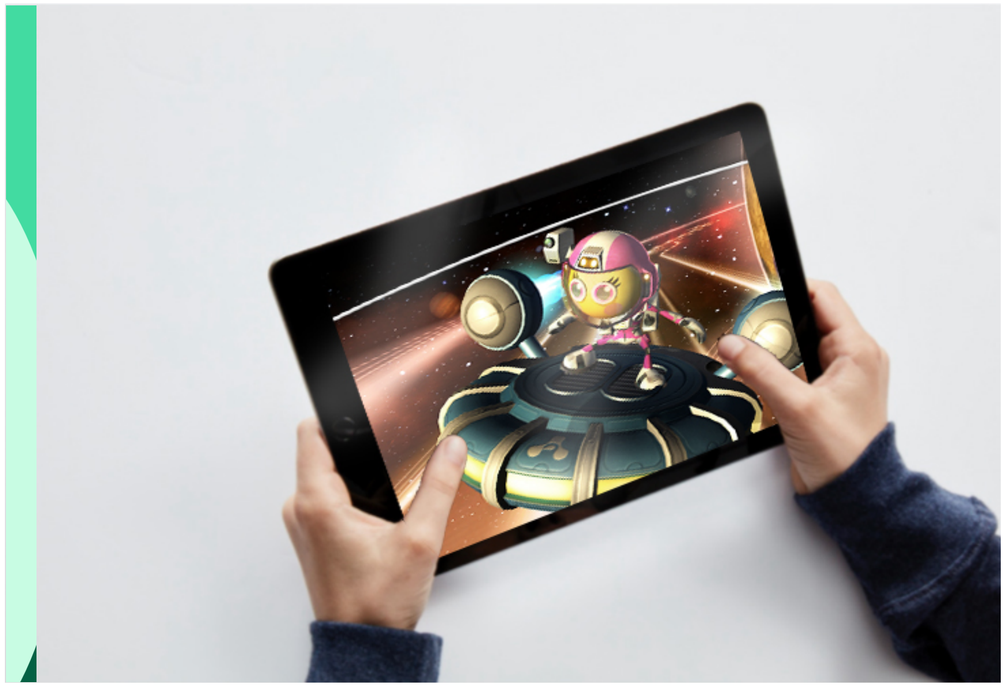
Q. I can't play all 5 missions.

If played right around midnight in your local time, some of the missions 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 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.

Compatible Devices



iOS DEVICE MINIMUM REQUIREMENTS

iOS version	**12.0**
Hardware	**16 GB**
Chip	**1.3 Ghz dual-core with 64-bit architecture CPU**
Memory size	**1 GB**
Network Infrastructure	**WiFi**

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

NOTE: EndeavorRx is not currently compatible with Android OS.

Clinical Research Behind EndeavorRx (AKL-T01)

For Physicians and Healthcare Professionals

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

Clinical Research Behind EndeavorRx (AKL-T01)

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

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 EndeavorRx (AKL-T01)

INTRODUCTION

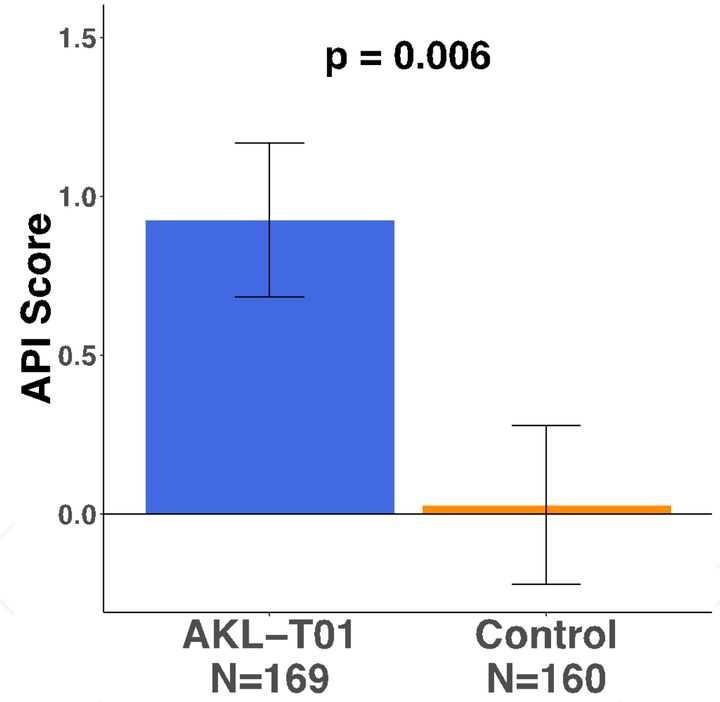
EndeavorRx (AKL-T01) has been studied in over 600 children with ADHD across 5 clinical studies. 3 studies in ADHD (STARS-ADHD, STARS-Adjunct and ADHD-POC) and 2 pilot studies in ADHD with different comorbidities (Sensory Processing Disorder and Autism Spectrum Disorder).

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 played (SD, 29·2 sessions).

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

Clinical Research (cont.)

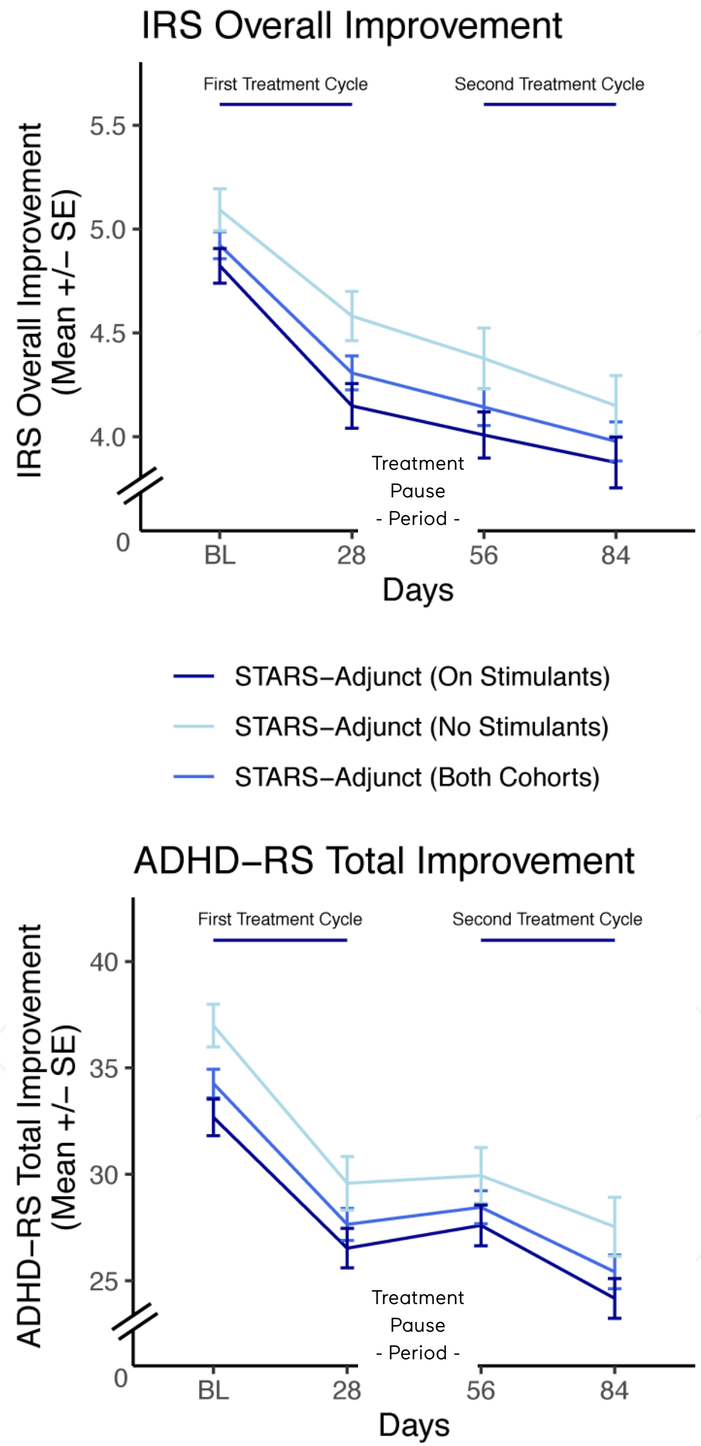
STARS-Adjunct Study[1]

Study design: A multicenter, 12-week, open-label study of EndeavorRx (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-I, 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 adverse events (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.



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

Clinical Research (cont.)

ADHD Proof of Concept Study[1]

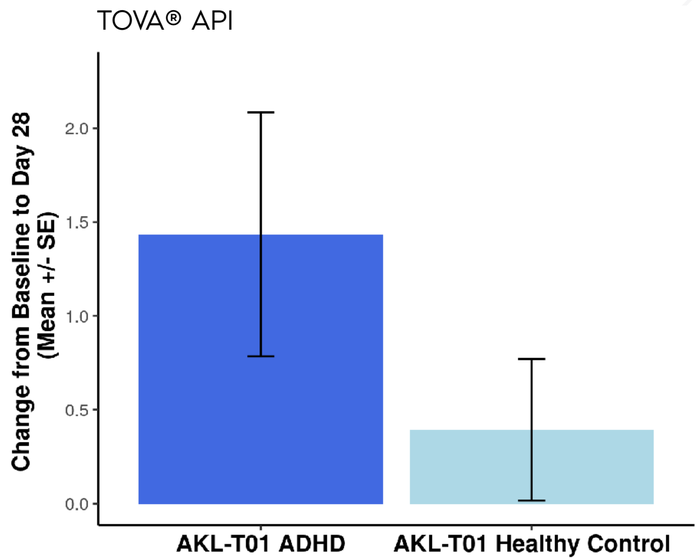
Study Design: A 4-week, open-label study of EndeavorRx (AKL-T01) in children aged 8-12 years old, comparing 40 children with ADHD to 40 neurotypical children (healthy controls). The ADHD group were required to have an in-clinic diagnosis of ADHD, not be taking ADHD medications and have an ADHD-RS total 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 adverse events. 84% of treatment sessions were completed.



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

Clinical Research (cont.)

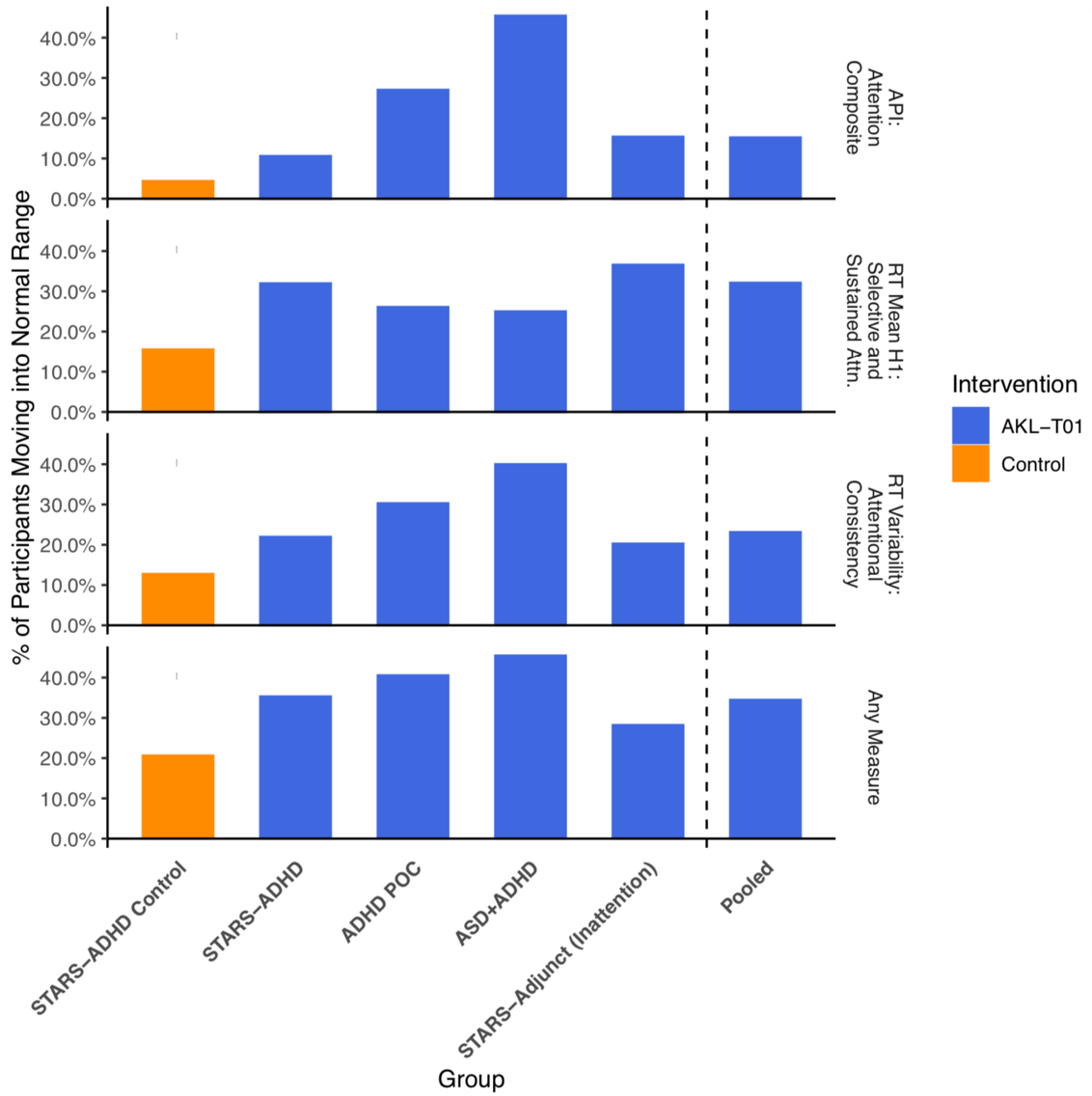
ADDITIONAL STUDIES

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 adverse event (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.



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[1] *Anguera 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. Of 538 participants using EndeavorRx (AKL-T01), 50 participants (9.3%) experienced treatment-related adverse events (probable, likely), and three participants experienced treatment-related adverse events with the digital control, in studies where a control was used. AKL-T01 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 subject reported lasting or irreversible effects after discontinuation.

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 healthcare provider.

INDICATIONS FOR USE

EndeavorRx 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 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.

EndeavorRx™

Model: Treatment 1

CAT 50002063901 LOT Release 1.5.2 (October 23, 2020)

Rx Only

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CAT	Catalog Number
	Consult Instructions For Use
	Caution (Consult accompanying documents)
Rx Only	Prescription Only
LOT	Lot Number
	Manufacturer