December 13, 2023

Akili Interactive Labs, Inc.
Bhupinder Singh
Head of Quality and Regulatory Affairs
22 Boston Wharf Road
7th Floor
Boston, MA 02210

Re: K231337
Trade/Device Name: EndeavorRx
Regulation Number: 21 CFR 882.5803
Regulation Name: Digital therapy device for attention deficit hyperactivity disorder
Regulatory Class: Class II
Product Code: QFT
Dated: November 13, 2023
Received: November 13, 2023

Dear Bhupinder Singh:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Robert Kang -S

for Pamela Scott, MS
Assistant Director
DHT5B: Division of Neuromodulation
and Rehabilitation Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K231337

Device Name
EndeavorRx

Indications for Use *(Describe)*
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 demonstrated attention issue. Patients who engage with EndeavorRx demonstrate improvements in a digitally assessed measure Tests of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. 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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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8. 510(k) Summary

This 510(k) summary of safety and effectiveness information is prepared in accordance with 21 CFR § 807.92.

Date Prepared:	May 5, 2023
Legal Manufacturer:	Akili Interactive Labs, Inc. 125 Broad Street, 5th Floor Boston, MA 02110
Primary Contact Person:	Bhupinder Singh Head of Quality and Regulatory Affairs Phone: +1 (408) 832-7124 E-mail: bsingh@akiliinteractive.com

Regulatory Information

Device Trade Name:	EndeavorRx
Device Classification Name:	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder
Regulation Number:	21 CFR § 882.5803
Classification Product Code:	QFT
Review Advisory Committee:	Neurology
Device Classification:	Class II

Predicate Device Information

Device Manufacturer:	Akili Interactive Labs, Inc.
Submission Number:	DEN200026
Device Name:	EndeavorRx

Device Description:

EndeavorRx is a modification to the previously granted EndeavorRx (DEN200026) with the primary difference being the expansion of the indicated patient population from 8-12 years old to 8-17 years old. In addition, minor software changes were made to improve app accessibility and user engagement. The core therapeutic software technology was not changed.

EndeavorRx is a prescription-only digital therapeutic software indicated for use in the treatment of attention impairment in pediatric patients (8-17 years of age) with primarily inattentive or combined-type ADHD. EndeavorRx is a software-as-a-medical device (SaMD) that resides on the user's mobile device and can be executed at home.

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.

The basic program inputs are steering, which is accomplished by using the mobile device's internal accelerometer to measure the degree to which it is tilted, and tapping, which is accomplished using the touch screen to measure correct and incorrect targeting. The basic outputs are the visual display of the game progression along with audio, which is accomplished by using the internal high resolution display and internal speaker. The program includes features to ensure it is used per the prescribed regimen (approximately 25 minutes per day, 5 days per week, for 4 weeks or as recommended by the 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 demonstrated attention issue. Patients who engage with EndeavorRx demonstrate improvements in a digitally assessed measure Tests of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. 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	Prescription-only medical device restricted to sale by or on the order of a licensed health care provider. 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. 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.

Summary Comparison of technological Characteristics

Attribute	Subject Device: EndeavorRx v3.0	Predicate Device: EndeavorRx (DEN200026)	Comparison
Manufacturer	Akili Interactive Labs, Inc.	Akili Interactive Labs, Inc.	Same
Device Classification Name	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder	Same
Product Code	QFT	QFT	Same
Regulation Number	21 CFR § 882.5803	21 CFR § 882.5803	Same
Intended Use	Digital therapeutic adaptive stimulus software for the closed-loop treatment of	Digital therapeutic adaptive stimulus software for the closed-loop treatment of	Same

	psychiatric disorders and cognitive dysfunction associated with medical conditions.	psychiatric disorders and cognitive dysfunction associated with medical conditions.	
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 Tests 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 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 Tests 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.	Substantially equivalent. EndeavorRx v3.0 is indicated for a larger range of pediatric patients (8-17 years of age) compared to the predicate device (8-12 years of age). This does not change the intended use of the device, and clinical testing demonstrates the subject device is safe and effective in the expanded population.
System Components	Patient facing video game application Mobile device platform	Patient facing video game application Mobile device platform	Same
Proprietary Algorithm	Selective Stimulus Management Engine (SSME™)	Selective Stimulus Management Engine (SSME™)	Same
Basic Operations	Steering, Tapping, Multi-tasking	Steering, Tapping, Multi-tasking	Same
Presentation	Structured manner across	Structured manner across	Same

	game “Challenges” and “Worlds”	game “Challenges” and “Worlds”	
Mobile Platform Compatibility	iOS and Android	iOS	Substantially equivalent. Addition of Android compatibility does not present different questions.
Access	Prescription use only. Authorized and overseen by a licensed health care provider.	Prescription use only. Authorized and overseen by a licensed health care provider.	Same

Summary of Non-Clinical Performance Data:

Bench software testing has been performed on the EndeavorRx and demonstrates compliance with the following international and FDA-recognized consensus standards and FDA guidance documents:

- **ISO 14971:2019** Medical devices - Application of risk management to medical devices
- **IEC 62304 Edition 1.1 2015-06 CONSOLIDATED VERSION** Medical device software - Software life cycle processes
- **IEC 82304-1 Edition 1.0 2016-10** Health software - Part 1: General requirements for product safety
- FDA Guidance Document for Industry and FDA Staff - *Guidance for the content of Premarket Submissions for Software Contained in Medical Devices*, issued May 11, 2005
- FDA Guidance Document for Industry and FDA Staff - *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices*, issued October 2, 2015

The results of bench software verification and validation testing supports that EndeavorRx functions as intended.

Summary of Clinical Data:

Clinical performance testing was conducted to evaluate the efficacy and safety of EndeavorRx in adolescents 13 to 17 years of age. Efficacy was determined primarily by the change from baseline in a digitally assessed measure of sustained and selective attention, the Test of Variables of Attention (TOVA®), after 4 weeks of treatment. The multi-center open-label study enrolled 162 adolescents subjects with inattentive or combined-type ADHD. The results of the clinical performance study support the performance and safety of

EndeavorRx in the expanded pediatric age range. Analysis of the primary efficacy endpoint in the Efficacy Population (N=146) showed a significant positive mean change from baseline to study day 28 in the TOVA of 2.639 (SD 3.7986 [95% CI: 2.018, 3.261]; P < 0.0001). Overall, 4 (2.5%) subjects experienced a treatment-emergent adverse device event (3 decreased frustration tolerance, 1 headache; all mild or moderate). There were no serious adverse device events.

Prior clinical trial results that supported the original clearance of EndeavorRx for 8-12 year old patients under DEN200026 support the use of EndeavorRx in the younger cohort.

The clinical performance studies demonstrate that EndeavorRx is safe and effective for its intended use in the indicated patient population.

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 (SE)	-5.11 (0.22)	-4.16 (0.28)	0.93 (0.24)
95% CI			0.45, 1.40
p-value1			0.0002
Efficacy Population (CCA, assumes MCAR)			
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-value1			<0.0001
Safety Population (ITT with MI,2 assumes MAR)			
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-value1			<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.

Clinical Study Comparison Summary Table

	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
Population Under Study	Verified ADHD diagnosis with impaired attention; on or off medication	Verified ADHD diagnosis with impaired attention; medication exclusionary	Similar - adolescent study allowed for medication as long as use was stable for ≥4 weeks prior to study enrollment and throughout the study. A prior study demonstrated benefits of intervention on the pediatric population with ADHD both on and off medication.
Study Design	Single arm, open label; 25 min/day, 5 days/week, 4 weeks; multi-site study across US	Randomized, controlled, parallel arm; 25 min/day, 5 days/week, 4 weeks; multi-site study across US	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 three primary reasons: 1) the safety and efficacy of the product was already

	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			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; and 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..
Outcomes	Significant treatment effect on primary outcome measure (attention function); treatment effects in key prespecified secondary outcomes (ADHD symptoms)	Significant treatment effect on primary outcome measure (attention function); treatment effects in key prespecified secondary outcomes (responder analysis for impairment)	Similar - primary outcomes are the same. Both studies had ADHD-RS as secondary measures. Whereas the STARS study listed multiple secondary measures, the adolescent study focused on ADHD-RS as the secondary measure, which previous studies showed to be sensitive to the AKL-T01 treatment. The TOVA-ACS (primary outcome) is not susceptible to placebo effect when measuring attentional control processes within the context of ADHD, and this is supported by the predicate RCT and multiple published

	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			studies in the literature.
Safety	Low rates of adverse device events; no serious adverse device events; no study discontinuations related to adverse device events	Low rates of adverse device events; no serious adverse device events; no study discontinuations related to adverse device events	Similar

Clinical Study Design Comparison Table

Study Design	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
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 three primary reasons: 1) the safety and efficacy of the product was already established in a randomized

Study Design	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			controlled trial in the younger population;2) the primary endpoint used in STARS-Adolescent was identical to the original STARS RCT.; and 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.. Additionally, 4) AKL-T01 is a low-risk device, and 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

Study Design	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			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	No differences
Participant Duration	Approximately 4 weeks on treatment	Approximately 4 weeks on treatment	No differences

Comparison of Inclusion/Exclusion Criteria for Subject and Predicate Studies

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
1. Diagnosis of ADHD	Inclusion: Confirmed diagnosis of ADHD combined or inattentive type, according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as confirmed by Mini- International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid) Version 7.0.2	Inclusion: Confirmed ADHD diagnosis, any presentation, at screening based on DSM-5 criteria and established via the MINI-KID administered by a trained clinician	Similar
2. High inattention as measured by TOVA or other validated measures of attention	Inclusion: Baseline visit score on the TOVA-ACS score ≤ -1.8	Inclusion: Screening/baseline (Visit 1 or 1a) score on the TOVA API ≤ -1.8	Same - ACS is the updated term for API. TOVA-ACS was determined as the primary outcome for this single arm study because TOVA-ACS is not susceptible to Placebo when measuring attentional control processes within the context of ADHD, and this has been supported by the predicate RCT and multiple published studies of children

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			and adolescents with ADHD..
3. Stably on or off ADHD medications	Inclusion: Stably on or off ADHD medication for ≥4 weeks prior to study enrollment and throughout the 4-week study	Inclusion: Not undergoing pharmacological treatment with methylphenidate or amphetamine-based products at time of screening; or, if undergoing pharmacological treatment, must be willing and appropriate (i.e., not optimally treated in the investigator's judgment) to wash out of current regimen Exclusion: Participants currently treated with a nonstimulant medication for ADHD (i.e., atomoxetine, clonidine, or guanfacine)	Adolescent study allowed the use of ADHD medications as long as the participant was stable on medication prior to and throughout study participation. A prior study demonstrated benefits of intervention on the pediatric population with ADHD both on and off medication.
4. Not on psychoactive medications	Inclusion: Stably on or off psychoactive medications for ≥4 weeks prior to study enrollment and throughout the 4-week study	Exclusion: Regular use of psychoactive drugs (nonstimulant) that, in the opinion of the investigator, could confound study data/assessments	Different - the adolescent study allowed the use of psychoactive medication as long as use and dosage was stable prior to and throughout study participation. A prior study

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
			demonstrated benefits of intervention on the pediatric population with ADHD both on and off medication.
5. Stably on or off nonpharmacological treatments	Exclusion: Plans to initiate, or to make significant changes in frequency, of nonpharmacological behavioral therapy during the study Exclusion: Plans to initiate or to make significant changes in frequency or duration of non-pharmacological trainings with the aim to improve cognition by means of game or app-based cognitive trainings or neurofeedback, during the study	Exclusion: Initiation of behavioral therapy within the last 4 weeks. Participants who had been in behavior therapy consistently for more than 4 weeks could participate provided their routine was unchanged during the course of the study. Participants planning on changing or initiating behavior therapy during the course of the study were excluded	Similar
6. Absence of comorbid psychiatric diagnosis and/or treatments that may confound study	Exclusion: Current controlled or uncontrolled, comorbid psychiatric diagnosis that in the opinion of the Investigator may confound study data/assessments	Exclusion: Current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis, based on MINI-KID and subsequent clinical	No differences

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
data/assessments		interviewing, with significant symptoms including, but not limited to, posttraumatic stress disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, severe depressive or severe anxiety disorder, conduct disorder, or other symptomatic manifestations that in the opinion of the investigator may confound study data/assessments. Participants with a clinical history of learning disorders were allowed to participate, provided the disorder did not impact their ability to participate in the trial, based on PI judgment Exclusion: Regular use of psychoactive drugs (nonstimulant) that, in the opinion of the investigator, could confound study data/assessments	
7. Meets IQ level threshold	Inclusion: Estimated IQ score ≥80 as assessed by the Kaufmann Brief Intelligence Test, Second	Inclusion: Estimated IQ score ≥ 80 as assessed by the Kaufmann Brief Intelligence Test, Second	Same

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
	Edition (KBIT-II)	Edition	
8. Not considered at-risk of attempting suicide at time of enrollment	Exclusion: Participant is currently considered at risk for attempting suicide, has made a suicide attempt within the past year, or is currently demonstrating active suicidal ideation or self-injurious behavior, in the opinion of the Investigator based on the MINI-kid clinical interview	Exclusion: Participants currently considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a history of, or were currently demonstrating, active suicidal ideation or selfinjurious behavior, as measured by the Columbia Suicide Severity Rating Scale at screening	Similar
9. Absence of conditions that would prevent the proper use of the investigational product	Exclusion: Motor condition (e.g., physical deformity of the hands/arms) that prevents game playing as reported by the participant or observed by the Investigator Exclusion: Color blindness as detected by Ishihara Color Blindness Test Exclusion: Known sensitivity to playing video games, such as photosensitive epilepsy, light-headedness, dizziness, nausea, or motion sickness	Exclusion: Motor condition (e.g., physical deformity of the hands/arms; prostheses) that prevented playing the digital therapy, as reported by the parent or observed by the investigator Exclusion: Diagnosis of or parent-reported color blindness (confirmed in clinic via Ishihara Color Blindness Test) Exclusion: History of seizures (exclusive of febrile seizures) or significant motor or vocal tics including, but not limited to,	Similar

Key Eligibility Criteria	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)	STARS (ages 8-12)	
	Exclusion: History of seizures (excluding febrile seizures), significant tics, or a current diagnosis of Tourette's Disorder	Tourette syndrome	
10. Absence of recent substance use	Exclusion: Recent history (6 months prior to screening) of substance use disorder Exclusion: Urine test positive for nicotine or marijuana	Exclusion: Recent history (within the past 6 months) of suspected substance abuse or dependence	Similar - an exclusion due to drug test was included in the adolescent study since the adolescent population is more likely than pediatric populations to have access to substances
11. Absence of other conditions, treatments, or involvements that may confound study data/assessments	Exclusion: Any other medical condition that in the opinion of the Investigator may confound study data/assessments. Exclusion: Participation in a clinical trial within 3 months prior to screening Exclusion: Previous exposure to Akili Products within the 6 months prior to study enrollment	Exclusion: Any other medical condition that, in the opinion of the investigator, could confound study data/assessments Exclusion: Had participated in a clinical trial within 90 days before screening Exclusion: Had previously participated in a study of Akili's videogame-like digital therapy	Similar

Clinical Study Outcome Comparison Table

Outcome Measure	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)(Efficacy Population; n=146)	STARS (ages 8-12)(IIT; n=180)	
1. pre-post change score on TOVA ACS (Positive change indicates improvement)	2.64	0.93	Adolescents show nearly 3 times the improvement in TOVA ACS than in STARS
2. pre-post change score on ADHD-RS Inattention subscale (Negative change indicates improvement)	-3.0	-3.6	Adolescents show a smaller absolute mean change, but given lower overall Baseline scores for adolescents, the proportional change was similar
3. pre-post change score on ADHD-RS Total Score (Negative change indicates improvement)	-4.6	-6.2	Adolescents show a smaller absolute mean change, but given lower overall Baseline scores for adolescents, the proportional change was similar. Clinically meaningful improvement based on literature for the ADHD-RS is estimated at 10 point difference[1] or a 30%

[1] Nasser A, Kosheleff AR, Hull JT, et al. Translating Attention-Deficit/Hyperactivity Disorder Rating Scale-5 and Weiss Functional Impairment Rating Scale-Parent Effectiveness Scores into Clinical Global Impressions Clinical

Outcome Measure	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)(Efficacy Population; n=146)	STARS (ages 8-12)(IIT; n=180)	
			change in Total Score.[2]
4. % Responders with final TOVA score >0	24.7%	11%	The percentage of responders with final TOVA score ≥0 is more than doubled in adolescents as compared to STARS
5. % Responders with > 1.4 point change on TOVA-ACS	N/A (66.4% for ≥ 1.0 point improvement from Baseline to Day 28)	46.7%	Adolescents show a similarly positive rate
6. % Responders with >30% change in ADHD-RS Total Score	27%	24%	Higher percentage of responders in adolescents than STARS. Clinically meaningful improvement based on literature for the ADHD-RS is estimated at 10 point difference[3] or a 30% change in Total

Significance Levels in Four Randomized Clinical Trials of SPN-812 (Viloxazine Extended-Release) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2021;31(3):214-226. doi:10.1089/cap.2020.0148

[2] **Zhang, S., Faries, D. E., Vowles, M., & Michelson, D. (2005). ADHD rating scale IV: psychometric properties from a multinational study as clinician-administered instrument. International journal of methods in psychiatric research, 14(4), 186-201.**

[3] Nasser A, Kosheleff AR, Hull JT, et al. Translating Attention-Deficit/Hyperactivity Disorder Rating Scale-5 and Weiss Functional Impairment Rating Scale-Parent Effectiveness Scores into Clinical Global Impressions Clinical Significance Levels in Four Randomized Clinical Trials of SPN-812 (Viloxazine Extended-Release) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2021;31(3):214-226. doi:10.1089/cap.2020.0148

Outcome Measure	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)(Efficacy Population; n=146)	STARS (ages 8-12)(IIT; n=180)	
			Score.[4]

Clinical Safety Outcome Comparison Table

Safety Outcomes	Clinical Study for Subject Device EndeavorRx v3.0 (K231337)	Clinical Study for Predicate Device (DEN200026)	Comparison
	Adolescents (ages 13-17)(Efficacy Population; n=162)	STARS (ages 8-12)(IIT; n=180)	
1. Any TE-ADE	4 (2.5%)	12 (6.7%)	Adolescents show better (lower) TE-ADE rate
2. TE-ADE related to study treatment (possibly, probably, and definitely-related)	4 (2.5%)	12 (6.7%)	Adolescents show better (lower) TE-ADE rate
3. Serious TE-ADE	0 (0%)	0 (0%)	No difference
4. TE-ADE leading to study discontinuation	0 (0%)	0 (0%)	No difference
5. Unanticipated TE-ADE	0 (0%)	0 (0%)	No difference

[4] Zhang, S., Faries, D. E., Vowles, M., & Michelson, D. (2005). ADHD rating scale IV: psychometric properties from a multinational study as clinician-administered instrument. International journal of methods in psychiatric research, 14(4), 186-201.

Substantial Equivalence Discussion:	EndeavorRx has the same intended use and similar indications, technological characteristics, and principles of operation as the predicate device, EndeavorRx (DEN200026). Moreover, EndeavorRx complies with the same special controls as the predicate Endeavor Rx (DEN200026) set forth in 21 CFR § 882.5803. The expanded age range and minor software changes do not raise different questions of safety or efficacy. Substantial equivalence was supported by clinical and non-clinical performance (verification and validation) tests, which complied with the requirements specified in the international and FDA-recognized consensus standards, ISO 14971, IEC 62304, and IEC 82304. The non-clinical testing included software testing, which verified the minor software changes in EndeavorRx. Clinical testing validated the safety and effectiveness of EndeavorRx for its intended use in the indicated patient age range of 8-17 years old. The prior clinical trial results that supported the original clearance of EndeavorRx for 8-12 year old patients under DEN200026 support the use of EndeavorRx in the younger cohort. A new clinical study was executed to demonstrate the performance and safety of EndeavorRx in the older cohort of adolescents 13 to 17 years of age. The clinical trial results showed a significant improvement in the primary effectiveness measure, TOVA, a digitally assessed measure of sustained and selective attention. Results also showed improvements in ADHD symptoms as assessed in key secondary measures, the ADHD-RS inattention scale and ADHD-RS total score. These results were similar to the findings of the prior clinical trial that supported the original clearance of EndeavorRx for 8-12 year-old patients under DEN200026. The clinical testing also showed no new or increased safety risks in the expanded patient population compared to the predicate device. The results of these tests demonstrate that EndeavorRx is as safe and effective as its predicate device. Therefore, EndeavorRx is substantially equivalent.
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, 16 participants (9.88%) 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 AE's were resolved. Given the favorable safety profile, even small benefit would justify use of the product.