

DE NOVO CLASSIFICATION REQUEST FOR

EndeavorRx

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Digital therapy device for Attention Deficit Hyperactivity Disorder. A digital therapy device for Attention Deficit Hyperactivity Disorder (ADHD) is a software intended to provide therapy for ADHD or any of its individual symptoms as an adjunct to clinician supervised treatment.

NEW REGULATION NUMBER: 21 CFR 882.5803

CLASSIFICATION: Class II

PRODUCT CODE: QFT

BACKGROUND

DEVICE NAME: EndeavorRx

SUBMISSION NUMBER: DEN200026

DATE DE NOVO RECEIVED: April 16, 2020

SPONSOR INFORMATION:

Akili Interactive Labs Inc.
125 Broad Street, 4th Floor
Boston, MA 02110

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.

LIMITATIONS

The sale, distribution, and use of EndeavorRx are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended to be used as a stand-alone therapeutic device.

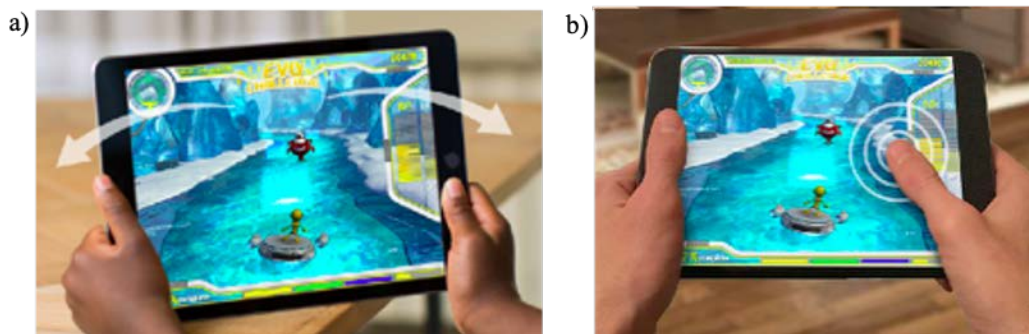
EndeavorRx may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict use of a mobile device; parents should consult with their child's healthcare provider.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

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 an attention issue. The EndeavorRx program is a software-as-medical device (SaMD) that resides on the user's mobile device and can be executed at home.

Figure 1. EndeavorRx Medical Device Software



EndeavorRx is engineered as a therapeutically active treatment for attention in pediatric patients affected by ADHD. EndeavorRx is built on Akili's proprietary, patented, technology platform and uses adaptive algorithms (also known as Selective Stimulus Management Engine, SSME™) to deliver stimuli that are designed to engage the patient in a manner that improves their attention function. In a closed-loop system, the adaptive SSME™ algorithms automatically adjust the difficulty level for a personalized treatment experience that is tailored to the needs of each individual patient.

EndeavorRx is delivered through a video game experience which leverages art, music, storytelling, and reward cycles to keep patients engaged. The adaptive algorithm constantly pushes patients precisely at predefined performance bounds relative to each individual, such that they are continuously encouraged to exceed their historic performance. The science behind EndeavorRx was developed at the University of California, San Francisco by Adam Gazzaley, M.D., Ph.D., Founding Director of the University of California San Francisco's Neuroscape and Akili's Chief Science Advisor.¹

The basic program inputs are steering, which is accomplished by using the internal accelerometer to measure the degree to which the mobile device is tilted (**Figure 1a**), and tapping, which is accomplished using the touch screen to measure correct and incorrect targeting (**Figure 1b**). The basic outputs are visual display of the game progression along with audio, which is accomplished by using the internal high-resolution display and internal speaker.

¹ J.A. Anguera et al., "Video Game Training Enhances Cognitive Control in Older Adults," *Nature* 501, no. 7465 (September 5, 2013): 97–101, <https://doi.org/10.1038/nature12486>.

The program includes features to ensure it is used per the prescribed regimen (approximately 25 minutes per day for 5 days per week), including lock-out after the allocated gameplay, as well as reminders to the user (and parents) to maximize compliance with the regimen.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

EndeavorRx Proprietary Software as a Medical Devices (SaMD) was reviewed according to the FDA Guidance document, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” issued May 11, 2005. The software was found to have a MODERATE level of concern because a failure of the device may result in a minor injury, either to a patient or to a user of the device prior to risk mitigation. FDA review of the software documentation provided in support of EndeavorRx was found to be acceptable.

SUMMARY OF CLINICAL INFORMATION

Note: In early clinical evaluations, EndeavorRx was referred to as “ProjectEvo” and in later evaluations as “AKL-T01.” Therefore “ProjectEVO” and “AKL-T01” will appear in the cited publications.

Five clinical studies have been conducted with EndeavorRx in over 600 children with ADHD including: the STARS-ADHD, STARS-Adjunct, and ADHD POC studies, or with comorbid ADHD, including: the SPD+ADHD Pilot and ASD+ADHD Pilot studies. Each trial is summarized below.

STARS-ADHD

Background and Trial Design

Patient population and duration of device use:

Children with ADHD in STARS-ADHD used EndeavorRx for 4 weeks.

Overview of trial design:

The STARS-ADHD pivotal study² of EndeavorRx was a multi-center, randomized, double-blind, digital controlled study in 348 children aged 8-12 years, who were diagnosed with ADHD and had a demonstrated attention issue. Children were randomized 1:1 to EndeavorRx or a digital control. Both groups used the treatment or digital control at home on a tablet device for four weeks. The digital control mimicked the reward and engagement of EndeavorRx but deployed different stimuli and did not include Akili’s SSME adaptive algorithms.

The primary outcome measure was, change in the Test of Variables of Attention (TOVA) Attention Performance Index (API). TOVA is an FDA-cleared continuous performance test measuring attention, which also aids in the evaluation of ADHD treatments. *TOVA Attention Performance Index (TOVA ACS/API³)* is an attentional composite measure that captures attentional functioning at a broad scale. Two of its subcomponents measure more specific attentional processes as follows: *Reaction Time Mean First*

² Scott H. Kollins et al., “A Novel Digital Intervention for Actively Reducing Severity of Paediatric ADHD (STARS-ADHD): A Randomised Controlled Trial,” *The Lancet Digital Health* 2, no. 4 (April 1, 2020): e168–78, [https://doi.org/10.1016/S2589-7500\(20\)30017-0](https://doi.org/10.1016/S2589-7500(20)30017-0).

³ TOVA Attention Composite Score (TOVA ACS) is exactly the same as the TOVA API above and was simply a name change in the measure between TOVA V8 and TOVA V9.

Half (RT Mean HI) measures selective and sustained attention, and Reaction Time Variability (RT Var) measures attentional consistency.^{4,5}

Secondary endpoints included: mean changes in ADHD-RS (Total, Inattentive, Hyperactive), ADHD Impairment Rating Scale (IRS), CGI-I, and BRIEF (working memory scale, inhibit scale). The study was managed by the Duke Clinical Research Institute and was conducted at 20 sites in the USA.

Inclusion and exclusion criteria included: children with an ADHD diagnosis based on the DSM V, with a MINI-KID and ADHD-RS Total score ≥ 28 and who demonstrated an attention issue based on a TOVA API baseline score < -1.8 at screening. Participants had to be stable and off ADHD medication or therapy (3-7 days before baseline), and not present other significant comorbid psychiatric diagnoses. Nonverbal IQ was required to be ≥ 80 .

Enrollment

857 children were screened and 509 were excluded as follows:

- 482 did not meet inclusion criteria primarily because they did not have a demonstrated attention issue as assessed with TOVA API
- 32 met exclusion criteria
- 4 enrolled late

The remaining 348 children were allocated to EndeavorRx (n=180) and digital control (n=168).

Demographics

The mean age of the participants in this study was 9.6 years and mostly male (b) (4) (Table 1). The majority of children presented with the combined (72%) or inattentive (26%) ADHD subtype. All children were currently off of any ADHD medication.

Table 1. STARS-ADHD: Demographics / Baseline Characteristics

	EndeavorRx	Digital Control	Total
N	(b) (4)		
Age Mean (SD)	(b) (4)		
Sex (Male)	(b) (4)		
Race (White)	(b) (4)		

Accountability

97% of participants completed the study. Reasons for discontinuation were lost to follow-up (5/9), withdrawal by parent or guardian (3/9) and investigator decision (1/9). Both groups showed high engagement completing $>80\%$ of recommended sessions.

⁴ Gordon B. Forbes, "Clinical Utility of the Test of Variables of Attention (TOVA) in the Diagnosis of Attention-Deficit/Hyperactivity Disorder," *Journal of Clinical Psychology* 54, no. 4 (June 1998): 461-476, [https://doi.org/10.1002/\(SICI\)1097-4679\(199806\)54:4<461::AID-JCLP8>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1097-4679(199806)54:4<461::AID-JCLP8>3.0.CO;2-Q).

⁵ Marcela P. Henríquez-Henríquez et al., "Low Serum Sphingolipids in Children with Attention Deficit-Hyperactivity Disorder," *Frontiers in Neuroscience* 9 (2015): 300, <https://doi.org/10.3389/fnins.2015.00300>.

Results

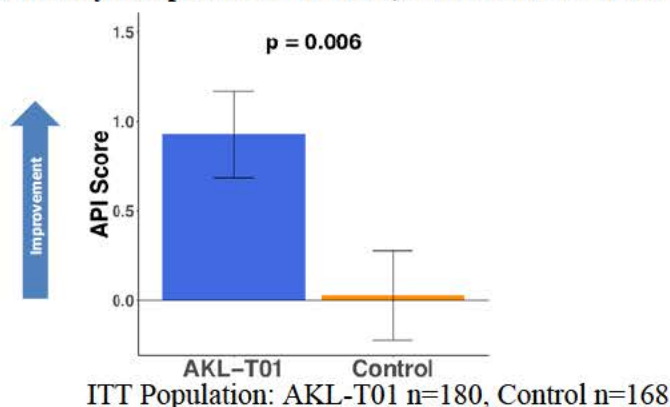
Safety

EndeavorRx was shown to be safe in this study, with no deaths or other serious adverse events (AEs) reported. Fifteen (15/348, 4.3%) participants experienced treatment-related AEs, either definitely related or possibly related, across both EndeavorRx and the digital control groups. Twelve of the AEs (12/180, 6.7%) were within the EndeavorRx group. Three categories of AEs were experienced by more than 1% of study participants within the EndeavorRx group: decreased frustration tolerance (5/180, 2.8%), headache (3/180, 1.7%), and emotional reaction (2/180, 1.1%). AEs experienced by the EndeavorRx participants were mostly transient and considered mild except 3 which were moderate. No AEs led to treatment discontinuation.

Effectiveness

The predefined primary endpoint was achieved in that EndeavorRx showed a statistically significant improvement from baseline in the TOVA API compared to the digital control (0.93 vs 0.03; $p=0.006$) (Figure 2).

Figure 2 Primary Endpoint: TOVA API, STARS-ADHD Pivotal Trial



Of the five secondary Clinical Outcomes, mean improvements in three of these (ADHD-RS Total, ADHD-RS Inattention and IRS) numerically favored EndeavorRx over the control, and a trend was observed in favor of EndeavorRx on IRS (b) (4). Notably, of these eleven response rate outcomes, all favored EndeavorRx treatment over control, including 3 to a statistically significant degree (all TOVA responder rates (a) (b) (4), the IRS response rate (b) (4), and the parent perspective of improved attention response rate (b) (4)). There was no statistically meaningful difference in a non-parametric analysis of the 7 secondary parental or clinical rating scales (b) (4).

STARS-Adjunct

Background and Trial Design

Patient population and duration of device use:

Children with ADHD in the STARS-Adjunct study used EndeavorRx for 1 month, followed by a 1-month treatment pause, and then a second treatment month.

Overview of study design:

The goal of the STARS-Adjunct trial was to study the effects of EndeavorRx on symptoms and impairments in children either on or off stimulant medication, investigating the durability of effects, one month after treatment, and the effects of an additional treatment month.

Participants in the On Stimulants cohort were stable on a stimulant medication but inadequately managed by that stimulant. Participants in the No Stimulants cohort were stable without any stimulant (or other ADHD medication) for at least 30 days before baseline. Neither cohort was on non-ADHD medications.

During the first treatment month (Days 1 through 28) participants in the On Stimulants cohort received stimulant plus EndeavorRx, and participants in the No Stimulants cohort received EndeavorRx only. During the 1-month pause (Days 29 through 56) between treatment phases, participants in the On Stimulants cohort remained on stimulant, and participants in No Stimulants cohort remained off ADHD medication. During the second treatment month (Days 57 through 84), participants in the On Stimulants cohort received stimulant plus EndeavorRx, and participants in the No Stimulants cohort received EndeavorRx.

Inclusion and exclusion criteria included: children between the age of 8 to 14 with an ADHD diagnosis of inattentive or combined subtype per DSM V, MINI-KID and ADHD related impairment based on the ADHD Impairment Rating Scale, IRS Total ≥ 3). Participants had to be either stable on (On Stimulants group) or off ADHD medication (No Stimulants group), and not present other significant comorbid psychiatric diagnoses. Nonverbal IQ was required to be ≥ 80 .

Enrollment

A total of 236 participants were screened for inclusion in this study, 130 were enrolled in the On Stimulants group, and 76 in the No Stimulants group.

Accountability

195/206 (95%) completed the study through the primary endpoint (1st month). Overall, 179/206 (87%) participants completed the full 3-month study, and 27 (13.1%) participants discontinued the study. A total of 124 and 71 participants completed the study through day 28 in the On Stimulants and No Stimulants cohorts, respectively.

Demographics

The overall mean (SD) age of participants was 10.6 (1.77) years. Overall, the majority of participants were white (b) (4) and male (b) (4)

Table 2. STARS-Adjunct: Demographics / Baseline Characteristics

	On Stimulants	Off Stimulants	Total
N	(b) (4)		
Age Mean (SD)	(b) (4)		
Sex (Male)	(b) (4)		
Race (White)	(b) (4)		

Results

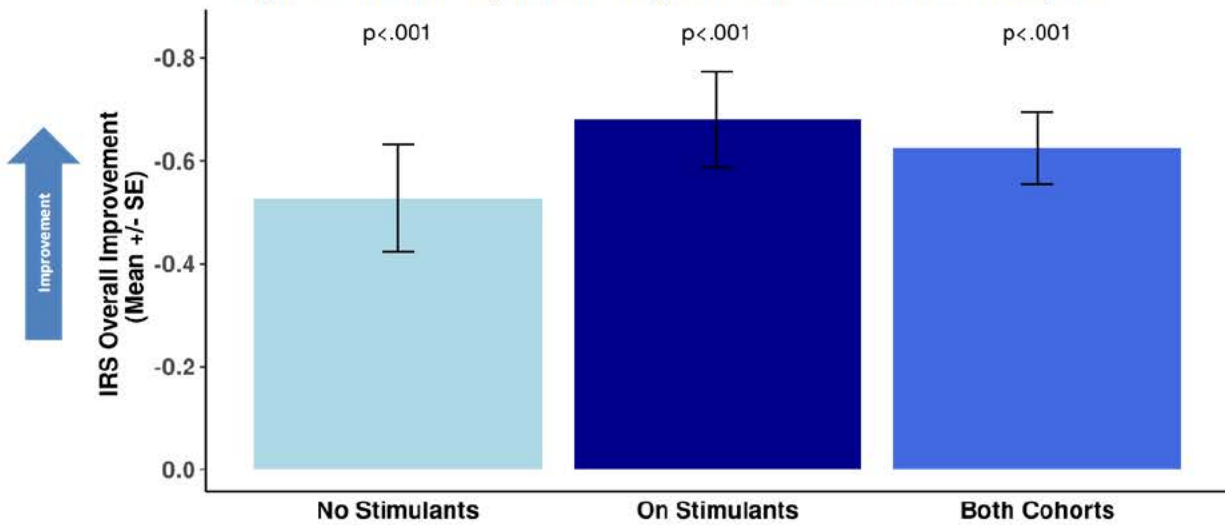
Safety

37 (18%) participants experienced a device-related AE across the two treatment months. The most common device-related AEs experienced by participants were decreased frustration tolerance (27 [13.1%] participants), headache (4 [1.9%] participants), and irritability (3 [1.5%] participants). All device-related AEs were either mild or moderate in severity. No serious device-related AEs occurred during this trial. There were 3 participants who discontinued treatment due to a treatment-related adverse event. All 3 of these participants experienced decreased frustration tolerance.

Effectiveness

The primary endpoint was the change in ADHD Impairment Rating Scale (IRS), which is a parent or clinician rating of ADHD-specific impairment across domains such as social functioning, academic progress, and self-esteem, including an overall impairment. The results of this study demonstrate that 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) groups compared to baseline (**Figure 4**). The ADHD-RS Total, ADHD-RS Inattentive, and ADHD-RS Hyperactive subscales and the CGI-I were also significantly improved for both cohorts compared to baseline at day 28. We found that the symptoms and impairments as measured with the IRS, ADHD-RS and CGI-I remained significantly improved from baseline after the 1-month treatment pause. An additional month of treatment led to further improvement in impairment and symptom measures (IRS: **Figure 5**, ADHD-RS: **Figure 6** and CGI-I not shown; all p-values <0.001 relative to baseline).

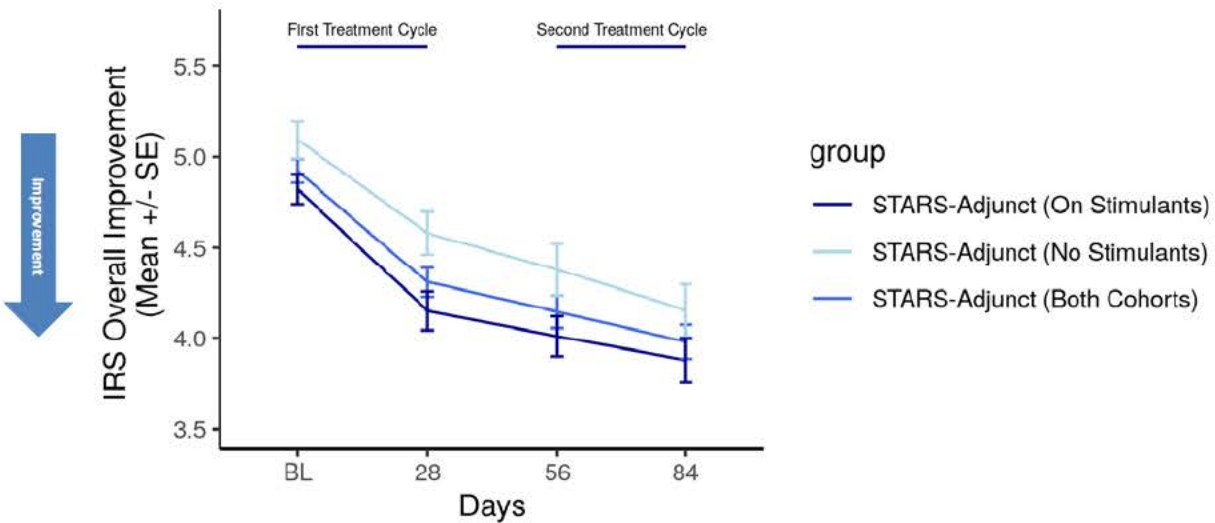
Figure 3. STARS-Adjunct IRS Improvement from Baseline to Day 28



ITT Population: No Stimulants n=76, On Stimulants n=130, Both Cohorts n=206

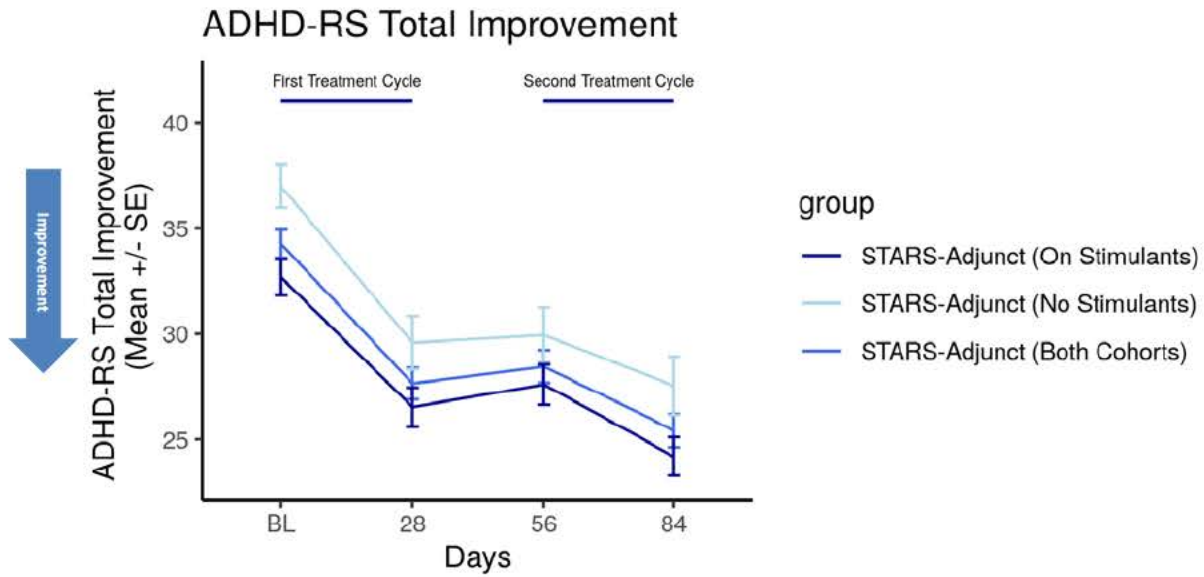
Figure 4. STARS-Adjunct IRS Improvement over Two Treatment Months

IRS Overall Improvement



ITT Population: No Stimulants n=76, On Stimulants n=130, Both Cohorts n=206

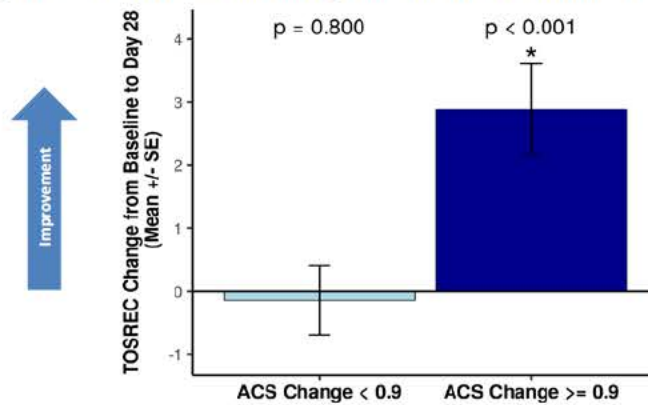
Figure 5. STARS-Adjunct ADHD-RS Total Improvement over Two Treatment Months



ITT Population: No Stimulants n=76, On Stimulants n=130, Both Cohorts n=206

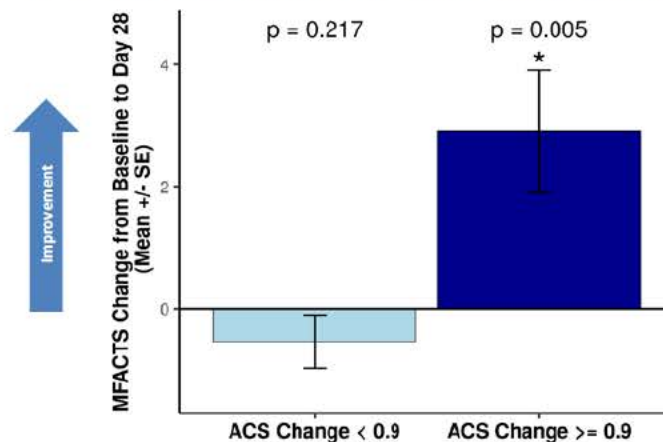
The TOVA ACS and TOVA API performance was significantly correlated to academic performance measures of TOSREC and MFaCTS at each time point throughout the study and an improvement in the TOVA ACS and TOVA API was related to an improvement in both of these academic performance measures (**Figures 7 and 8**).

Figure 6. TOSREC Following 1st Month of EndeavorRx Treatment



ITT Population: ACS/API Change < 0.9 n=129, ACS/API Change \geq 0.9 n=71

Figure 7. MFaCTS Following 1st Month of EndeavorRx Treatment



ITT Population: ACS/API Change < 0.9 n=129, ACS/API Change \geq 0.9 n=71

ADHD Proof Of Concept (POC)

Background and Trial Design

Patient population and duration of device use:

Children in ADHD POC used EndeavorRx for 4 weeks.

Overview of trial design

Akili Interactive conducted an initial proof-of-concept study⁶, ADHD POC, to assess the feasibility, acceptability and efficacy of EndeavorRx in 8 to 12-year old children with ADHD. This open-label study compared 40 children with ADHD to 40 Healthy Controls. The ADHD group had a diagnosis of ADHD and were not taking ADHD medications. The study was conducted at 3 sites in the US. The study regimen began with a day 0 in-clinic assessment. Participants were then sent home and instructed to complete approximately 25 minutes of EndeavorRx per day for 5 days per week for 4 weeks. A final in-clinic assessment was completed on day 28.

Study objectives were: 1) To assess treatment compliance and acceptability of an at-home intervention; and 2) To explore whether participants demonstrated improvements in attention function, as measured by TOVA, following the intervention period.

Inclusion and exclusion criteria included: Children 8-12 years old, the ADHD group required a diagnosis of ADHD, with ADHD-RS Total score of \geq 24 at baseline, was not on any ADHD medication and had no comorbid psychiatric diagnosis. Healthy Controls had an ADHD-RS Total score \leq 13.

Enrollment

87 participants were screened for participation in the trial. Of these, 3 failed to meet screening criteria. 40 children were in the ADHD group and 44 consisted of Healthy Controls. 4 Healthy Controls were terminated early due to insufficient gameplay. The final analyzed sample consisted of 40 children in the ADHD group and 40 in the Control group (children completing 4 weeks of at-home play and returning to the clinic on Day 28). The safety population included all participants randomized to EndeavorRx.

⁶ Naomi O. Davis, Jeffrey Bower, and Scott H. Kollins, "Proof-of-Concept Study of an at-Home, Engaging, Digital Intervention for Pediatric ADHD," *PLoS One* 13, no. 1 (2018): e0189749, <https://doi.org/10.1371/journal.pone.0189749>.

Accountability

Eighty-four percent of treatment sessions were completed. The ADHD group completed an average of (b)(4) hours of intervention), the non-ADHD group completed an average of (b)(4) hours of intervention) of the required at-home sessions.

Demographics

The ADHD group mean age was 10.4 years and 24/40 (b)(4) were male. The Healthy Controls had similar characteristics (mean age 10.5 years and (b)(4) male). The ADHD group had significantly higher ADHD symptom scores (ADHD-RS Total: (b)(4)).

Statistical Analysis

The means of the pre-test scores were compared to the means of the post-test scores using a (b)(4).

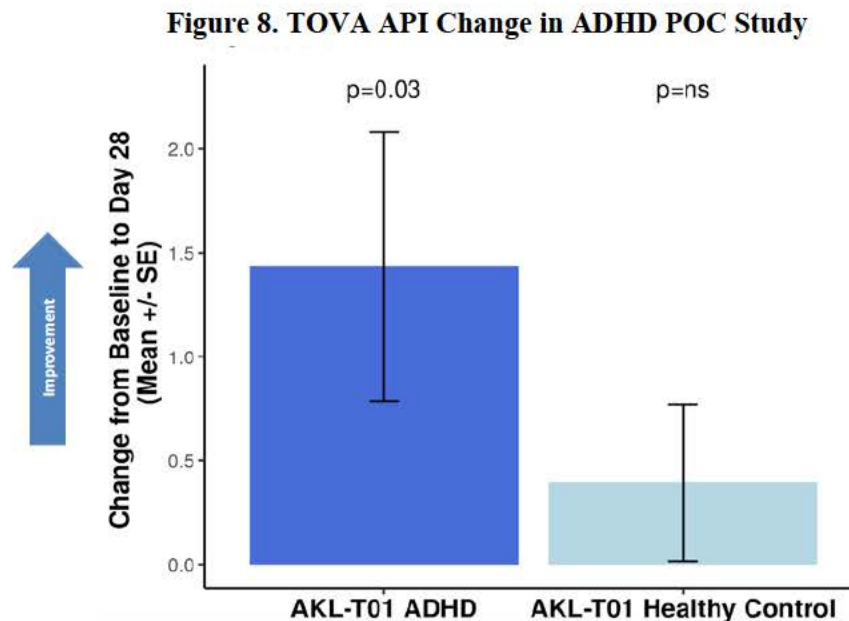
Results

Safety

A total of 9 adverse events were reported over all study phases; however, none of those adverse events were judged by the investigator as related to EndeavorRx.

Effectiveness

Significant improvements were observed on the TOVA API in the ADHD group (mean of improvement 1.43, $p=0.03$). There was no significant change for the Healthy Control group (0.39, $p=0.3$) (**Figure 9**).



ITT Population: AKL-T01 n=40, AKL-T01 Healthy Control n=40

The following additional studies have been performed in smaller populations with largely similar results:

The ASD Pilot⁷ was a randomized, double-blind, controlled study in 19 children, ages 9 to 15 years old, who were diagnosed with Autism Spectrum Disorder (ASD) and comorbid ADHD, 11 were randomized to EndeavorRx and 8 to digital control. The EndeavorRx group numerically improved in the TOVA API (1.86, p=0.12) while the Control group worsened (-0.82, p=ns). The EndeavorRx group improved significantly in ADHD symptoms. For example, on the ADHD-RS Total, the group had -6.72 change (p=0.003) from baseline. Both groups had high compliance with their intervention. There was one non-serious adverse event of decreased frustration tolerance in the EndeavorRx group.

The SPD Pilot⁸ investigated the effects of EndeavorRx in children ages 8 to 12 years old diagnosed with Sensory Processing Disorder (SPD) and comorbid ADHD (SPD+ADHD, n=20), SPD only (n=13), and Healthy Controls (n=24). All groups received EndeavorRx for 4 weeks.

There was significant improvement irrespective of group in TOVA measures (RT Mean H1 and RT Var H1), but only the SPD+ADHD group showed a significant improvement in parent-reported ADHD-inattentive symptoms (-4.5, p<0.001), which correlated with EEG measures. There were 8 children lost to follow-up. No treatment-related adverse events were reported.

In sum, all five studies of the device demonstrate safety, and support the effectiveness and favorable risk^{9,10,11}/benefit profile for use in improving the inattention component of ADHD.

LABELING

The EndeavorRx Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 for prescription devices. Although there are no contraindications, it is noted in the labeling that EndeavorRx may not be appropriate for patients with photo-sensitive epilepsy, color blindness or physical limitations that restrict use of a mobile device. The labeling indicates that for these circumstances the healthcare provider should be consulted.

The following precautionary statements are included within the device labeling:

- Please follow all 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 seizure, stop the treatment and contact your child's healthcare provider.
- Federal law restricts this device to sale by or on the order of a physician.
- Summary of Side Effects / Adverse Events.

⁷ Benjamin Yerys 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," *Journal of Autism and Developmental Disorders* 49, no. 4 (2019): 1727–37, <https://doi.org/10.1007/s10803-018-3856-7>.

⁸ Joaquin A. Anguera et al., "A Pilot Study to Determine the Feasibility of Enhancing Cognitive Abilities in Children with Sensory Processing Dysfunction," *PLoS One* 12, no. 4 (2017): e0172616, <https://doi.org/10.1371/journal.pone.0172616>.

⁹ Ferrie C. D et al., "Video game induced seizures," *J Neurol Neurosurg Psychiatry* 1994 Aug; 57 (8): pp925-931

¹⁰ Christine L. Mathews, Holly E. R. Morrell & Jon E. Molle (2019) Video game addiction, ADHD symptomatology, and video game reinforcement, *The American Journal of Drug and Alcohol Abuse*, 45:1, 67-76, DOI: 10.1080/00952990.2018.1472269

¹¹ Becker S. P et al., "Nighttime Media Use in Adolescents with ADHD: Links to Sleep Problems and Internalizing Symptoms," *Sleep Med.* 2018 November ; 51: 171–178. doi:10.1016/j.sleep.2018.06.021.

RISKS TO HEALTH

Table 3 identifies the risks to health that may be associated with digital therapy device for Attention Deficit Hyperactivity Disorder and the measures necessary to mitigate these risks.

Table 3. Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Ineffective treatment leading to worsening or uncontrolled symptoms	Clinical performance testing Labeling
Device software failure leading to delayed access	Software verification and validation Labeling
Treatment results in frustration, emotional reaction, dizziness, nausea, headache, eye-strain, or joint pain	Labeling Clinical performance testing Software verification, validation, and hazard analysis
Treatment results in seizure	Labeling Clinical performance testing
Treatment results in screen addiction	Labeling Clinical performance testing
Treatment results in decreased sleep quality	Labeling Clinical performance testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the digital therapy device for Attention Deficit Hyperactivity Disorder is subject to the following special controls:

1. Clinical performance testing must demonstrate and document the following under the labeled conditions for use, which include considerations for the ability of the device to:
 - a. Use a validated measure to evaluate effectiveness of device to provide therapy for ADHD or any of its individual symptoms; and
 - b. Capture all adverse events.
2. Software must be described and provided in a clear and detailed manner to include all features and functions of the software implementing the digital therapy. Software verification, validation, and hazard analysis must also be provided.
3. The labeling must include the following items:
 - a. Patient and physician labeling must include instructions for use, including images that demonstrate how to interact with the device;
 - b. Patient and physician labeling must list the minimum operating system (OS) requirements that support the software of the device;
 - c. Patient and physician labeling must include a warning that the digital therapy device is not intended for use as a standalone therapeutic device;
 - d. Patient and physician labeling must include a warning that the digital therapy device does not represent a substitution for the patient's medication; and
 - e. Physician labeling must include a summary of the clinical performance testing conducted with the device.

BENEFIT-RISK DETERMINATION

Across five clinical studies of over 600 children with ADHD, 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, academic performance measures, and other assessment tools, in children with ADHD with a demonstrated attention issue. Across all studies, 34.5% of EndeavorRx treated participants moved into the normative range on at least one objective measure of attention, a clinically meaningful improvement in attention. Improvements in ADHD symptoms and impairment favored EndeavorRx over control, including clinically meaningful response rates. The STARS-Adjunct study demonstrated improvements in clinical symptoms and impairment measures seen after 1 month treatment with EndeavorRx, remained stable after a one-month treatment pause and then further increased with a second month of treatment, independent of medication status. Children who improved in objective attention (TOVA API) also showed improvement in math and reading performance measures.

The risks associated with EndeavorRx are minimal: Of 538 participants using EndeavorRx, 50 (9.3%) experienced treatment-related adverse events. No serious adverse events were reported. All adverse events were generally transient. Only three events led to device discontinuation, and no subject reported lasting or irreversible effects after discontinuation.

Therefore, the probable benefits of the EndeavorRx outweigh the probable risks in light of the listed special controls and the general controls.

Patient Perspectives

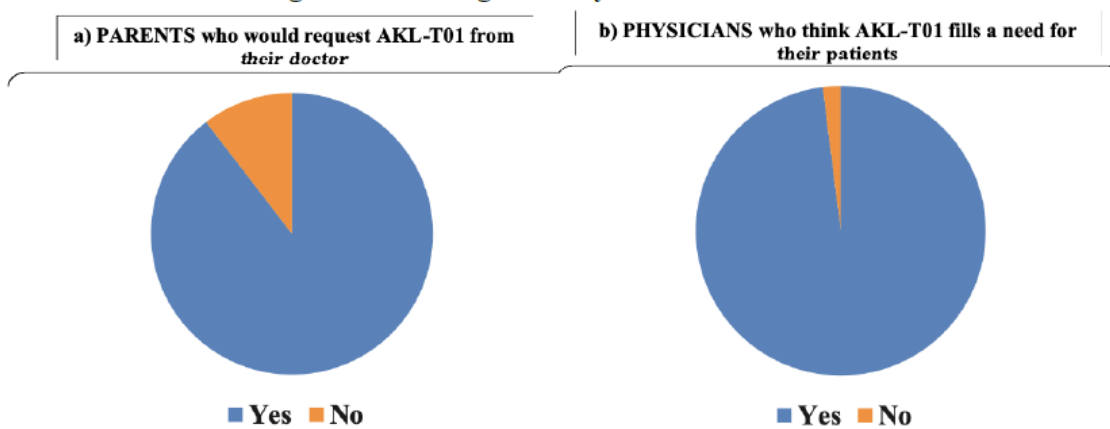
Patient perspectives considered for the EndeavorRx during the review include:

1. Market research studies involving caregivers, physicians and health insurers to understand their perspective when considering medication for ADHD children, challenges with the current paradigm, and the need for alternative additional treatment options.

~90% of caregivers in one study involving caregivers of children currently or formerly on medication, reported they would request a non-drug prescription digital treatment with the profile of EndeavorRx from their physician if it was available. The profile reflected a 6%, non-serious side effect profile (including frustration and headache) and efficacy related to attention.

Parents expressed their desire for the product for multiple reasons in two market research studies: 75% of caregivers in the Armature-Caregiver study thought it would be an effective treatment overall, and most respondents believed it would strengthen their child’s cognitive function (>82%, Armature-Caregiver study) and improve concentration and focus (>83%, Armature-Caregiver study) among other issues. In the GfK-Caregiver study, over 80% of caregivers thought it would help with their child’s ADHD. Finally, eight in ten parents in the GfK-Caregiver study believed the treatment is easy to use, and half believe it will be extremely easy to use.

Figure 13-3. Caregiver / Physician Considerations



2. A post-treatment survey of parents and their child to assess how treatment impacted their attention was conducted in the ASD-Pilot study.

For parents, the following question was asked, “Do you think playing the app improved your child’s ability to pay attention?” For children the following question was asked, “Do you think playing the app improved your ability to pay attention?” For both the parent and child questions, the answer options were “yes” or “no.” Seventy-three percent (73%) of children who received EndeavorRx reported that it improved their attention, versus 50% in the Control group who received the digital control. In addition, 64% of parents believed that EndeavorRx improved their child's attention in real life, versus 50% in the Control group. The survey revealed that 63.6% of parents reported that the time playing EndeavorRx was very worthwhile for their child, versus 50% in the Control group, and 90.9% would want their child to continue to play (selected ‘yes’ or ‘maybe’) versus 62.5% in the Control group.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

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 (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.

the probable benefits outweigh the probable risks for the EndeavorRx. The device provides benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the EndeavorRx is granted and the device is classified as follows:

Product Code: QFT

Device Type: Digital therapy device for Attention Deficit Hyperactivity Disorder

Regulation Number: 21 CFR 882.5803

Class: II