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Cannabidiol for treatment of irritability and aggressive behavior in children and adolescents with autism spectrum disorder: background and methods of the cannabidiol study in children with autism spectrum disorder study

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder commonly associated with behavioral challenges. There are few evidence based pharmacological interventions available for the treatment of behavioral symptoms associated with ASD. Cannabidiol (CBD), the non-intoxicating component of cannabis, has known neuroprotective, antiepileptic, anxiolytic, and antipsychotic effects and may be useful in treating the behavioral symptoms of ASD.

Methods: We describe the research methods of a 27-week randomized placebo-controlled crossover trial to evaluate the safety and efficacy of oral CBD for the treatment of irritability and aggression associated with ASD, as measured by the irritability subscale of the aberrant behavior checklist-2nd edition (ABC-2) in children and adolescents.

Conclusions: There is significant need for clinical research exploring alternative medications for the treatment of behavioral symptoms of ASD. Upcoming results from this trial will help answer the question of whether CBD may be a useful intervention in the management of ASD.

Clinical trial registry: NCT04520685.

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Keywords

Autism spectrum disorder; Cannabidiol; Medication; Clinical trial

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and restricted and repetitive patterns of behavior. As described by the diagnostic and statistical manual for mental disorders (DSM-5), the social communication deficits of ASD include impaired use of nonverbal communication, decreased reciprocity in conversation, and lack of ability to read social cues. Additional criteria include inflexible adherence to routines, intense or restricted interests, sensory sensitivities, and stereotyped behaviors.[1] Beyond the core symptoms of ASD, many individuals have behavioral challenges including irritability, aggression, self-injury, anxiety, and sleep dysregulation.[2]

The prevalence of ASD has increased over the past few decades with current estimates from the United States centers for disease control of 1 case in every 36 children.[3] However, available treatments for ASD have not significantly changed, and there is no medication treatment for the core symptoms of ASD. The only medications approved by the US food and drug administration (FDA) for irritability and aggression associated with ASD are aripiprazole and risperidone.[4,5] While shown to be effective in phase III clinical trials, these medications come with the potential for side effects, including risk of diabetes, hypertension, weight gain, elevated triglycerides and movement disorders. Further, these medications are only effective for a segment of the population, and many patients continue to have sub-optimal benefit, leading to high risk of polypharmacy.[6] Incomplete treatment response and family preferences have led to great interest in cannabinoid products as a treatment for symptoms of ASD.

CBD is a non-intoxicating molecule found in strains of the cannabis or hemp plants which demonstrates neuroprotective, antiepileptic, anxiolytic, and antipsychotic properties by interacting with the body’s endogenous cannabinoid receptors and pathways. There are multiple proposed ways that CBD exerts its effects on the endocannabinoid system, including modulation of neurotransmitter levels, neurotransmitter binding, cell signaling, neurogenesis, and/or by altering circulating levels of endocannabinoids.[7] Studies have demonstrated a potential role of the endocannabinoid system in the pathogenesis and treatment of ASD.[8] Human and mouse studies indicate alterations in both endocannabinoid ligands and receptors in people with autism as compared to controls.[9]

There are multiple anecdotal reports, retrospective and open label trials showing improvements in the behavioral features of ASD with CBD treatment. The majority of these investigations include the use of CBD rich cannabis, rather than pure CBD.[10–13] The potential concern is that CBD rich cannabis can also contain small amounts of THC (the psychoactive ingredient of the marijuana plant) which can lead to poor tolerability, adverse psychoactive effects, and are often not desired by caregivers of children with ASD. Further, potential long term negative effects of THC on brain development are a common concern.[14]

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A more recent placebo-controlled trial used pharmaceutically manufactured CBD topical gel to treat patients with Fragile X syndrome, the most common inherited genetic cause of ASD.[15] The trial showed decreased irritability and improved social interactions in the subset of participants with full methylation of the Fragile X gene, and the intervention was well tolerated. The results of these trials indicate a need for further research, including a placebo-controlled trial of pure CBD in patients with ASD.

The pharmaceutical formulation of plant-derived, highly purified CBD is FDA approved as Epidiolex ® in the United States for seizures associated with three rare epilepsy syndromes (Lennox Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex) in patients ≥1 year.[16] Multiple double-blind, placebo-controlled studies demonstrated the general safety profile of Epidiolex ® in pediatric and adult populations with developmental and epileptic encephalopathies, and efficacy in decreasing seizure frequency.[17–19]

We describe methods of a double-blind, placebo-controlled study to evaluate the efficacy and safety of CBD for the treatment of irritability and aggression in youth with ASD. We hypothesize that CBD will be more efficacious than placebo in decreasing irritability in youth with ASD.

METHODS

Overall study design

This is a single-site, double-blind, randomized, placebo-controlled study with modified cross-over design to evaluate the efficacy and safety of oral CBD for the treatment of irritability and aggression in youth aged 5–17 years with ASD. Development of the protocol followed the SPIRIT guidelines (Standard protocol items: recommendations for interventional trials).

There are three treatment arms (A, B, and C). Arm A receives CBD for the first twelve weeks (Period 1), followed by a three-week washout, and then 12 weeks of placebo (Period 2). Arm B receives placebo for the first twelve weeks followed by a three-week washout and then 12 weeks of active study drug. Arm C receives CBD for the entire 27 weeks, allowing for evaluation of longer-term drug effects.

The primary outcome is change in the irritability subscale score of the ABC-2 after 12 weeks of treatment.[20] The ABC-2 irritability subscale was selected as it was used in the FDA approval of aripiprazole and risperidone in the treatment of irritability and aggression in ASD.[4,5] Secondary aims compare CBD to placebo in the domains of anxiety, social skills, repetitive behaviors, executive functioning, sleep, caregiver stress, quality of life, and overall autism symptoms. Each of these domains is assessed using validated scales for evaluation of children and adolescents with ASD (Table 1). The third aim evaluates for safety and adverse effects in youth with ASD treated with CBD compared to placebo. Beyond these three aims, a small sample of participants receives CBD for the entire 27 weeks to provide pilot information on its continuing efficacy and safety.

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Study participants

Participants are recruited from children's hospital Colorado clinics with high volumes of individuals with ASD and organizations in Colorado that support families with ASD. The study is listed on clinicaltrials.gov (NCT04520685) and approved by the Colorado multiple institution review board (COMIRB).

Inclusion criteria include healthy individuals aged 5–17 years with a previous diagnosis of ASD and a baseline ABC-2 irritability subscale score of at least twelve.

Participants can take up to two psychopharmacological medications and participate in behavioral therapies if there have been no changes for four weeks and no changes planned during study.

Seizure medications which impact the metabolism of CBD are exclusionary, as well as severe, unstable or progressive psychiatric symptoms.

Full inclusion and exclusion criteria are listed in the Table 2.

Randomization and blinding

After screening, eligible participants are randomized. A permuted block randomization scheme is generated to randomly assign participants to one of the 3 study arms: CBD/placebo (Arm A), placebo/CBD (Arm B), or CBD/CBD (Arm C). Because the CBD/CBD group was designed to have 1/3 as many participants as the other two groups, 2/3 of the assignments to the CBD/CBD group are sequentially deleted from the randomization scheme, leaving only 12 participants in that group. The pharmacist then translates the result into a final randomization list so that other investigators, participants, their caregivers, study coordinators, and examiners are blind to randomized group assignment.

During the study, the blind is broken only in emergencies when knowledge of the patient's treatment group is necessary for further management, e.g. severe adverse side effects (Figure 1).

Intervention

The investigational product is CBD 100 mg/mL liquid (Epidiolex ®; Jazz Pharmaceuticals). Placebo contains identical packaging and ingredients minus the CBD. Bottles labelled bottle A and bottle B are dispensed at the beginning of period 1 and period 2, and dosing instructions are provided. Caregivers of participants receive training on administration of the study drug. Daily dosing diaries are completed by caregivers.

During the periods of CBD treatment, the dose is started at 5 mg/kg/day divided twice per day, increased to 10 mg/kg/day divided twice per day after 1 week, and continued for 11 weeks for arms A and B and for 26 weeks for arm C (Figure 1). Following CBD treatment, the dose decreases to 5 mg/kg/day for 1 week and is then discontinued. Blinding is maintained by administering the same volume of medication from 2 different bottles labelled bottle 1 and bottle 2, with specific instructions provided by the research pharmacy. For all 3 arms, a dose decrease to 5 mg/kg/day is allowed if adverse effects occur that

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are possibly related to study drug. If adverse effects do not resolve, the participant is discontinued from the study.

Study visits and assessments

At the screening visit, documentation of previous ASD diagnosis is reviewed and confirmed. If the participant does not meet criteria for ASD based on DSM-5 criteria, they are not eligible. Additional baseline assessments include the Stanford Binet intelligence scale (SB-5 ABIQ) and Vineland adaptive behavior scales-3rd edition.[21,22] Cognitive and adaptive scores are utilized to characterize the study population, not as study endpoints.

Medical and developmental history are collected at screening including demographics, medical diagnoses, neurodevelopmental diagnoses and comorbidities, current and previous medication use, educational setting and therapies. Subsequent visits inquire about any changes to these variables.

The study schedule includes in-person visits at screening, baseline (week 0), week 2, week 7, week 12 (end of period 1), week 15 (start of period 2), week 17, week 22, and week 27. In most cases, screening and baseline (week 0) visits are combined into a single visit. Phone visits occur at week 1, week 4, week 16, week 19, and week 30. Outcome measures (Table 2) are collected at baseline, week 7, and week 12 for both period 1 and period 2. All in-person visits include vital signs, physical examination, adverse event monitoring, review of the medication diary, measurement of study product, blood draw for safety laboratory analyses, and suicidality screening if developmentally appropriate. Phone visits monitor tolerability, adverse events, screen for suicidality, and answer any additional questions.

Early termination visits are scheduled prior to discontinuation of study drug if a participant is going to withdraw, unless the study drug needs to be stopped for safety concerns prior to the visit. A post-study survey obtained 4 weeks after study completion collects feedback about experiences of participation, caregiver perception of the study arm assignment, and future plans to use CBD for their child. Social stories and visual schedules are provided to caretakers prior to visits for participant preparation. Reinforcers are utilized to improve motivation and participation.

Baseline assessments

ASD DSM-5 checklist: ASD DSM-5 checklist contains the diagnostic criteria for ASD including the domains of social communication and restricted, repetitive behaviors and confirms eligibility for the study based on diagnosis.[1]

SB-5 ABIQ: The SB-5 is a standardized measure of cognitive skills, with a set of subtests identified as a reliable estimate of IQ which make up the ABIQ (Abbreviated IQ) score.[21]

Vineland adaptive behavior scales (Vineland-3): The Vineland-3 adaptive behavior scales aids in diagnosing and classifying disability in different domains of adaptive functioning including communication, daily living skills, socialization, and motor skills.[22]

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Outcome measures

ABC-2: The ABC-2 is a symptom checklist assessing problem behaviors in individuals with intellectual disability across settings. The five subscales are: irritability/aggression, hyperactivity, social avoidance, stereotypy, and inappropriate speech.[23]

ADAMS: The ADAMS is parent-report scale designed for individuals with autism and other disabilities to measure domains of anxiety, depression, and mood.[24]

OACIS-S and OACIS-I: The OACIS-S and OACIS-I assess severity and improvements, in domains of social interaction, aberrant behavior, repetitive or ritualistic behavior, verbal communication, nonverbal communication, hyperactivity and inattention, anxiety, sensory sensitivities, restricted interests, and a global rating of autism severity.[25]

SRS-2: The SRS-2 is a standardized caregiver-report questionnaire that provides T-scores in domains of communication, motivation, cognition, and restrictive/repetitive behaviors.[26]

ASIEP-3: The ASIEP is a video-taped play-based assessment that evaluates social interactions and responses.[27]

RBS-R: The RBS-R is a caregiver questionnaire assessing repetitive behaviors with 6 subscales: stereotyped, ritualistic, self-injurious, compulsive, restricted, and sameness.[28]

Pediatric sleep clinical global impressions scales: The pediatric sleep CGI scales measure pediatric insomnia in ASD and have been validated against the gold-standard sleep questionnaire and actigraphy. It includes a structured sleep history form, with questions about falling and staying asleep independently; bedtime resistance; sleep onset delay; night awakening; caregiver satisfaction with the child's sleep patterns; and family functioning.[29]

Behavioral rating inventory of executive functioning (BRIEF-2): The BRIEF-2 is a standardized rating scale that measures domains of executive functioning, including behavior regulation, emotional, and cognitive regulation.[30]

AFEQ: The AFEQ measures family quality of life with domains specific to raising a child with ASD, the child's development and wellbeing, and family functioning.[31]

NIH toolbox measures: National institutes of health patient reported outcome measures information system (NIH PROMIS) is used to quantify psychological wellbeing and quality of life.[32]

Pediatric quality of life inventory (PedsQL): The PedsQL is a caregiver questionnaire to evaluate overall quality of life in different domains.[33]

Tele-FBA: The Tele-FBA protocol is an optional assessment in which a functional analysis is performed to evaluate behavior in natural settings. Common reinforcers for problem behavior (access to attention/tangibles; escape from demands) are evaluated in a series of

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test and control conditions. Sessions are conducted within 3 days of the study visits at baseline, week 10–11, and at week 25–26.

Safety monitoring

Safety monitoring includes vital signs, physical examination, laboratory tests, adverse medical or behavioral symptoms, and screening for suicidality (via the Columbia suicide severity rating scale, C-SSRS).[34] Electrocardiogram is obtained at baseline. Laboratory tests collected at each in-person visit include comprehensive metabolic profile, complete blood count, and hemoglobin A1c. Blood samples also include analysis of CBD levels, CBD metabolites, THC, and other cannabinoid levels, as well as optional biobanking for future genetic and metabolic studies. Urine pregnancy test is conducted at each visit for pubertal females. Adverse medical and behavioral symptoms are recorded at each visit and phone call.

Statistical and power analysis

Power analyses: Using SAS proc power and reported estimates on the ABC-2 irritability subscale score, we specified a significance level of alpha=0.05, two-tailed, and allowed for increased variability to determine the minimum difference between groups detectable with 70 subjects, where 40 receive CBD and 30 cross over to placebo.[20] Note that for the 10 patients who do not cross over to placebo (those providing sustainability information), their data during the first CBD phase can still be included in the mixed model analyses. Even though data for the placebo phase is missing for these participants, the models allow for missing data, assuming data are missing at random. As a simplistic and likely conservative estimate of power based on a paired t-test that does not account for covariates and assumes no period effect, this design provides 80% power to detect a 5.75 point or greater difference on the ABC-2 irritability subscale between CBD and placebo groups and 80% power to detect a treatment response rate (OACIS total autism score-I of 1 or 2) in the CBD group of 52% or greater, assuming a 20% response rate in the placebo group.

Analyses: Primary and secondary outcomes for aims 1 and 2 are analyzed for the intent to treat sample (i.e. all randomized subjects) with linear and generalized linear mixed models that can include participants with missing data; the potential period effects (i.e. order effects) are evaluated and included if significant. Models specify condition (CBD, placebo), time (0, 7 and 12 weeks) and condition by time interaction as fixed effects and subject as a random effect, where subject is assumed independently normally distributed with mean 0 and variance independent of random errors and assuming an unstructured covariance. These are mixed model analyses of covariance (ANCOVAs) where means are estimated at each time point and are on the link function scale when general linear mixed models are utilized. A significance level of alpha=0.05 is used to evaluate a priori planned comparisons. Closed testing procedures with hierarchical evaluation provide some protection against multiple comparisons. Tests for group differences at each time are conducted only for those outcomes with significant group by time interactions. Efficacy is determined by significantly greater improvement in irritability score in the CBD group vs. placebo at week 12. Secondary models evaluate variables such as sex, age, IQ and autism severity as potential covariates and report any differences in results compared to the primary models. To address attrition,

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sensitivity analyses are conducted as appropriate and/or results are compared with and without incorporating multiple imputed values from a generalized linear mixed model approach for missing data.

DISCUSSION

Preliminary evidence of sustainability of outcomes is evaluated via visual and descriptive comparisons of mean scores throughout both 12-week periods (including washout) for the 10 patients who continue CBD for both study periods. For each patient, we evaluate the reduction in ABC-2 irritability subscale score (and secondary outcomes) after the first 12-week period and consider maintenance of at least 70% of that reduction during the second period on CBD as preliminarily evidence of sustainability.

Rates of adverse events, treatment response, and the pattern of missing data are evaluated with logistic and/or binomial regressions comparing the CBD and placebo phases that account for repeated measures on the subjects.

Limitations

Limitations of the study include limited treatment duration for evaluation of long-term effects and sample size with insufficient power to analyze drug effect in regards to sex and race/ethnicity differences, varying levels of ASD symptoms and intellectual function. Further, allowing participants with concomitant psychiatric medications decreases the ability to study the effect of CBD alone on baseline symptoms, leading to potential underestimation of efficacy as the other medications are already addressing some symptoms. While drug naïve participants are included, duration of time for recruitment of an entirely drug naïve cohort is limiting. Further, life changes and other unanticipated stressors (big or small) can lead to behavioral changes for some individuals with ASD, and while randomized and enrolled at different timepoints throughout the school year, the impact of life events on behavioral outcomes may differ between groups. There is also risk for placebo effect as this is a vulnerable and often challenging population with caregivers heavily invested in potential treatments leading to behavioral improvements.

CONCLUSION

There is a great need for safe medications to address irritability, aggression and other challenging behavioral symptoms associated with autism spectrum disorder in children. FDA approval for aripiprazole and risperidone occurred almost 15 years ago (2009 and 2006, respectively) and there continues to be a dearth of available, effective, and well tolerated medication options to treat this population. While still limited, research to date on use of cannabinoid products including CBD in autism have demonstrated promise in improving negative behavioral symptoms, while also showing a relatively strong safety profile. Thus, there is clear justification for additional placebo-controlled trials with larger sample sizes such as the CASCADE study, as well as additional trials with longer follow-up.

To our knowledge, there are currently 4 other active or recruiting placebo-controlled studies investigating the effects of CBD on children and adolescents with ASD which will also

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contribute to answering this question.[36] If positive, further trials comparing efficacy to current treatments as well as studies evaluating CBD in combination with evidence-based behavioral treatments are important. However, publication of negative study results is also important, as the ASD community in general is historically and currently plagued by trends of different anecdotal and non-evidence based treatments that can lead to unnecessary expense, wasted time, emotional disappointment, and risks to health and safety of autistic individuals and their families. Determination of the safety and efficacy of CBD for treatment of irritability and aggression in individuals with ASD is vital, as many families are already using CBD products to treat their loved ones.

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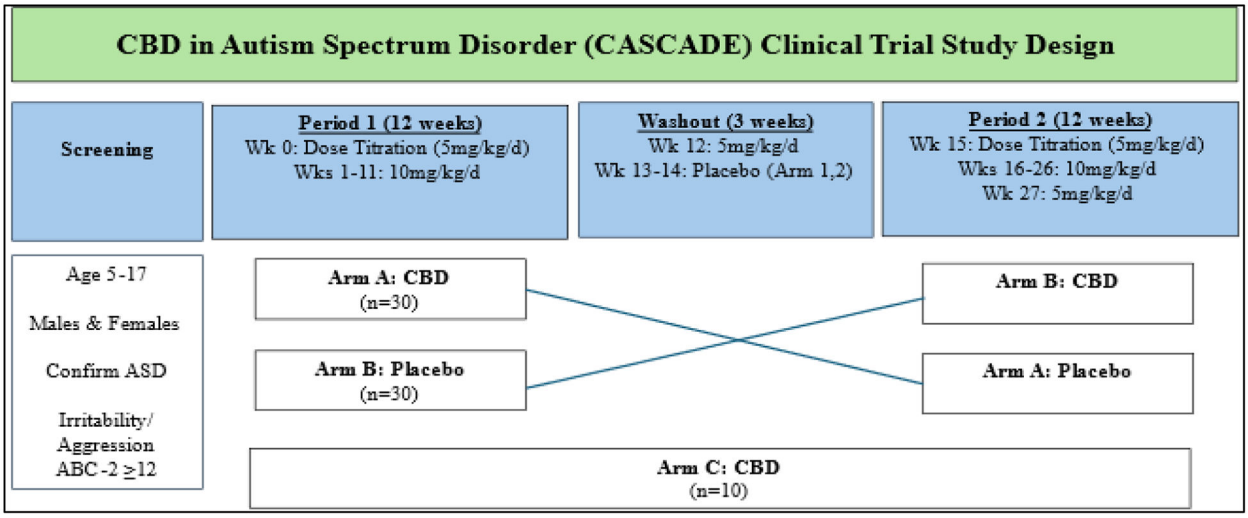

Figure 1:
CASCADE study design and dosing schedule.

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Table 1:

Summary of outcome measures.

Outcome measures	
Primary outcome	
Irritability and aggression	ABC-2 irritability subscale raw score
Secondary outcomes	
Irritability and aggression	Ohio autism clinical impressions scale-severity (OACIS-S) and Ohio autism clinical impressions scale-improvement (OACIS-I)
	Irritability subscale severity and improvement scales
Anxiety	Anxiety, depression, and mood scale (ADAMS)
	Total score
	General anxiety subscale
	Social avoidance subscale
	OACIS
	Anxiety subscale severity and improvement scales
Social skills	Social responsiveness scale-2nd edition (SRS-2)
	Total T-score
	OACIS-S and OACIS-I
	Socialization subscale severity and improvement scales
	Autism screening instrument for educational planning-3 (ASIEP-3): Interaction assessment autism interaction score
Repetitive behaviors	Repetitive behavior scale-revised (RBS-R)
Attention and executive functioning	Brief rating inventory of executive functioning-2nd Ed (BRIEF-2)
	Global executive functioning score
	Index scores (Metacognition, behavioral regulation, overall)
	ADHD score
	OACIS-S and OACIS-I
	Attention and hyperactivity subscales severity and improvement scales
Sleep	Sleep clinical global impression
	Severity scale (Sleep CGI-S)
	Improvement scale (Sleep CGI-I)
Caregiver stress	Autism family experience questionnaire (AFEQ)

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Outcome measures	
Quality of life	NIH toolbox scales
	Satisfaction with social roles and activities
	PedsQL core questions and cognitive functioning scale
	Caregiver
	Self-report for participants ages nine and older (if cognitively able to respond to questions)
	NIH toolbox scales
	Life satisfaction (caregiver and self report)
	Positive affect scales (caregiver and self report)
Overall autism symptoms	OACIS overall score
	Caregiver improvement scale
Behavioral symptoms of ASD	Telehealth functional behavior analysis (Tele-FBA)

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Table 2:

Eligibility criteria.

Inclusion criteria	Exclusion criteria
Children and adolescents aged 5–17 years	Pregnant, nursing, or planning a pregnancy. Unwilling or unable to use standard acceptable methods of contraception for duration and one month after the last dose of study medication.
In good health based upon results of medical history, physical examination, 12-lead ECG, and clinical laboratory tests.	History of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to any compound/chemical class related to Epidiolex®.
Previous documented diagnosis of ASD	Exposure to any investigational drug or device <30 days prior to screening or at any time during the study.
ABC-2 irritability subscale ≥12 at screening.	Use of any THC or CBD-containing product within 4 weeks of screening visit, planned use during the study, or positive THC urine test at screening.
OACIS-S autism global rating scale score ≥3 at screening.	Using the following medications: clobazam (Onfi, Frisium), felbamate (Felbatol), vigabatrin (Sabril), or everolimus (Afinitor).
Stable regimen of ≤2 psychiatric medications for ≥4 weeks preceding study screening. Must maintain regimen throughout study. As needed medications for procedures not counted.	Plan to initiate or change pharmacologic or non-pharmacologic interventions during the study.
For patients with history of a seizure disorder: a) must currently be on a stable regimen of 1–2 antiepileptic drugs, or b) must be seizure-free for 1 year if not currently receiving anti-epileptic drugs.	ALT, AST, total bilirubin, or creatinine levels ≥2 times the upper limit of normal, alkaline phosphatase levels ≥3 times the upper limit of normal, or hematocrit <1.2 times lower limit of normal.
For patients with history of a seizure disorder: must be on a stable AED regimen for 3 months prior to and throughout study.	Severe or unstable symptoms of ASD
Non-pharmacological educational, behavioral, and/or dietary interventions or therapies must be stable for ≥2 months.	Acute or progressive neurological disease or psychiatric disorder
Body mass index between 12–32 kg/m^2	Suspected or confirmed cardiovascular disease.
Females of childbearing potential must have negative serum pregnancy test at screening and all designated visits.	History of treatment for, or evidence of, drug or alcohol abuse within the past year.
Agree to abide by all study restrictions and procedures.	
Able to read and respond to questions and questionnaires in English.	
Adequately informed of the nature and risks of study	
Written consent to assist in study drug administration.	
Reliable and willing and able to comply with all protocol requirements and procedures.	