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A PHASE 2 STUDY OF CANNABIDIOL AS A NEW TREATMENT FOR AUTISM SPECTRUM DISORDER IN CHILDREN AND ADOLESCENTS [CBD4ASD-open]

Protocol Number: s18-00250

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
6.1.2	We removed sections in 6.1.2. Dosing and Administration, asking caregivers to provide information on typical eating habits at baseline. Caregivers will also no longer be requested to provide preferred meals with adequate fat content at drug administration times. No data on food administered with the cannabidiol will be collected.	Preliminary analyses with n=19 showed low inter-participant variability in caregiver data on dietary intake and no appreciable relationships to plasma levels of cannabidiol or to outcome measures. Therefore, we will stop collecting these data to minimize burden on caregivers.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase 2 Study of Cannabidiol as a New Treatment for Autism Spectrum Disorder in Children and Adolescents [CBD4ASD-open]
Study Description:	We propose a 6-week open trial to identify the optimal dosing of cannabidiol (CBD) in youth with autism spectrum disorder (ASD), and to guide decisions on the primary outcome for a subsequent double-blind randomized clinical trial. As there are currently no effective pharmacological interventions for the core symptoms of ASD, we are primarily interested in examining the potential for CBD to fill this gap. Given emerging literature demonstrating the effectiveness of CBD in increasing social responding within mouse models and the proposed mechanism of action of CBD mapping on to the leading hypotheses of the pathophysiologic processes that may contribute to ASD, CBD could be a promising treatment for core symptoms. Further, we will also evaluate change in symptoms commonly associated with ASD, as evidence suggests that CBD may be effective in addressing difficulties such as irritability and anxiety, while maintaining a benign adverse effect (AE) profile in children and adolescents. Notably, data are limited in regard to guidelines for most promising dose and multiple lines of evidence suggest that an inverted-U shaped dose response curve may be present; therefore, exploration of optimal dosing is essential and will be conducted in relation to improvement in both core and associated symptoms as outlined in this protocol in Part 1 of the trial. Following the completion of the BOIN design, we will engage in Part 2 of the study, in which we will examine the remaining dose (9 mg/kg/day) in a subset of youth with the clinical profile that most closely resembles those youth who were categorized as responders in Part 1 of the trial.

Objectives:	Primary Objective: Determine the optimal dose of CBD in children and adolescents with ASD Secondary Objectives: Examine change in core and associated symptoms, and identify the primary outcome measure for a subsequent double-blind placebo-controlled randomized clinical trial Exploratory Objectives: Assess underlying mechanisms using functional magnetic resonance imaging (MRI)
Endpoints:	Primary Endpoint: Optimal dose of CBD in children and adolescents with ASD, defined as the dose at which the greatest proportion of participants respond in an individualized target symptom domain designated for each individual prior to beginning CBD treatment Secondary Endpoints: Effect sizes of changes in symptoms from baseline of measures developed to assess ASD symptoms, symptoms often associated with ASD, and global functioning Exploratory Endpoints: Effect sizes of changes in MRI signals (i.e., resting-state functional connectivity) from baseline to the final week of treatment
Study Population:	Sample will include 30 male and female participants with ASD between the ages of 7 and 17 years old. Participants will have fluent speech and an estimated IQ greater than or equal to 80. Individuals of all races and ethnic origins are eligible for participation. Following the completion of the BOIN design, in Part 2 of the trial, we will recruit youth with clinical profiles that most closely resemble youth classified as responders in Part 1 of the trial.
Phase:	This is a Phase 2 study.
Description of Sites/Facilities Enrolling Participants:	The study will be conducted at the Child Study Center, Hassenfeld Children's Hospital, NYU Langone Health.
Description of Study Intervention:	Study intervention will be 98% pure CBD. The CBD will be Greenwich Biosciences, Inc.'s 100mg/mL oral solution, brand name Epidiolex (V). A Bayesian optimal interval (BOIN) design will be used, such that participants will be assigned to cohorts of size 3 receiving doses of 3, 6, or 9 mg/kg/day, depending on the treatment response of participants in prior cohorts.
Study Duration:	The duration of the trial is approximately 100 weeks.
Participant Duration:	Expected duration of subject participation is 8 to 10 weeks, with in-person visits scheduled every other week. Between in-person visits, participants will be contacted via secure email and/or phone to assess for the presence of AE.

1.2 SCHEMA

Pre-trial — Telephone Pre-screening

- Interested parents/legal guardians will speak with study staff over the phone to determine basic inclusionary and exclusionary information
- If the caregiver endorses any exclusionary criteria or fails to endorse inclusionary criteria over the phone, cargivers will be informed that the study would not be appropriate
- If the parent/legal guardian does not endorse any exclusionary criteria and endorses all inclusionary criteria, the study staff will schedule the screening visit
- Of note, if the child does not qualify for the study as a result of pre-screening or the family decides not to proceed with the study after pre-screening, their data will be discarded and will not be used in this research.

Pre-trial — Screening Visit

- Screen n=5 at a time; total n=50 for screening
- Obtain informed consent and assent and patient history
- Screen potential participants by inclusion and exclusion criteria according to the assessments outlined in the Schedule of Activities (SOA)

Day 0 — Enrollment/Baseline

- Enroll cohorts of size 3
- Arrive at clinician group consensus on individualized primary target(s) based on results of assessment with parent input
- Administer specified dose of study intervention to the cohort
- Refer to Section 1.3, SOA for battery of baseline assessments

Day 7 +/- 3 days — Follow-up phone call

- Assess for AE

Day 14 +/- 3 days — Assessment of study endpoints and safety

- Administer study intervention
- Refer to Section 1.3, SOA for battery of assessments

Day 21 +/- 3 days — Follow-up phone call

- Assess for AE

Day 28 +/- 3 days — Assessment of study endpoints and safety

- Administer study intervention
- Refer to Section 1.3, SOA for battery of assessments

Day 35 +/- 3 days — Follow-up phone call

- Assess for AE

Day 42 +/- 3 days — End of Study Assessments

- Discontinue study intervention
- Refer to Section 1.3, SOA for battery of assessments
- Group consensus on response to treatment based on the designated target symptom for each study participant

Repeat Screening to Day 42 — Repeat with subsequent cohorts

- Following completion of each cohort, a new group of ~5 children will be scheduled for screening
- Enroll subsequent cohort of size 3 and follow the same schedule as above
- Total Enrolled (n = 30; 10 cohorts)
- The dose of each subsequent cohort is determined by the dose response of participants in previous cohorts, according to the rules detailed within the Dosing and Adminstration subsection

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Study Visit 1 Enrollment/Baseline	Telephone Follow-Up 1	Study Visit 2	Telephone Follow-Up 2	Study Visit 3	Telephone Follow-Up 3	Study Visit 4 Final Study Visit	2-Week Post-Trial Telephone Follow-Up	4-Week Post-Trial Telephone Follow-Up	6-Week Post-Trial Follow-Up	3-Month Telephone Follow-Up(s)[c]
Informed consent and assent	X											
Demographics	X											
Medical, Psychiatric, and Treatment history	X											
Administer study intervention		X		X		X						
Concomitant medication review	X	X	X	X	X	X	X	X	X	X		X
Physical exam (including height and weight)	X*							X				
Vital signs	X*	X		X*		X*		X				
Test of hepatic and hematologic function [a]	X					X*		X				
Pregnancy test [b]	X											
Plasma for CBD levels								X				
Urine drug screen	X											
Adverse event review and evaluation			X	X	X	X	X	X	X	X		
UKU Side Effects Rating Scale				X		X		X				
Mock MRI scan	X											
MRI		X						X				
Aberrant Behavior Checklist (ABC)		X•						X			X	
Anxiety, Depression, and Mood Scale (ADAMS)		X•						X			X	
Anxiety Scale for Children – Autism Spectrum Disorder – Child version (ASC-ASD-C)		X•						X				
Anxiety Scale for Children – Autism Spectrum Disorder – Parent version (ASC-ASD-P)		X•						X			X	
Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-2)	X*											
Childhood Autism Rating Scale, 2nd Edition, High Functioning (CARS-2-HF)	X											
Autism Family Experience Questionnaire (AFEQ)		X•						X				
Autism Symptom Interview (ASI)	X											
Behavioral Inflexibility Scale (BIS)		X•						X			X	
~~Brief Observation of Social Communication Change (BOSCC)~~		~~X~~						~~X~~				
Clinical Global Impression Scale – Improvement (CGI-I)								X				
Clinical Global Impression-Severity (CGI-S)	X	X						X				
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X		X		X		X				
Computerized Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-COMP)	X											
Home Situations Questionnaire – ASD (HSQ-ASD)		X•						X			X	
OSU Autism Clinical Global Impression: Severity Subscale	X	X						X				
OSU Autism Clinical Global Impression: Improvement Subscale								X				
Repetitive Behavior Scale – Revised (RBS-R)		X•						X			X	
Screen for Child Anxiety Related Disorders (SCARED), Parent Version		X•						X			X	
Sleep Disturbance Scale for Children (SDSC)		X•						X			X	
Social Responsiveness Scale, 2nd Edition (SRS-2)	X							X			X	
Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior (SWAN)		X•						X			X	
Vineland Adaptive Behavior Scales-3 Parent/Caregiver Form (Vineland-3)		X•						X				

Procedures	Screening	Study Visit 1 Enrollment/Baseline	Telephone Follow-Up 1	Study Visit 2	Telephone Follow-Up 2	Study Visit 3	Telephone Follow-Up 3	Study Visit 4 Final Study Visit	2-Week Post-Trial Telephone Follow-Up	4-Week Post-Trial Telephone Follow-Up	6-Week Post-Trial Follow-Up	3-Month Telephone Follow-Up(s)[c]
Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II)	X											

a: Albumin, alkaline phosphatase, AST, ALT, total bilirubin, LDH, total protein; complete blood count.
b: Urine pregnancy test (females of childbearing potential)
c: Parents/guardians will be asked if they can be contacted every 3 months following the completion of the trial to provide data on longer-term behavior changes and parental choice in treatment, including whether they pursued continuation of CBD, for up to 1 year.
*As in-person visits have transitioned to virtual visits following re-initiation after a pause due to the COVID-19 pandemic, select procedures to be completed in certain cases (e.g., family prefers to attend in-person visit and agrees to in-person procedures; Week 4 blood draw clinically indicated from baseline blood draw results as per clinical judgement of PI)
•Questionnaires must be completed prior to medication administration; however, caregivers will be given the option to complete them during screening or baseline.

2 INTRODUCTION

2.1 STUDY RATIONALE

Autism spectrum disorder (ASD), a lifelong profoundly impairing neurodevelopmental disorder, is far more common than previously appreciated. Currently, only two medications, risperidone and aripiprazole, are Food and Drug Administration (FDA)-approved for treating irritability in pediatric ASD. Unfortunately, these medications are associated with significant AE. There are currently no medications that target core autism symptoms; however, a wide range of psychotropic medications have been applied for either core or associated difficulties with little evidence of effectiveness and numerous AE. Regardless of the thin evidence base, up to 65% of patients with ASD have been prescribed at least one psychotropic medication, with many taking multiple medications simultaneously. Thus there is a large, unmet need for additional treatment options.

Notably, a recent preliminary, retrospective study evaluating the efficacy, safety, and tolerability of CBD for ASD found significant improvements in communication problems and reduction in the associated symptoms of anxiety, disruptive behaviors, and behavioral outbreaks following treatment (1). However, this preliminary study was exploratory, with numerous limitations. Cannabidiol (CBD) was also reported to increase social responding in a mouse model of Dravet syndrome (2) and to decrease a broad range of behavioral difficulties in a small open study of children and adolescents with Fragile X syndrome [*http://zynerba.com/zynerba-pharmaceuticals-announces-positive-top-line-results-zyn002-open-label-phase-2-fab-c-study-children-fragile-x-syndrome/*]. Further, CBD decreases anxiety-like behaviors in animal studies and shows anxiolytic effects in human trials. Crucially, both open and placebo-controlled randomized controlled trials (RCT) have found that CBD is well-tolerated by children and adolescents. The combination of a benign AE profile, potential benefits for core and associated symptoms, and the lack of alternatives all suggest that CBD should be considered as a potential treatment for core and associated ASD symptoms.

The rationale for considering CBD as a therapeutic option for ASD also rests on the leading hypotheses of the pathophysiologic processes that may contribute to ASD. These include synaptic excitatory/inhibitory (EI) imbalance and low-level chronic inflammation. CBD shows effects to reduce

EI imbalance (i.e., three RCTs showing efficacy in patients with Dravet and Lennox Gastaut Syndromes and extensive animal models of epilepsy spanning multiple species and epilepsy models) and neuroinflammation (3-5). Additional pathophysiological mechanisms thought to underlie the neurobehavioral deficits present in ASD include aberrant synaptic plasticity, immune dysfunction, and metabolic disturbances, all of which are susceptible to modulation by the endocannabinoid system (ECS) and which are likely influenced by CBD (6).

In summary, CBD appears to address many of the mechanisms that have been implicated in the pathophysiology of ASD. Accordingly, this study aims to explore the efficacy of CBD in addressing core autism symptoms, as pharmacological treatment options do not exist. We will focus on children and adolescents with high-functioning autism (HFA; i.e., those with fluent language and broadly average intelligence), as this subpopulation is not often prioritized in pharmacological research, including studies currently underway evaluating CBD for ASD. Further, despite often having reduced symptom severity compared to lower functioning groups, individuals with HFA continue to experience poor long-term prognoses, including increased prevalence of psychiatric disorders and heightened under-/unemployment rates (7, 8).

While we aspire to identify improvement in core symptoms, we recognize that CBD may be beneficial for youth with ASD in other ways, specifically by ameliorating common comorbid symptoms (1). Because research into the therapeutic benefit of CBD for ASD is in its infancy, it would be inappropriate for us to limit this exploratory study to target only core symptoms when improvements in a wide range of outcomes could be possible. Therefore, a secondary goal for the study is to identify changes in symptoms associated with ASD (e.g., anxiety, irritability), which will enable the selection of primary and secondary outcomes to be used in a subsequent double-blind placebo-controlled trial.

Of note, there is limited data available to suggest most promising dosage and there is preliminary research evidence suggesting the possibility of nonlinearity in the dose response across a variety of outcomes (2, 9). Determining the optimal dose of CBD is essential in maximizing potential for treatment of core and associated ASD symptoms. Therefore, we will evaluate varying dose levels by implementing an adaptive design to determine at which dose the largest proportion of participants respond. The definition of treatment response will be individualized for each participant based upon a predetermined target symptom cluster that is considered most interfering at study outset. Lastly, we also intend to collect brain MRI data before and after open CBD treatment to provide insights into feasibility of incorporating biomarkers into subsequent studies, and potentially yield testable hypotheses.

2.2 BACKGROUND

The Centers for Disease Control and Prevention (CDC) estimate 1 in 59 children have ASD (10). Autism spectrum disorder (ASD) is characterized by core deficits in social communication and interaction and the presence of restricted and repetitive behaviors (RRB), and is commonly associated with a range of challenging behaviors (e.g., aggression, irritability, tantrums), sleep problems, and comorbid psychopathology, all of which entail a high caregiver burden (11-14). Currently, only risperidone and aripiprazole are FDA-approved for treating irritability in pediatric ASD, and are associated with significant AE (e.g., weight gain, metabolic syndrome, type 2 diabetes, prolactin elevation, development of breast tissue, extrapyramidal/movement-related side effects) (15, 16). Beyond risperidone and aripiprazole, a wide range of psychotropic medications have been applied to target core and associated autism symptoms, including antipsychotics, antidepressants, anticonvulsants, mood stabilizers,

stimulants, and alpha-2 agonists. However, findings of effectiveness have been mixed and AE have been numerous (17). Despite the thin evidence base, a majority of patients with ASD are or have been prescribed at least one psychotropic medication (18). The lack of available evidence-based treatments for core and associated symptoms in conjunction with the AE profiles of currently approved treatments suggest that there is a large need for additional treatment options. Given emerging literature, CBD may be a promising treatment to fill this gap.

Limited research has been conducted examining the use of CBD with the ASD population. There is a growing pool of anecdotal evidence suggesting potential benefit; however, no formal studies have been conducted. Recently, a preliminary study was presented demonstrating the effects of varying CBD-rich strains on the areas of communication, anxiety, behavioral outbreaks, and disruptive behavior in approximately 60 children with ASD. Improvements in anxiety were noted in 39% of the sample; improvements in communication problems were noted in 47% of the sample; and, improvements in behavioral outbreaks were noted in 61% of the sample. Adverse events (AEs) were infrequent and not severe (1). While these data are promising, there were numerous limitations and more well-designed research is needed to make conclusions about the potential for CBD in ASD.

Outside of the ASD population, CBD has been found to reduce anxiety-like behaviors in animal models (19-24) and to reduce anxiety associated with public speaking in humans (9, 25). CBD lacks agonist effects at CB1 or CB2 receptors, but acts as an agonist at 5-hydroxytryptophan 1A (5HT1A) receptors (21, 22, 24), which are implicated in the anti-anxiety effects of buspirone in ASD (26). With respect to social behavior, CBD increased social responding in a mouse model of Dravet syndrome (2) and decreased a broad range of behavioral difficulties in a small open study of children and adolescents with Fragile X syndrome [*http://zynerba.com/zynerba-pharmaceuticals-announces-positive-top-line-results-zyn002-open-label-phase-2-fab-c-study-children-fragile-x-syndrome/*]. Importantly, CBD has largely been well-tolerated by pediatric patients (3, 27).

The rationale for considering CBD as a therapeutic option for ASD also rests on the hypothesized pathophysiologic processes that may contribute to ASD (28). These include synaptic EI imbalance and low-level chronic inflammation. Evidence of EI imbalance, due to abnormal GABAergic or glutamatergic neurotransmission has implicated key brain regions, including parietal-occipital and frontal cortical regions (29). Abnormalities in EI balance in these regions in animal models can result in seizures, in addition to behavioral changes and social dysfunction, including irritability, repetitive and disruptive behaviors, and social avoidance and withdrawal. Cannabidiol attenuates seizures in many animal models and in human epilepsy; CBD's impact on seizures and EI imbalance supports its potential as a treatment for non-epileptiform dysfunctional mechanisms in ASD that could result in increased irritability, repetitive behaviors and social dysfunction (28).

Cannabidiol is a multi-target drug, interacting both with non-endocannabinoid systems and within the endocannabinoid system, including inhibition of the equilibrative nucleoside transporter and the orphan G-protein-coupled receptor 55 (GPR55) (6, 30-32) modulating the presynaptic release of glutamate (33). Besides activating 5HT1A receptors (21, 22, 24, 33-39), CBD inhibits adenosine reuptake through multiple mechanisms (40, 41). Cannabidiol may exert some of its effects by modulating intracellular calcium flux via GPR55; the voltage dependent anion selective channel protein 1 (VDAC1); or by reducing neuronal excitability and neuronal transmission, and engaging inflammatory pathways by inhibiting adenosine reuptake or modulating the release of pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) (41, 42). These multiple effects parallel many of the hypothesized molecular mechanisms implicated in the pathophysiology of ASD, i.e., aberrant EI balance (43),

immune dysfunction (44, 45), and metabolic disturbances (46). The effects of CBD on EI imbalance are a principal focus of the Tsien lab, in collaboration with Devinsky and colleagues. Work in progress recently reported at the 2018 NYU Neuroscience Retreat shows that CBD decreases excitability of pyramidal neurons and increases inhibitory drive in hippocampal area CA1 (47). Parallel work is also revealing that CBD restores EI balance by decreasing excessive excitation and strengthening inhibition via antagonism of GPR55 (48).

While research indicates that CBD may be therapeutically beneficial for ASD, there is some evidence to suggest the presence of an inverted-U shaped dose response. For instance, Kaplan et al. studied a mouse model of Dravet syndrome and found that high doses attenuated seizures but only moderate doses improved social interaction deficits (2). Similarly, Zuardi et al. examined the anxiolytic effect of CBD during a public speaking task in healthy adults and found that a 300 mg dose reduced anxiety more effectively than 100 and 900 mg doses (9). Further support for a potential inverted-U dose response curve was provided in a personal communication from Dr. Adi Aran, an Israeli researcher conducting the only currently active clinical trial testing CBD for ASD. Dr. Aran reported that of the over 300 children with ASD he has treated with CBD, most appear to respond optimally to moderate doses (e.g., 5-7 mg/kg/day) and some patients who have had excellent responses on 3-4 mg/kg/day have worsened on higher doses (personal communication Dr. Adi Aran, July 3, 2018).

Together this suggests that CBD is a multi-target drug that may address multiple mechanisms implicated in the pathophysiology of ASD (49) and common comorbid disorders (50). However, continued study of its efficacy for core and associated ASD symptoms is necessary. Because the CBD dose response curve is unknown and data suggest the potential for nonlinearity, determining optimal dose is paramount in informing future research. Given the preliminary evidence of therapeutic effects across a range of domains, selecting primary and secondary outcomes is also essential in the design of a subsequent double-blind placebo-controlled trial. In regard to our exploratory objectives, collecting brain MRI data before and after the open trial may also provide insights into feasibility of incorporating biomarkers into subsequent studies, and potentially will yield testable hypotheses.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of the study intervention

Cannabidiol (CBD) has been used alone and in combination with tetrahydrocannabinol (THC) in numerous clinical trials and is approved with THC to treat spasms in patients with multiple sclerosis in more than 20 countries. Scientific studies using only CBD are more limited, involving <10,000 patient-years, with limited data on long-term AEs. Data from open-label and RCTs in epilepsy reveal a consistent profile of AEs (3, 27, 51). Serious adverse events (SAE) were more common in the CBD group than in the placebo groups (e.g., 16% vs. 5%), and AEs led to the withdrawal CBD-treated patients more than those in the placebo group (e.g., 8/61 v. 1/60). The large majority of AEs were mild to moderate in severity. Adverse effects (AEs) seen more frequently in the CBD group included somnolence (36% in the CBD group vs. 10% in the placebo group), loss of appetite (28% vs. 5%), and diarrhea (31% vs. 10%) (3, 27, 52, 53). Abnormalities of hepatic aminotransferase levels occurred most often in patients taking valproate, suggesting an interaction in which CBD may potentiate a valproic acid-induced change in hepatic aminotransferase levels (3). Nevertheless, the FDA label for Epidiolex (Reference ID: 4282447) does note that the incidence of ALT elevations in patients who were not taking valproate or clobazam was 3%. The label also notes that “resolution of transaminase elevations occurred with discontinuation of Epidiolex

or reduction of Epidiolex and/or concomitant valproate in about two-thirds of cases. In about one-third of cases, transaminase elevations resolved during continued treatment with Epidiolex, without dose reduction."

Other AEs reported more frequently in the treatment group include upper respiratory tract infection, pyrexia, and vomiting. Possible AEs of CBD that were not more common in the CBD versus placebo groups included headache, dizziness, fatigue, oral numbness, dry mouth, neck pain, feeling strange, depression, lack of taste or changed taste, feeling weak, falls, shakiness, muscle stiffness, unusual dreams, nosebleeds, hot or cold flashes, heartburn, trouble swallowing, and decreased pulse (3, 4, 27, 52, 54).

Potential drug interactions may occur as CBD is a potent inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, although research is limited on pharmacokinetic interaction with other pharmacological agents when CBD serves as the primary cannabinoid in treatment (55).

Given that CBD is extracted from cannabis, one concern could be that individuals who require drug testing for employment or school may test positive for cannabinoids. Fortunately, the CBD formulation to be administered has an extremely low concentration of Δ^9-THC, making it extremely unlikely, albeit not impossible, that subjects would test positive for THC while participating in this study.

Other Associated Risks

MRI: MRI scans are considered a safe way to noninvasively visualize tissue in adults and children. This study will be performed on a FDA approved scanner. There are no known significant risks or side effects associated with MRI procedures except the risk of metallic projectiles in the magnetic field or metallic objects in the body. Some participants report mild discomfort when undergoing magnetic resonance scans. Some participants have experienced claustrophobia (fear of enclosed spaces).

The major risk of having a research brain MRI is the identification of incidental findings, most of which turn out to be inconsequential. Nevertheless, being informed of a possible abnormality in a brain scan is anxiety provoking. In the largest pediatric brain imaging study to date, of 11,679 children ages 9-10 years-old, 17.2% had a finding that was judged to not require a referral, 3.7% had incidental findings for which referral was considered, and 20 (0.2%) were found to merit considering an immediate referral (99). The PI has nearly 30 years' experience in conducting pediatric neuroimaging studies and has always directly communicated any concerning findings to parents/guardians in a sensitive and forthright manner.

The MRI scanner also makes loud knocking or beeping sounds during imaging. Due to the rapid rate of change of the magnetic gradients during imaging, peripheral nerve stimulation is a possibility. If this happens, participants may feel creeping or tingling sensations, typically along their arms or lower back. Dizziness and nausea may occur if participants move their head rapidly in the bore of the magnet. Finally, there may be some heating from the radio frequency coils, the cables to the coils, and response and physiological monitoring devices. We do not use cables that can conduct electricity in the proximity of participants and have had no such untoward events in the past in over 15 years scanning young children.

Blood draw: This study involves blood draws, which may cause some discomfort, bruising, or transient pain at site of needle entry into the vein as with any blood draw. There is a slight risk of fainting. Infection can also occur at site where needle penetrates the skin.

Pregnancy-related risks: There are no data available on the risks associated with CBD use in pregnancy.

Burden of study time commitment: This proposal calls for participants and their caregivers to return to the clinic/attend virtual visits over WebEx regularly and participate in a relatively lengthy battery of assessments.

Mandated reporting of suspected child abuse or neglect: As mandated reporters, evidence of suspected child abuse or neglect would need to be reported to the appropriate authorities. This exception to confidentiality is explicitly provided in the consent document. If required, parents/guardians will be informed of the referral.

2.3.2 KNOWN POTENTIAL BENEFITS

It is possible that some study subjects will experience an improvement in their ASD and related symptoms while taking CBD during the study. For participants who experience benefit without significant side effects, parents/guardians may elect to continue CBD prescribed by their own physician. CBD is now available legally in New York State. It is also possible subjects may not benefit from being in this research study. Others with ASD may benefit in the future from what we learn in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The common AE associated with CBD in previous research are typically mild (e.g., headaches, gastrointestinal symptoms), particularly when compared to the AE profile of currently approved medications for ASD. Nonetheless, all participants will be closely monitored for AEs during the treatment period and assessment of the need for discontinuation of treatment will be conducted as appropriate.

In regard to the potential for drug interaction effects, participants taking medications metabolized primarily by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP2D6 isoenzymes will be excluded. Adverse effects related to the interaction between medications will be monitored, including tests of hepatic and hematological function at Baseline and at Weeks 6. Further, if a subject's baseline blood draw suggests borderline clinical abnormalities (that did not meet the cutoff for exclusion), they will be required to complete a Week 4 blood draw. Since transaminase elevations of greater than 3 times the upper level of normal (ULN) (plus elevated bilirubin levels) are significant predictors of severe liver injury and given that CBD can cause dose-related elevations in liver transaminases, potential participants with elevated baseline transaminase levels greater than 3 times the ULN plus elevations in bilirubin greater than 2 times the ULN, will be excluded from trial participation.

Further, while there are no data to suggest 9 mg/kg/day will be associated with increased risk, out of an abundance of caution, participants assigned to the highest dose (9 mg/kg/day) will be instructed to take half the dose (4.5 mg/kg/day, divided in two doses) per day for the first week of treatment before increasing to the full dose to minimize the chance for adverse events upon treatment initiation.

Lastly, if families are concerned about CBD showing up on a urine drug test, the study team will provide documentation that the subject is in a research study using a cannabis-related compound that has no psychoactive effects. Additionally, we will exclude participants with a history of cannabis usage or substance use disorders or a positive urine toxicological screen.

MRI scanning is optional. Participants who have no contraindications for MRI scanning and who agree to undergo MRI scanning and their parents/guardians, if they enter the scanning suite, will be carefully

screened for previous exposure to metallic fragments and for devices such as electrically, magnetically or mechanically activated implants, e.g., cardiac pacemakers, clips on blood vessels in their brain, or other metallic objects in their body, e.g., shrapnel, bullets, buckshot, or metal fragments. They will also be asked to leave all metallic and magnetic objects in their possession (e.g., keys, jewelry, credit cards) outside the magnet room. To manage the noise associated with the scan, earplugs are provided. Participants will also be instructed how to use an emergency handheld device to inform the operator if they feel discomfort, and/or wish to immediately stop scanning and be removed from the magnet. It is worth noting that the MRI scanning environment necessarily predicates the utmost concern for the complete comfort of the participant. We emphasize that even slight discomfort tends to result in participants moving during the scan, which degrades image quality. Therefore, prior to the imaging session, we have participants complete a mock scanner session using an MRI simulator, and also spend extra time when we place them on the gantry to make sure they are comfortable, and readjust as needed whenever they let us know that they are even slightly uncomfortable. For participants prone to fear of tight spaces (claustrophobia), special care will be taken during the mock scanner session to test if proceeding with training and the real MRI will be feasible for them. In general, once a participant has gotten over the novelty of entering the magnet bore, and has habituated to the knocking noises, the main issue is boredom, and staying awake for functional scans. Participants are asked to keep their eyes open during resting state scans to facilitate monitoring of wake status. Participants are free to sleep or watch a DVD or listen to music during several of the scanning sequences (e.g., structural scans). Given that we are using instruments that are calibrated to deliver energy levels judged to be well within safe limits, we expect no adverse events. Nonetheless, we will monitor all participants during scanning and be available for any follow-up that may be required.

In regard to AE associated with blood draws, the study team will offer EMLA cream to minimize discomfort, and precautions will be taken to prevent infection by using sterile technique.

Because risks of CBD use in pregnancy as well as MRI scanning in pregnancy are unknown, all potentially fertile subjects are required to use abstinence or a valid method of contraception to participate in the study. Menstruating females will undergo urine pregnancy test before initiation of study drug, as well as before each MRI scan. If a subject becomes pregnant during the study, she will immediately be discontinued from the medication. Subjects who become pregnant during the study, or within 30 days after completing the study, will be followed throughout the course of the pregnancy for safety, with the subject's permission and that of her parent/guardian. Information about the risks of the pregnancy and the possible effects on the fetus will be provided to support an informed decision in cooperation with the treating physician and the obstetrician. Any spontaneous abortion will be classified as a SAE.

Regarding the time commitment of participation, every effort has been made to reduce the time burden on participants and caregivers. A majority of the assessments are completed by the caregiver, and child assessments are kept to a minimum, with only diagnostic/screening measures completed at screening and a brief observational measure (~10-15 minutes) completed twice, at baseline and study completion at in-person visits. If virtual visits are conducted, the brief observational measure will not be administered and the diagnostic/screening measure will be conducted over WebEx. If needed, enrollment/baseline visits can be split into two visits. Caregivers may prefer to attend one of those visits (virtually or in-person) without their child to complete their measures. Caregivers will be encouraged to complete measures using secure electronic entry as much as possible. To give caregivers more flexibility, we will allow them the option to complete measures during the screening visit before the child has been confirmed eligible for the study or during the baseline visit. To improve

ease of scheduling, the participant will be given a window of time around the next visit date of +/-3 days. Reimbursement for time and travel will also be provided at each visit ($75/each at the enrollment/baseline, 4-week and 6-week visits and $40/each for the screening and 2-week visits; $75 for each MRI scan; an additional $10 will be provided on visits that include blood draws and brain MRIs [e.g., Screening Visit, Baseline Visit, Week-4 Visit, Week-6 Visit] to cover additional travel expenses). Of note, the time commitment and study burden are similar to those of other ASD treatment studies.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the optimal dose of CBD in children and adolescents with ASD	Establishment of optimal dose of CBD in children and adolescents with ASD, defined as the dose at which the greatest proportion of participants respond. Discussed further in the Dosing and Administration section, the definition of treatment response will be individualized for each participant based upon a predetermined target symptom cluster.	Identification of the optimal dose of CBD (within the range tested) is desirable given the insufficient research in this area and the potential for dose-dependent inverted-U effects (2, 9).
Secondary		
Identify the primary outcome measure for a subsequent double-blind placebo-controlled RCT	Change in core and associated symptoms from baseline based upon measures developed to assess ASD symptoms, symptoms often associated with ASD, and global functioning including: - ABC Social Withdrawal and Irritability Subscales - ASC-ASD-Child and Parent - AFEQ - ADAMS - BIS - CGI-I - CGI-S - HSQ-ASD - OSU Autism CGI Severity - OSU Autism CGI Improvement - RBS-R - SCARED - SDSC - SRS-2 - SWAN (Part 2 of the trial) - Vineland-3	Measures were selected because they have been widely used in prior trials in ASD (ABC, CGI, HSQ-ASD, OSU Autism CGI, RBS-R, SCARED, SRS-2, SWAN [Part 2], Vineland-3), or have been used in a recent trial of CBD in Fragile X syndrome (ADAMS) or have been used in medication trials more broadly (SDSC), or represent new and innovative tools available in the ASD field (ASC-ASD; AFEQ; BIS).
Tertiary/Exploratory		
Assess underlying brain mechanisms using MRI	Change in brain activity, indexed by resting-state functional connectivity. Otherwise, results will be reported	Inform the feasibility of incorporating biomarkers (e.g., resting-state functional

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	qualitatively (conducted at in-person visits only, if participants agree)	connectivity) in our future studies and potentially yield testable hypotheses.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The primary objective is to determine the optimal dose of CBD in children and adolescents with ASD; the hypothesis is that dose $_{response}$ curve may not be linear and that moderate doses of CBD may be therapeutically beneficial for core and associated symptoms in children and adolescents with ASD. The second objective of this study is to determine effect sizes for a variety of outcome measures, with the longer term goal of facilitating the selection of primary and secondary outcome measures for a subsequent placebo-controlled RCT. The third objective is to assess the feasibility of quantifying candidate biomarkers (e.g., resting-state functional connectivity) using MRI.

This single group single-site study will seek to enroll youth between the ages of 7 and 17 years who have a diagnosis of ASD with broadly average intelligence and who are fluently verbal. An adaptive design will be employed to allow for evaluation of optimal dosing while collecting data on core and associated ASD symptoms and any Aes that may present. Under the adaptive design algorithm we implemented, we ended recruitment after enrolling 15 participants and testing two doses. Given the higher rate of response on the higher of the two doses tested (44% vs. 16%), and the suggestion that higher doses of CBD may particularly target dopamine type 2 high affinity receptors ($D2R_{high}$) in the striatum, we have modified the study by implementing part 2 (described further on page 17-20), to recruit up to 15 youth (within the previously approved total accrual of 30 who would enroll) with clinical profiles that most closely resemble youth classified as responders in Part 1 of the trial.

It is important to note that all endpoints in this study are exploratory; the research base is too limited to make confident predictions. Nonetheless, given the lack of alternative pharmacological options, the benign AE profile, and the potential for CBD to fill this treatment gap, this line of work is necessary to direct future research in the field.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Suggested dosing to address psychiatric symptoms may be substantially lower compared to dosing in epilepsy studies, which has been the focus of most pediatric CBD research. Further, previous research suggests that CBD has dose-dependent effects on social behavior and anxiety. Therefore, prior to conducting a double-blind trial, identifying optimal dosage is imperative. The BOIN design was employed as our dose finding approach. The BOIN design is flexible and sensitive to nonlinearity, and enables the designation of an optimal dose level based upon the proportion of participants who respond to the treatment.

The BOIN design allowed us to test the intermediate dose (n=9) and the low dose (n=6) and to observe a non-significantly higher rate of response (44%) on the intermediate dose than on the low dose (16%). Based on the overall excellent safety profile in part 1 (all participants completed treatment without any

severe adverse events or need to discontinue treatment) and the suggestion that higher doses of CBD may particularly target striatal $D2R_{high}$ receptors, we have modified the second part of the trial to administer only the still untested 9 mg/kg/day dose, and to focus on participants who present with both ASD and ADHD, as they appear to be the ones most likely to be classified as responders in part 1. This is described in further detail on pages 17-20.

4.3 JUSTIFICATION FOR DOSE

Chronic CBD dosing up to 1500 mg/day has been reported to be tolerated well without AE (60-63); minor AE were reported after CBD use in children with epilepsy being treated with multiple other medications in doses up to 50 mg/kg/day (3, 27). Accordingly, we believe an upper limit of 9 mg/kg/day orally in our dose finding approach is reasonable and safe. Our proposed dosage range is substantially lower than most pediatric studies registered in ClinicalTrials.gov (accessed on 06 February 2018). Our dose range (3-9 mg/kg/day) is comparable to the only ongoing study specifically addressing behavioral symptoms in ASD (NCT02956226; dose range 1 mg/kg/day to 10 mg/kg/day). As mentioned, participants assigned to the highest dose (9 mg/kg/day) will be instructed to take half the dose (4.5 mg/kg/day, divided in two doses) per day for the first week of treatment before increasing to the full dose to minimize the chance for adverse events upon treatment initiation. This will go into effect when the next cohort of participants begin treatment with CBD; therefore, all participants who have already been enrolled will not be re-consented or informed of the changes.

The BOIN design, discussed in detail within the Dosing and Administration section of the protocol, was informed by the observation of dose-dependent inverted-U effects on social behavior in a mouse model of Dravet syndrome in which social effects were observed at lower doses than anti-seizure effects (2), the increased efficacy of CBD in reducing anxiety during a public speaking task at a moderate dose compared to a low and high dose (9), and correspondence with Dr. Adi Aran regarding his clinical experiences in prescribing CBD to address associated symptoms of ASD. As noted, now that we've obtained data from 15 participants on the low and intermediate doses by implementing the BOIN design, we propose to test the remaining 9 mg/kg/day dose in up to 15 participants – within the originally approved accrual ceiling of 30.

Drs. Castellanos and Devinsky, the multiple PIs, and co-I's Drs. Friedman, Hirsch and Nishawala will review all data relating to safety and tolerability throughout the study, after every cohort of three, to monitor study conduct and assess participant safety throughout the dosage period of approximately 6 weeks. This will be conducted through clinical evaluations at enrollment/baseline and final visits, with weekly consultation via WebEx and telephone follow-up calls in between.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last in-person visit (Visit 4 shown in the SOA, Section 1.3).

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients who will be selected for this study will meet the following criteria:

- Male or female pediatric outpatients aged between and including 7 to 17.9 years old
- Diagnosis of ASD confirmed by the ADOS-2 or CARS-2-HF and DSM-5 criteria

- Part 2: Diagnosis of ADHD confirmed by clinician review of the K-SADS-COMP
- SRS-2 Total *T*-score of 66 or higher
- CGI-S score of 4 or higher
- Physical exam and laboratory results that are within normal range for their age
- Fluent speech
- Estimated IQ of at least 80
- Presence of a parent/legal guardian who is able to consent for their participation and complete assessments regarding the child's development and behavior throughout the study
  - Child Assent will be obtained.

5.2 EXCLUSION CRITERIA

Patients cannot be included in the study if:

- History of active seizure disorder or epilepsy; patients seizure free for > 5 years off of antiepileptic drugs and other than uncomplicated febrile seizures are not excluded
- History or current evidence of significantly impaired liver function, defined as 1) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN); 2) ALT or AST > 3 × ULN with concomitant total bilirubin > 2.0 × ULN; or 3) ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.
- Exposure to any investigational agent in the 30 days prior to initiation of trial
- Treatment with CBD or other cannabinoid within the previous two months
- Current use of medications metabolized primarily by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP2D6 isoenzymes. Methylphenidate is not contraindicated as it is rapidly and extensively metabolized by carboxylesterase CES1A1 to ritalinic acid, which has little to no pharmacologic activity per DrugBank (accessed 1/31/19: *www.DrugBank.ca/drugs)D800422*).
- History of drug abuse including marijuana/cannabis use in the past 3 months
- Positive urine sample results from drug screening indicating presence of the following drugs: THC, opiates, methamphetamine, or cocaine
- Diagnosis of a known genetic disorder (e.g., Prader-Willi Syndrome, Angelman Syndrome, etc.).
- Active suicidality (ideation and plan) is present
- A current psychiatric diagnosis of bipolar disorder, major depressive disorder (MDD), psychosis, schizophrenia, or post-traumatic stress disorder (PTSD)
  - These patients will be excluded due to potential confounding results.
- Pregnant or lactating patients or patients who will not agree to be abstinent or use contraception
  - CBD has not been studied in pregnant or lactating females.
- A medical condition that severely impacts the subject's ability to participate in the study, interferes with the conduct of the study, confounds interpretation of study results or endangers the subject's well-being
- Diagnosis of Rett Syndrome or Childhood Disintegrative Disorder or marked sensory impairment such as deafness or blindness
- Subjects who have had changes in allied health therapies, behavioral or educational interventions within 4 weeks prior to initiation of trial, other than those associated with school holidays
- Subjects who have had changes in non-exclusionary psychotropic medications within 4 weeks of initiation of trial

Lifestyle Considerations
During this study, participants are asked to:

- Refrain from making changes in allied health therapies, behavioral or educational interventions
- Refrain from making changes in non-exclusionary psychotropic medication (e.g., methylphenidate) regimen or dosage
- Abstain from illicit drugs, particularly THC, opiates, methamphetamine and cocaine
- Use abstinence or use a valid method of contraception

If prohibited medication, treatment, or practices are indicated during the trial, the participant will be withdrawn from the trial. Notably, if the patient/caregiver states they plan to discontinue exclusionary medications to participate in the trial, they will be required to do so under the care of their treating physician, and will remain under that clinician's care during the titration/discontinuation and throughout their participation in this study.

Importantly, participants will be screened for contraindications to MRI scanning (e.g., metal implants, pacemakers, metal foreign bodies, pregnancy). They will not be permitted to undergo optional scanning if they meet a condition that is contraindicated.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not enter the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor (e.g., changed treatment regimen 3 weeks prior to screening) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will occur through the NYU Langone Child Study Center and Comprehensive Epilepsy Center. Both sites have a good track record for recruitment of participants with ASD, and will use all successful recruitment methods as previously demonstrated, including use of a study flyer that will be available in the lobbies of the Child Study Center and the Comprehensive Epilepsy Center as well as published online. We expect to accrue the sample of 30 within 22 months of study initiation. If accrual slows at any time point during the study, additional staff effort and resources will be dedicated to recruitment efforts including attendance at autism support groups and events and the use of tools such as google search engine optimization. We will also employ an EHR query through NYU Langone Health's DataCore for individuals with an ASD diagnosis and will contact these individuals using the IRB-approved direct mail text (see 18-00250 direct mail recruitment notification). Only the pIs, co-I's, and other research personnel listed on the study will have access to information regarding potential participants.

Interested parents/legal guardians will speak with study staff over the phone for the purpose of screening to determine basic inclusionary and exclusionary information prior to scheduling a screening visit. If the parent/legal guardian endorses any exclusionary criteria or fails to endorse

inclusionary criteria over the phone, then the study staff will inform them that the study would not be appropriate. If the parent/legal guardian does not endorse any exclusionary criteria and endorses all inclusionary criteria, then the study staff will schedule the screening visit. Of note, if the child does not qualify for the study as a result of pre-screening or the family decides not to proceed with the study after pre-screening, their data will be discarded and will not be used in this research. We aim to obtain complete datasets from at least 30 child and adolescent participants with HFA. To reach this number, we anticipate enrolling up to 50 children for in-person screening visits to assess variables related to inclusionary and exclusionary criteria. Approximately five children will be screened for eligibility to enter each cohort of size 3. Therefore, screening visits will be scheduled across time, as each prior cohort approaches participation completion.

We will recruit and include both males and females. The male to female prevalence ratio for ASD without intellectual disability is estimated at approximately 5:1 (10); therefore, we will aim to recruit at least 15% female participants (n=4 to enroll; n=8 to screen) by prioritizing prospective female participants. In regard to age, this study is intended to examine the CBD dose response in a child and adolescent population. Therefore, youth aged 7 years to before their 18th birthday at the time of projected end of the trial will be recruited to participate. We aim to recruit participants across this age range to ensure representation of developmental stages. Finally, individuals of all races and ethnic origins are eligible for participation in this study. Based upon the demographics of prior ASD study samples at the NYU Child Study Center, we expect approximately 15% of participants to self-identify as Hispanic/Latino, and racial composition of participants to be approximately 64% Caucasian, 20% African American or Black, 4% Asian, 1% Native Hawaiian or Other Pacific Islander, <1% American Indian, and 10% more than one race.

This trial focuses on children and adolescents with HFA because of the greater potential for benefit in ASD core and associated symptoms in children and adolescents than in adults, balanced with the relatively low AE profile of CBD. The lower age limit is defined by feasibility of obtaining cooperation for extensive study procedures. In compliance with IRB standards for research with vulnerable populations, a description of risks and benefits is included in the protocol. We will not enroll emancipated minors or mature minors and will therefore require written consent by a parent or legal guardian as well as child assent, in accordance with IRB regulation.

Parents/guardians of participants will be compensated for study participation, subject to IRB approval, at the rate of $75/visit for the enrollment/baseline, week-4 and final visits, and $40/visit for the other two visits. If they agree to participate in optional MRI scanning, they will also be compensated $75 for each scan. A $10 stipend will also be provided for visits that include blood draws and MRI scans (e.g., Screening Visit, Baseline Visit, Week-4 Visit if indicated, Week-6 Visit) to cover any additional travel expenses. This practice is standard for research projects which require substantial effort, and serves to distinguish research from standard clinical practice.

In addition to compensation and because the study will occur across approximately 10 weeks, participants will receive visit reminders to enhance participant retention. Further, multiple methods including telephone calls and secure email will be used for contacting participants throughout the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Pure CBD is extracted from the plant *Cannabis sativa*. The most common elements for potential therapeutic use extracted from this plant include Δ^9-THC and CBD. Tetrahydrocannabinol (THC) is the main psychoactive element found in *Cannabis sativa*, while CBD has **no psychoactive properties**. Pure CBD can be found as a white crystalline solid. Figure 1 shows its chemical structure.

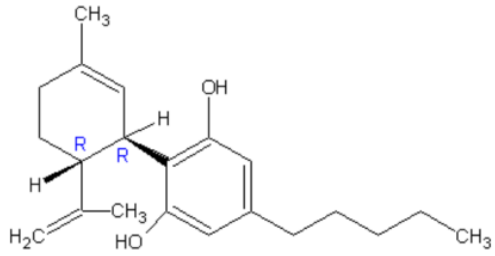

Figure 1. Cannabidiol Structure

The CBD will be Greenwich Biosciences, Inc.'s formulation of 100 mg/mL purified oral solution, dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. The drug is formulated from extracts prepared from Cannabis sativa L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (>95%) CBD that typically contains less than 0.5% (w/w) THC.

Cannabidiol is excreted in the urine and feces. The plasma peaks vary significantly between individuals but are typically between 1 to 3 hours (52). The half-life has been reported to be 2-5 days (64).

6.1.2 DOSING AND ADMINISTRATION

In regard to drug administration, participants will be required to take Epidiolex with food. Of note, symptoms of food selectivity and food refusal are seen frequently in ASD (65). Therefore, if caregivers report that their child has initial difficulties accepting the CBD, the study clinicians will work on increasing participant tolerance and acceptance of the CBD through the use of standard behavioral intervention strategies for up to one week. If the participant continues to reject the dose he/she was assigned after one week of trial initiation, he/she will be withdrawn from the study.

Related to dosing, in Part 1 of the study, we employed the BOIN design (66, 67) in the first five cohorts of this open trial to estimate the optimal dose. The BOIN design was selected because it is more flexible than the traditional 3+3 design and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (68).

We defined a target response rate for the optimal dose is $\phi = 0.60$ and a maximum sample size of 30. We enrolled and treated participants in cohorts of size 3. The trial design was implemented through the following three steps:

1. Participants in the first cohort were treated at Dose Level 2 (see Table 1).
2. To assign a dose to the next cohort of participants, we conducted dose escalation/de-escalation according to the rule displayed in Table 2, which minimizes the probability of incorrect dose assignment with response rates of $\phi_1 = 0.684$ and $\phi_2 = 0.52$ designated as the uncertainty interval. When using Table 2, please note the following:
    a. "Eliminate" means that we eliminate the current dose from the trial to prevent treating any future participants at this dose because the response rate is too low.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level.
    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new participants at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose.
    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose.
3. Repeat step 2 until the maximum sample size of 30 is reached.

Table 1. Dose levels

Dose Level 1	Dose Level 2	Dose Level 3
3 mg/kg/day	6 mg/kg/day	9 mg/kg/day

Table 2. Dose escalation/de-escalation/elimination rules for the BOIN Design and results in the first 5 cohorts

Cohort	1	2	3	4	5	6	7	8	9	10
Number of participants treated at the current dose	3	6	9	12	15	18	21	24	27	30
Dose administered (mg/kg/d)	6	6	3	3	6	-	-	-	-	-
Cumulative N of respondents	1	3	4	4	5	-	-	-	-	-
Escalate if # of responses >=	3	5	7	9	11	13	15	17	19	21
Deescalate if # of responses <=	NA	3	4	6	7	9	10	12	14	15
Eliminate if # of responses <=	NA	1	2	4	5	7	8	10	12	13

For purposes of the study design, participants were categorized as either “responders” or “non-responders” at the end of the 6-week intervention phase in order to determine the dose level for the following cohort. This categorization was based upon the following procedures.

- After completing and meeting eligibility criteria, study staff (including child psychologists and psychiatrists with expertise in ASD and comorbid symptoms) met to consensus on an individualized, primary outcome variable for each participant at the enrollment/baseline visit. The primary target was what is most interfering in the child’s functioning at the time of assessment and chosen based upon informant report, scores from a battery of standardized assessments covering a wide range of core and associated symptom

domains, and clinical observations. Clinician consensus also yielded a Clinical Global Impression-Severity (CGI-S) score to represent the study team's impression of the participant's current severity of illness.

- After the final study visit, study staff met again to consensus on the degree of improvement observed in the predetermined primary outcome variable for each child. A CGI-S score was also determined. Definitions of response and non-response are provided below.
  - Response: In the absence of dose limiting effects, a Clinical Global Impression Scale – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) determined by consensus based upon clinical judgment, informant report, and change in scores on measures (using the Reliable Change Index when possible) relevant to the predetermined primary outcome.
  - Non-response: no-to-minimal therapeutic benefit captured by a CGI-I score of 3 (minimally improved) or greater (i.e., no change or any worsening) determined by consensus as indicated above, and/or severe AE, defined as severe cognitive or behavioral toxicity, impaired liver and renal function, or impaired hematopoiesis that is deemed to be potentially or likely related to study medication (also see section 8.3.2), causing early discontinuation of study intervention.

While applying a uniform statistically derived algorithm for defining treatment response and non-response for all patients would have been preferable, the above procedures were implemented given the exploratory nature of the study and the wide range of therapeutic effects that CBD may exert. The intent of this exploratory study has been to provide the foundation for a well-defined subsequent RCT.

Over the first 15 participants, we have identified five as responders, for an overall response rate of 33%, and a response rate of 4/9 = 44% on 6 mg/kg/day, as opposed to the 60% rate anticipated on the optimal dose. The response rate on 3 mg/kg/day was 1/6 = 16%. Per the BOIN design that we implemented, we have excluded both the 6 mg/kg/day and 3 mg/kg/day dose for further testing. We believe that it would be scientifically valuable to test the 9 mg/kg/day dose on the remaining 15 participants that were originally approved for this open trial. The purpose would be to further confirm the overall safety of the AE profile – which is likely given the pediatric experience with 10 mg/kg/day and 20 mg/kg/day in patients with refractory epilepsy who are more medically fragile. It has also been hypothesized that higher doses of CBD may have preferential effects on $D2_{high}$ receptors in the striatum. If so, that might explain why all five responders had ASD, as well as ADHD.

Accordingly, we now request that we amend the open trial to test only the dose of 9 mg/kg/day and that we require the combination of ASD and ADHD for inclusion. All other aspects of the trial would be unchanged, other than adding the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior (SWAN) as a dimensional measure of ADHD and completing the K-SADS-COMP at the screening visit rather than the baseline/enrollment visit so that the study clinicians can confirm the presence of an ADHD diagnosis.

Given our experience with the first 15 participants, we anticipate that at least 1/3 will be classified as responders. If none of the first 6 participants on 9 mg/kg/day are responders, then we would eliminate the dose and terminate the trial. A low, non-zero response rate, as shown below in Table 3, would also determine terminating the trial, as it would be tantamount to evidence that the optimal dose was 6 mg/kg/day, our initial starting dose.

Table 3. Dose elimination rules for cohorts 6 to 10

Cohort	1	2	3	4	5	6	7	8	9	10
Number of participants to be treated at the current dose	3	6	9	12	15	18	21	24	27	30
Dose administered (mg/kg/d)	6	6	3	3	6	9	9	9	9	9
Cumulative N of respondents	1	3	4	4	5	-	-	-	-	-
Terminate if # of responses <=						NA	5	6	7	

Thus, we propose to enroll at least six more participants on the dose of 9 mg/kg/day. If none of them respond, the cumulative number of respondents would remain 5, and we will discontinue the trial; if at least 1 responds within the first 6, we will enroll 3 additional participants. If the total number of responders remains 6, we will discontinue the trial. If the number of responders is 7 or more after 9 participants are enrolled, we will enroll an additional 3 participants for a total of 12 on this dose. If the number of responders does not increase beyond a total of 7, we will terminate due to likely futility.

Table 4 provides the operating characteristics of this design extension for a variety of true response rates.

Table 4. Operating characteristics of 9 mg/kg/day evaluation

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
True response rate	0.1	0.2	0.3	0.4	0.5
Probability of early termination(%)	90.4	60.8	31.0	11.9	3.5

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The drug will be shipped to the responsible person, such as the PI, who will check the amount received and the condition of the drug. Details of the drug received will be recorded in an accountability record. We will acknowledge drug receipt to Greenwich Biosciences, Inc. and will complete any receipt forms required. As directed in the investigational brochure, all supplies, including unused, partially used, or empty containers, will be returned to Greenwich Biosciences, Inc. or destroyed at the center if agreed in writing by the study monitor.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The CBD will be packaged as Epidiolex (V), 100mg/mL oral solution in a 100 mL bottle. Each bottle of 100mg/mL solution will contain 100 mL of oral CBD solution. The CBD will be shipped in separate subject-specific boxes from Greenwich Biosciences, Inc. The subject drug kits will contain a 100mL amber glass bottle of 100 mg/mL CBD in sesame oil vehicle with sucralose sweetener and strawberry flavoring. The bottle will have a child-resistant cap. The bottles will be in a white cardboard carton with cardboard insert. The outer sides of carton will bear a label with appropriate instructions. The box will also contain a graduated oral syringe for accurate dosing administration and a patient information leaflet. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling.

6.2.3 PRODUCT STORAGE AND STABILITY

The CBD will be stored in a locked file-cabinet inside a locked office at room temperature. The CBD must be stored in temperatures less than 30°C, with limited access to light.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to protocol will be assessed by requiring a participant drug log in which dose and time of administration will be recorded by the parent/guardian.

6.5 CONCOMITANT THERAPY

For this protocol, concomitant pharmacologic, educational, behavioral, and/or dietary therapies will be reviewed at each contact. Concomitant therapies will be reported in the Case Report Form (CRF). The subjects will be asked to continue any non-exclusionary psychopharmacologic (i.e., stimulant such as methylphenidate), educational, behavioral, and/or dietary interventions that were stable for 4 weeks prior to initiation of trial and to maintain them stable through the trial. Change in outside therapy, including pharmacological treatment, could skew results. Any participant who experiences a change of services (other than those associated with school holidays) will be withdrawn from the study as per the PI.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

A participant may be discontinued from the study intervention at any time if the participant or participant's legal guardian or the investigator feels that it is not in the participant's best interest to

continue. Study intervention may be discontinued following parental withdrawal of consent, failure to remain compliant with study procedures, protocol violation requiring discontinuation, or SAE. If a participant must discontinue the study treatment, the method of CBD discontinuation will be determined based on type of reaction and/or reason for withdrawal. For example, if the participant experiences a rapidly progressive rash it would lead to abrupt cessation of CBD, but if participant experiences excess tiredness, CBD would be tapered off. A discussion of the method of cessation will occur between the participant and/or participant's parent/legal guardian and the physician.

If a participant requires discontinuation of CBD due to AEs, the participant will be considered a "non-responder." Participants who are discontinued from study intervention will receive the 3-month follow-up telephone call to gather descriptive information about current functioning and treatment choice.

While there will be no temporary discontinuations on the basis of AE, participants may experience a temporary discontinuation if a follow-up session is not attended within the +/- 3 day timeframe. In this case, the investigator will determine how to proceed based on report of effects and AEs, and results from safety assessments. If all variables indicate good tolerability, continuation will occur. The participant's participation in the trial will be extended by one week to ensure that data has been collected across three time points after enrollment/baseline. If AE is a concern, the investigator will determine if any change in participant management is needed.

The data to be collected at the time of study intervention discontinuation will include the following:

- Physical exam and vital signs
- Clinical labs (i.e., test of hepatic and hematological function including total bilirubin; plasma for CBD levels)
- AE review and evaluation
- MRI
- Standardized measures of symptom improvement (i.e., ABC, ADAMS, ASC-ASD-Child, ASC-ASD-Parent, AFEQ, BIS, CGI-I, CGI-S, HSQ-ASD, OSU Autism CGI-I, OSU Autism CGI-S, RBS-R, SCARED, SDSC, SRS-2, SWAN [Part 2], Vineland-3)

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may be discontinued from study treatment at any time if the participant or participant's legal guardian or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Parental/guardian withdrawal of consent
- Subject is not compliant with study procedures
- Protocol violation requiring discontinuation of study treatment
- SAE, including significant toxicity such as severe cognitive or behavioral toxicity, impaired liver function, or impaired hematopoiesis that is deemed to be potentially or likely related to study medication

If subject must come off of study treatment, the method of CBD discontinuation will be determined based on type of reaction and/or reason for withdrawal. For example, if the participant experiences a rapidly progressive rash it would lead to abrupt cessation of CBD, but if participant experiences excess tiredness, CBD would be tapered off. A discussion of the method of cessation will occur between the participant and/or participant's parent/legal guardian and the physician.

Subjects for whom a parent/guardian has signed the informed consent form, who have received the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 or more scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within a week +/- 3 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, secure email, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Primary Endpoint

Treatment response will be determined according to the Clinical Global Impression Scale – Improvement (CGI-I), based upon clinical judgment and scores from relevant measures within the Secondary Endpoints subsection:

- Clinical Global Impression Scale – Improvement (CGI-I): The CGI-I is a clinician rated global measure of improvement and is made up of a 7-point scale where: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse (69). The CGI-I has been used as an outcome measure in multiple clinical psychopharmacology trials and will be completed through expert consensus, including a team of child psychologists and psychiatrists with expertise in ASD, based upon scores from relevant measures and clinical judgment. This will be completed at the final study visit (Week 6).

Secondary Endpoints – Symptom Measurement

Autism Measures

- Behavioral Inflexibility Scale (BIS): The BIS is a newly developed parent-report measure designed to assess rigid patterns of behavior, commonly associated with ASD, in children and adolescents 3-18 years of age. The BIS includes 38 items rated on a 6-point Likert scale where 0=Not at all a problem and 5=Very severe or extreme problem. Psychometric properties resulting from initial evaluations of the measure are strong (70). The BIS will be completed by caregivers at the enrollment/baseline visit (or at the screening visit), at the final study visit (Week 6), and 6 weeks after medication discontinuation (optional).

- OSU Autism Clinical Global Impression-Severity and Improvement Subscales: The OSU Autism CGI-Severity and Improvement scales are adapted versions of the classic CGI-S and CGI-I developed by the OSU Research Unit on Pediatric Psychopharmacology (RUPP) to better account for autism symptoms in clinician ratings. The indications are more directly and specifically related to ASD compared to those in the CGI. Importantly, the OSU Autism CGI has been found reliable when used by experienced clinicians (73). The OSU Autism CGI-S will be completed by the research team at the enrollment/baseline visit and final visit (Week 6) to obtain an estimate of severity of ASD symptoms. The OSU Autism CGI-I will be completed in the final visit (Week 6) by the research team to quantify improvement in core ASD symptoms only. These uses are differentiated from our use of the CGI-S and the CGI-I in the current study, as both the CGI-S and CGI-I will be used to assign ratings to each participant's individualized target symptom domain whereas the OSU Autism CGI-S and OSU Autism CGI-I ratings will relate to ASD symptoms only.
- Repetitive Behavior Scale-Revised (RBS-R): The RBS-R is a questionnaire used to measure the range of RRBs expressed by individuals with ASD. The RBS-R consists of six subscales covering a range of RRB subtypes including: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Routine Behavior, Sameness Behavior, and Restricted Behavior. The subscales have no overlap of item content, permitting differential identification and scoring of discrete varieties of RRB. The presence and frequency of behaviors are rated on a 4-point scale (ranging from 0=behavior does not occur to 3=behavior occurs and is a severe problem) (74-76). The RBS-R will be completed by caregivers at the enrollment/baseline visit (or at the screening visit), at the final study visit (Week 6), and 6 weeks after medication discontinuation (optional), and takes approximately 20 minutes to complete.
- Social Responsiveness Scale, 2nd Edition (SRS-2), School-Age Form: The SRS-2 is a measure of social impairment related to ASD in children aged 4 to 18 years old. Five domains are assessed including: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior. Items are scored on a 4-point scale (ranging from 1=not true to 4=almost always true). Excellent psychometric properties have been previously established for the SRS for use in children and adults (77, 78). The SRS-2 will be administered at screening and at the final study visit (Week 6), and 6 weeks after medication discontinuation (optional). The SRS-2 takes approximately 20 minutes to complete.

Measures of Associated Symptoms

- Aberrant Behavior Checklist (ABC) – Irritability and Social Withdrawal Subscales: The ABC was designed to measure behavior problems in individuals with developmental disabilities and ASD through informant report. The subscales of the ABC include: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech. Items are rated on a 4-point scale (ranging from 0=no problem at all to 3 = problem is severe in degree) (79-81). The ABC has been used in multiple ASD trials to measure changes in irritability and social withdrawal, with success. It will be completed by caregivers at the enrollment/baseline visit (or at the screening visit), the final study visit (Week 6), and 6 weeks after medication discontinuation (optional), and takes approximately 20 minutes to complete.
- Anxiety, Depression and Mood Scale (ADAMS): The ADAMS was developed to provide a psychometrically sound instrument for quantifying anxiety, depression and mood disorders among individuals with intellectual disabilities above age 10 (82). It contains 55 symptom items that resolve into five subscales labeled: Manic/Hyperactive Behavior, Depressed Mood, Social Avoidance, General Anxiety, and Compulsive Behavior. The ADAMS total score was the top-line outcome measure in the previously mentioned pilot trial of CBD in FXS. The ADAMS will be administered at the enrollment/baseline visit (or at the screening visit), at the final

study visit (Week 6), and 6 weeks after medication discontinuation (optional). It takes approximately 10 minutes to complete.

- Anxiety Scale for Children – Autism Spectrum Disorder – Child and Parent versions (ASC-ASD): The ASD-ASD was developed as the first anxiety measure specifically designed to detect symptoms in youth with ASD. Psychometrics of this new measure are promising (83). Both the parent and child versions are 24 items in length, making up four subscales: Performance Anxiety, Uncertainty, Anxious Arousal, and Separation Anxiety. The ASC-ASD-Parent and the ASC-ASD-Child will be administered at the enrollment/baseline visit (or at the screening visit) and final visit (Week 6) and both take approximately 15 minutes to complete. The ASC-ASD-Parent will also be administered 6 weeks after medication discontinuation (optional).
- Computerized Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-COMP): The KSADS-COMP is a DSM-5 based instrument administered by a secure web-based computer program to parents/guardians derived from the KSADS (85). The responses and the algorithmically determined presumptive diagnoses are then immediately provided for follow-up and clarification, as needed, by a licensed clinician. The KSADS-COMP will be used in the current study to allow for further clinical characterization of the sample and will be administered to caregivers online at the enrollment/baseline visit (or at the screening visit). In Part 2 of the trial, the K-SADS-COMP will be administered at the screening visit and will also be used to confirm the presence of an ADHD diagnosis.
- Home Situations Questionnaire – Modified for ASD (HSQ-ASD): The HSQ-ASD is a 24-item questionnaire that measures behavioral noncompliance in everyday settings for children with ASD (86). The HSQ-ASD is a modified version of the HSQ (87), a measure that was initially designed for assessing noncompliance in children with disruptive behavior disorders. In its modified form, the HSQ-ASD includes an additional 7 items that address a broader range of situations in which children with ASD may display noncompliance and consists of two 12-item factors: Socially Inflexible and Demand Specific. To complete the form, caregivers indicate whether the child has a problem with compliance in each situation and, if so, to rate the severity of non-compliance on a 1–9 Likert scale. Higher scores indicate greater non-compliance. The HSQ-ASD will be completed by caregivers at the enrollment/baseline visit (or at the screening visit) and the final study visit (Week 6), and 6 weeks after medication discontinuation (optional), and takes approximately 10 minutes to complete.
- Screen for Child Anxiety Related Disorders (SCARED), Parent Version: The SCARED, Parent Version is a parent report measure with strong psychometrics developed to measure child anxiety symptoms. Subscales include Somatic Symptoms/Panic Disorder, Generalized Anxiety Disorder, Separation Anxiety, Social Phobia, and School Phobia. Research exists demonstrating the utility of the SCARED for assessing anxiety in the ASD population (88). The SCARED, Parent Version takes approximately 10 minutes to complete and will be administered to parents/guardians at the enrollment/baseline visit (or at the screening visit), at the final study visit (Week 6), and 6 weeks after medication discontinuation (optional).
- The Sleep Disturbance Scale for Children (SDSC): The SDSC is an informant-report measure designed to assess the most common areas of sleep disorders in childhood and adolescence (89). The SDSC has six subscales including Disorders of Initiating and Maintaining Sleep, Sleep Breathing Disorders, Disorders of Arousal, Sleep Wake Transition Disorders, Disorders of Excessive Somnolence, and Sleep Hyperhydrosis. The SDSC takes approximately 10–15 minutes to complete and will be administered to caregivers of participants at the enrollment/baseline visit (or at the screening visit) and at the final study visit (Week 6), and 6 weeks after medication discontinuation (optional).

- Strengths and Weakness of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN): The SWAN is a parent report measure designed to assess symptoms of ADHD in children and adolescents. The SWAN consists of 18 items that make up two subscales (i.e., ADHD-Inattentive and ADHD-Hyperactive/Impulsive). The SWAN takes approximately 10 minutes to complete and will be administered to caregivers at the baseline/enrollment visit (or at the screening visit) and the final study visit (Week 6) and 6 weeks after medication discontinuation (optional) during Part 2 of the trial.
- Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), Parent/Caregiver Form: The Vineland-3 is frequently used to measure adaptive functioning across the areas of communication, daily living skills, socialization, motor skills, and maladaptive behavior (90). The Parent/Caregiver form is an informant-based questionnaire assessing three core domains (i.e., Communication, Daily Living Skills, and Socialization) and two optional domains (i.e., Motor Skills and Maladaptive Behavior). The core domains sum to a total Adaptive Behavior Composite. The Vineland-3 Parent/Caregiver Form was designed to assess the functioning of individuals 3 years of age or older and takes approximately 15 minutes to complete. The Vineland-3 will be administered at the baseline/enrollment visit (or at the screening visit) and the final visit. Because "high functioning autism" is often a misnomer, in that children with ASD with average to above average IQ and language skills often experience substantial functional impairments (96), the Vineland-3 will provide further characterization of the sample in addition to serving as an outcome measure.

General Functioning

- Autism Family Experience Questionnaire (AFEQ): The AFEQ was developed to measure the impact of autism interventions on family experience and quality of life. Recent research on the AFEQ demonstrated the measure was sensitive to change in response to intervention in young children with ASD (91). The measure includes 48 items that make up four domains: Parent, Family, Child Development, and Child Symptoms. Ratings on each item can also be summed to equal a total score. The AFEQ will be administered to parents at the enrollment/baseline visit (or at the screening visit) and at the final visit (Week 6) and takes about 15 minutes to complete.
- Clinical Global Impression-Severity (CGI-S): The CGI-S reflects clinician impression of the participant's current severity of illness on a 7-point scale ranging from 1=not at all ill to 7=among the most extremely ill (69). The CGI-S will be completed by the evaluating clinician at the screening visit, and by clinician consensus at the enrollment/baseline visit and the final study visit (Week 6).

Given the extent of the information we are requesting from caregivers, rating scales will be available to complete online from home during the time period between the screening and enrollment/baseline visits, and in the sixth week of treatment up until the final study visit. Caregivers can choose to complete these forms in the clinic or online. Caregivers can choose to complete these forms prior to their child being found eligible for participation, in the case the additional time makes completion of the measures more feasible for the caregiver and scheduling of subsequent visits more efficient. An eligible child will not be administered the study drug until all forms are submitted. If the caregiver does not complete the forms prior to coming to the final study visit, all forms must be completed at the clinic during that visit.

8.2 SAFETY AND OTHER ASSESSMENTS

Prior to the in-person portions of the screening visit, patients and caregivers will be consented and an interview will be conducted regarding medical, psychiatric, and treatment history relevant to the

exclusionary criteria virtually over WebEx. If families prefer to do the full visit in person, parents/guardians will then be set up in a room to complete necessary parent-report measures. Otherwise, they will be instructed to complete these online. Child testing will be conducted. The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) or Childhood Autism Rating Scale, 2nd Edition, High Functioning version (CARS-2-HF) will be administered to ensure patients meet inclusionary criteria for ASD symptom score, language requirements, and IQ. The CGI-S will be completed by the evaluating clinician. These tests are discussed below.

Screening measures

- Autism Diagnostic Observation Schedule – 2 (ADOS-2): The ADOS-2 is a diagnostic tool used to document the presence of ASD. During a semi-structured evaluation, the individual is observed in a naturalistic social situation and assessed across areas of social communication, imagination, and RRBs. The ADOS includes four modules for use with different age groups and language levels; Modules 3 or 4 will be used in this study. The appropriate module of the ADOS will be administered by a certified rater at screening (92, 93). If the potential participant has been administered the ADOS assessment in the past and results are documented, given the substantial stability in ADOS scores across time, there will be no requirement to repeat it. The ADOS-2 takes approximately 45 minutes to complete and will only occur at the screening visit. Total scores must be at or above 7 to participate in the study.
- Autism Symptom Interview (ASI): The ASI is a brief interview derived from the Autism Diagnostic Interview-Revised (ADI-R); the ASI offers improved efficiency while maintaining sound psychometric properties (94). The ASI takes approximately 45 minutes and includes questions about current and past symptoms consistent with ASD. The ASI will be used in conjunction with other interviews, scores from the ADOS-2 and SRS-2, and clinical judgment to confirm ASD diagnoses by the DSM-5 diagnostic criteria at the screening visit.
- Childhood Autism Rating Scale, 2nd Edition, High Functioning (CARS-2-HF): The CARS-2-HF is similar to the ADOS and is a commonly used diagnostic tool to document the presence of ASD in children and adolescents over the age of 6 with broadly average IQ and verbal language. Because the ADOS cannot be administered validly over WebEx or when wearing personal protective equipment, we will administer the CARS-2-HF to participants that do not have documentation of a previous ADOS assessment. The CARS offers more flexibility than the ADOS, as the ADOS requires standardized materials and scripted activities. The psychologists on the team were trained by the developers of the CARS on virtual administration of the instrument, and activities completed within the CARS were adapted, so that administration is similar across participants and clinicians. Participants must score in the mild-to-moderate or severe symptoms of ASD range.
- Computerized Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-COMP): As described above, in Part 2 of the trial, the K-SADS-COMP will be administered at the screening visit and will also be used to confirm the presence of an ADHD diagnosis.
- Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II): The WASI-II was designed to swiftly and accurately assess cognitive functioning and has strong psychometric properties (95).The WASI-II, Two-Subtest Form will be administered in this study to obtain data on intellectual ability. This form consists of two subtests (i.e., Vocabulary and Matrix Reasoning) and takes approximately 10-20 minutes to complete. This will only be completed at screening. Estimated IQ must be at or above 80 to participate in the trial. As with the ADOS-2, the WASI-II will not be administered if a reliable and valid IQ assessment was performed by a qualified

professional and was documented within the previous 3 years of the screening visit or when the child was 6 years of age or older.

- Clinical Global Impression-Severity (CGI-S): Information regarding the CGI-S is provided within Section 8.1 Secondary Study Endpoints. Within the screening visit, patients must receive a rating of 4 (Moderately Ill) or higher on the CGI-S to participate in the trial.
- Social Responsiveness Scale, 2nd Edition (SRS-2), School-Age Form: Information regarding the SRS-2 is provided within Section 8.1 Secondary Study Endpoints. Patients must receive a total T-score of 66 to meet inclusionary criteria for participation in the study.

Further, in the case of virtual visits for participants who do not have prior documentation of an ADOS assessment, because confirming a diagnosis of ASD virtually is understudied, we will follow up cases for which clinicians report substantial uncertainty by administering a complete Autism Diagnostic Interview-Revised (ADI-R), the gold standard interview instrument for ASD that takes 1-3 hours to administer.

Following the child testing, the clinician will score the child and parent measures to determine if benchmarks for eligibility were met. If participants continue to be eligible for participation, a medical exam will be conducted. Patients will receive a brief physical exam, vital sign assessment, a blood draw, a urine drug screen, and, if female, a pregnancy test to further evaluate eligibility criteria. In the case of virtual visits, the urine drug screen and pregnancy test if applicable will be mailed to participating families and we will ask parents to collect urine and then test the urine over WebEx with a study team member "assisting" virtually. We will also accept a note from the child's pediatrician reporting that the child is in good health and is medically cleared to participate, rather than requiring a separate in-person physical exam. We will not collect vital signs during these virtual visits, as we did not detect any differences in heart rate or blood pressure in response to CBD administration in the first cohort of participants. We have also not noted any reports in the literature on such effects. To participate in the study, patients' vital signs and results from their tests of hepatic and hematologic function must be within the normal range for their age. Specifically, patients with baseline elevations greater than 3 times the upper limit of normal (UNL) in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) or elevations of total bilirubin greater than 2 times the ULN will be excluded. Patients will be excluded if they have a positive urine sample results from drug screening indicating presence of THC, opiates, methamphetamine or cocaine. Patients will also be excluded if pregnant. See table listing screening visit below.

Tasks	**Assessments**	**Inclusionary/Exclusionary Criteria**
Gather history	Medical History	☒ History of active seizure disorder/epilepsy ☒ Known genetic disorder ☒ Diagnosis of Rett syndrome or Childhood Disintegrative Disorder ☒ Marked sensory impairment (e.g., blindness, hearing impairment) ☒ Pregnant or lactating ☒ Current use of medications metabolized primarily by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP2D6 isoenzymes ☒ Refusal to remain abstinent or use contraception
	Psychiatric History	☒ Current psychiatric diagnosis of bipolar disorder, MDD, psychosis, schizophrenia, PTSD or active suicidality (ideation and plan)

		☒ History of drug abuse in the past 3 months
	Treatment History	☑ Stable interventions (i.e., allied health therapies, behavioral, educational, non-exclusionary antidepressant or stimulant medication/dosing of medication) for 4 weeks prior to randomization/for the duration of the study ☒ Prior treatment with CBD or an endocannabinoid treatment ☒ Current treatment with valproate or clobazam or other antiepileptic medication ☒ Exposure to investigational agent in 30 days prior to randomizations
Developmental and Psychiatric Evaluation	WASI-II	☑ Estimated IQ ≥ 80
	ADOS-2	☑ Qualify for administration of Module 3 or Module 4 (Indicating presence of fluent speech) ☑ Meets or exceeds autism spectrum cutoff on ADOS or CARS-2-HF
	SRS-2	☑ Total T-score ≥ 66
	CGI-S	☑ Score ≥ 4
	K-SADS-COMP (Part 2)	☑ Presence of ADHD diagnosis confirmed by clinician review of K-SADS-COMP results
Medical Examination	Physical Exam (Vital Signs, Height, Weight)	☑ Personal physician provides documentation indicating the participant is in good health to participate in the trial or physical exam results within normal limits or results of physical exam conducted by study PI within normal limits ☑ AST, ALT are less than 3 times the ULN and total bilirubin is less than 2 times ULN
	Clinical Labs	☑ Results that are within normal range for age
	Drug screen	☒ Positive urine sample results from drug screening indicating presence of: THC, opiates, methamphetamine or cocaine
	Pregnancy test	☒ Positive results of pregnancy test

Patients' parents/guardians will be notified about eligibility for the study and enrollment procedures within about 1 week following the receipt of all measures. As mentioned, patients will be screened at different times according to each cohort start date. We estimate screening approximately 5 children at a time to secure a cohort of size 3. After a patient is found eligible, the enrollment/baseline visit will be scheduled in accordance with the availability of cohort "slots" and family availability. If more than 8 weeks elapses following their screening visit, we will confirm continued eligibility by scheduling a telephone appointment. This provision for the possibility of extended time allows for an eligible participant to be assigned to a cohort that follows the one they were screened for. This will be important in the case that 5 children were screened for a cohort (as described) but more than 3 were eligible. It could also come into play when the family's anticipated schedule will conflict with trial attendance requirements. A cohort does not need to participate in the trial simultaneously. One or two

children within a cohort of size 3 could begin the trial without all three participants in the cohort having been recruited. This will minimize asking families to defer changes in treatment while waiting for a cohort to be established. Decisions regarding termination or continuation of Part 2 of the trial will still depend on the result of each three participant cohort, even if not performed contemporaneously.

Through the trial, safety will be assessed regularly using the assessment strategies listed below.

Safety assessment

- Brief physical examination (e.g., height and weight) to be completed at screening and Week 6. To minimize the time spent in in-person visits given the risks presented by COVID-19, and allow families the option to complete as much as possible virtually, we will accept documentation from the participant's physician stating that the participant is in good health to participate in the trial to replace the physical exam at screening. The Week 6 physical examination will be conducted by the study team.
- Vital signs (e.g., temperature, pulse, respirations, blood pressure) to be completed at each in-person visit. We will not collect vital signs during virtual visits (e.g., screening, Week 2, Week 4), as we did not detect any differences in heart rate or blood pressure in response to CBD administration in the first cohort of participants. We have also not noted any reports in the literature on such effects. Vital signs will be collected at baseline/enrollment and Week 6 visits.
- Test of hepatic and hematological function to be completed at screening, Week 4 and Week 6. To reduce in-person visits, we will make decisions regarding the necessity of a Week 4 blood draw on an individual basis. If a subject's baseline blood draw suggests borderline clinical abnormalities (that did not meet the cutoff for exclusion), they will be required to complete a Week 4 blood draw at the outpatient lab out of an abundance of caution. Otherwise, blood draws will be limited to two – one at baseline and one at the final visit (Week 6) – rather than three.
- Plasma for quantifying CBD levels to be completed at Weeks 6.
- AE report: UKU Side Effects Rating Scale – Patient Version (97) to be completed by parent/guardian at the Week 2, Week 4, and Week 6 visits. The participant will also be involved in these interviews when appropriate. Each UKU Side Effects Rating Scale will be reviewed by the PI. Symptoms of possible hepatic injury (i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever or rash) will be specifically queried.
- Columbia-Suicide Severity Rating Scale (98) to be completed by the participant at screening, baseline/enrollment, Week 2, Week 4, and Week 6 visits and reviewed by the PI. The C-SSRS is a brief assessment of suicidal ideation and behavior validated for use across the lifespan; the C-SSRS maintains strong psychometric properties (98). Screening for suicidality is necessary given that Epidiolex is classified within the anti-epileptic drug (AED) class, and AEDs have been shown to increase the risk of suicidal thoughts or behavior.

Exploratory endpoints

To examine potential underlying brain mechanisms related to CBD, the proposed study will use MRI to inform the feasibility of incorporating biomarkers (e.g., resting-state functional connectivity) in our future studies and potentially yield testable hypotheses.

During the screening visit, to effectively acclimate the child to the MR environment, we use an MR simulator. Habituating children in an MRI simulator minimizes data loss, which is pivotal for obtaining high-quality longitudinal and pre-/post-intervention brain scans. A Social Story will be read aloud to

prepare the child for the scanning experience. Our team has a long track-record of obtaining high-quality imaging data in neurodevelopmental disorders, including ADHD and autism, with children as young as 5 years old.

Following the mock scan, a scan will be scheduled for the Baseline visit. Imaging will be performed using scanning equipment which have been FDA-approved for clinical and research scans as minimal risk devices. No exogenous contrast agent will be used in any imaging sequence. At the beginning of the scan session, participants will be familiarized with the scanning environment and the research team, while the imaging procedures are being carefully explained. The Social Story will be read aloud again. The research staff will conduct a metal screening interview with the parent(s) to ensure MRI safety and will use a hand-held metal detector to search for any metal on the participant (and the parent, if they plan on entering the scanner suite while the child is being set-up). Additionally, female participants who have begun menstruation will be instructed to take a urine pregnancy test to ensure lack of pregnancy. If there are no contraindications, participants will be brought into the MRI room. The research staff will place earplugs, headphones, pneumatic belt, and finger transducer on the child and have them lay down on the scanner table. The participant will be positioned on their back on the scanner gantry with head straight aligned with the middle of the coil. The radio frequency imaging coil, which obtains the imaging data, will be positioned in front of the child's face. All participants will be asked to limit head motion. Foam padding will be used for comfort and to comfortably restrict head motion. Once the child is comfortable, we will slide the scanner table into the magnet and begin scanning. Between each scan, the child will be in contact with the research staff through a microphone mounted in the MRI scanner. While scanning is on, it gets loud, thus the speaker is turned off and we will not be able to hear the child. This is why the child will have a handheld squeeze-ball device to let the operator know if they wish to immediately stop scanning and be removed from the magnet. Upon being squeezed, the squeeze-ball emits a loud sound in the operator room to notify the research staff who will immediately stop the scan. We spend time during the mock MRI to instruct and coach the child of these procedures so they will be well prepared before the MRI scan.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the investigator it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE was expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The study clinician will immediately report to the IRB any adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Disease related events (DRE), such as behavioral disruptions (e.g., tantrums) will not be reported as AE, unless their severity or frequency far surpasses their prior levels.

All AEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

The investigator will be responsible for notifying the FDA of any unexpected or suspected severe adverse reaction as soon as possible, but in no case later than 7 calendar days after the investigator's initial receipt of the information. In addition, the investigator must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the investigator determines that the information qualifies for reporting.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the IRB any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

The investigator will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the investigator's initial receipt of the information. In addition, the investigator must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the investigator determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Parents/guardians will be informed about AEs and SAEs, and study-related results on an individual level. Similarly, parents/guardians will be informed of incidental findings that may emerge from study procedures. A summary of study participation will be provided at the conclusion of each participant's treatment, including any incidental findings of clinical relevance. Parents/guardians will be given the opportunity to discuss any such results directly with the investigational team.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Because risks of CBD use in pregnancy are unknown, all participants are required to use abstinence or use a valid method of contraception to participate in the study. Menstruating females will undergo urine pregnancy tests at the screening visit to ensure participant safety. If a participant becomes pregnant during the study, she will immediately be discontinued from the medication. Participants who become pregnant during the study, or within 30 days after completing the study, will be followed throughout the course of the pregnancy for safety, with the participant's permission and that of her parent/guardian. Information about the risks of the pregnancy and the possible effects on the fetus will be provided to support an informed decision in cooperation with the treating physician and the obstetrician. Any spontaneous abortion will be classified as a serious adverse event. Pregnancy of a participant will be reported to study leadership and the IRB.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report UPs to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 14 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 30 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Parents/guardians will be informed any UPs on an individual level. Parents/guardians will be given the opportunity to discuss any concerns regarding UPs directly with the investigational team.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The hypothesis of this phase 2 open trial is that moderate doses of CBD may be therapeutically beneficial for core and/or associated symptoms in children and adolescents with ASD.

9.2 SAMPLE SIZE DETERMINATION

No statistical methods were used to determine the sample size for this study. The total number of participants expected to participate at NYU Child Study Center and Comprehensive Epilepsy Center is 30.

9.3 POPULATIONS FOR ANALYSES

Participants included within the analysis datasets include all participants in the trial, including both responders and non-responders, to examine efficacy at varying doses as well as safety and tolerability across the whole sample.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The primary aim of this study is to determine the optimal dose of CBD in children and adolescents with ASD. Therefore, to increase sensitivity in capturing a nonlinear dose response, we will employ the BOIN design as discussed above. After the trial is completed, we will select the optimal dose based on isotonic regression as specified in Liu and Yuan (66).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

We will select as the optimal dose the dose for which the isotonic estimate of the response rate is closest to the target response rate. If there are ties, we will select the higher dose level when the isotonic estimate is lower than the target response rate and we will select the lower dose level when the isotonic estimate is greater than or equal to the target response rate.

As mentioned, response rate will be determined by the proportion of participants classified as responders. A treatment response is defined as a CGI-I score of 1 or 2 on the individualized, predetermined primary outcome variable, whereas a nonresponse is a CGI-I score of 3 or greater. Scores on the CGI-I will be determined by clinician consensus.

Table 5 shows the operating characteristics of a 5-dose BOIN design based on 1000 simulations. The operating characteristics show that the design selects the true optimal dose, if any, with high probability and allocates more participants to the dose levels with the response rate closest to the target of 0.6. Please refer to Tables 3 and 4 for the design and statistical expectations relevant to Part 2 of the study.

Table 5. Operating characteristics of the BOIN design: Part 1

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	# of Participants	% Early Stopping
True Response Rate	0.4	0.5	0.6	0.55	0.45		
Selection %	17.1	9.3	21.8	22.0	1.7		28.1
# Participants treated	5.84	4.39	10.55	5.36	0.86	27	

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Our secondary objective is to quantify the effect size of changes in a wide range of candidate measures that may reveal response to CBD. Effect sizes and 95% confidence intervals will be reported for all measures obtained at enrollment/baseline and at the final visit (or last observation, in cases of early termination).

9.4.4 SAFETY ANALYSES

Safety endpoints will be analyzed as summary statistics during treatment and as change scores from baselines. Adverse events will be coded per the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be counted once only for a given participant. Adverse events will be presented in terms of severity, frequency, and relationship of AEs to study intervention by System Organ Class (SOC) and preferred term groupings. For each AE, start date, stop date, severity, relationship, expectedness, outcome, and duration will be reported. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table. The information included here should be consistent with the information contained within **Section 8.2, Safety and Other Assessments**.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The demographic characteristics and the baseline measurements of all participants will be summarized using standard descriptive statistics (e.g., means, medians, standard deviations, and ranges for continuous variables and frequencies for categorical variables).

9.4.6 PLANNED INTERIM ANALYSES

After each cohort completes participation in the 6-week treatment period, classification of participants as “responders” or “non-responders” will occur based upon the definitions provided above. The subsequent cohort will be administered the dose level indicated given the response of the previous cohorts.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

The objective of obtaining MRI data is to determine the feasibility of obtaining possible biomarkers of treatment response in children and adolescents with ASD and to conduct preliminary analyses, if sufficient data are collected. For all participants who agree to undergo MRI before and after treatment with Epidiolex, resting-state functional connectivity analyses will be conducted.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the parents/guardians of participants and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent and assent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant's parent/guardian will be asked to read and review the document. The research staff will explain the research study to the participant's parent/guardian and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's parent/guardian comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants and their parent/guardian will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants and their parent/guardian should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant's parent/guardian will sign the informed consent document prior to any procedures being done specifically for the study. Participants and their parent/guardian must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participant's parent/guardian for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Importantly, while the COVID-19 pandemic still presents a risk to participants and staff, we will reduce the number of required in-person visits and instead conducting those visits virtually over WebEx. All procedures in the screening visit, with the exception of the blood draw, will be conducted virtually and will continue to be conducted virtually based on individual family preferences. Therefore, our written consent/assent processes will be conducted via WebEx, albeit in the same way it would be done in person. The parent/guardian will be provided the written consent form prior to the screening visit and

encouraged to review it. At the beginning of the virtual screening visit, while sharing the consent form on the screen, the research staff member will explain the research study to the participant's parent/guardian and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's parent/guardian's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. A research staff member will also meet with the child participant on WebEx to review the age-appropriate assent form in the same way. Participants and their parent/guardian will have the opportunity to carefully review the assent and consent forms and ask questions prior to signing electronically. To adjust the consenting process for virtual administration, we will present the consent and assent forms and collect signatures through REDCap survey. Parents will be provided REDCap links to the consent and assent forms so they can follow along while the research team reviews study procedures and can then provide signatures indicating consent/assent. A copy of the signed consent form on REDCap will be provided electronically to the participant's parent/guardian for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests (if any) in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IRB.

All research activities will be conducted in as private a setting as possible.

Representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NYU Child Study Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Child Study Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Child Study Center.

Audio/visual recordings of the BOSCC took place prior to discontinuing its administration due to the COVID-19 pandemic, as they are required to be able to score the behaviors during the interview to assess quantitatively whether social communication ability has changes. These recordings were labeled only with the participant's study identification number and will be kept in the Investigator's files. The video may show the participant's face, and if his/her name is spoken during the session, it will be recorded as part of the video. Parents were made aware of this, and consent was attained specifically for audio/visual recording. It was our intention to pursue expert analysis of these recording, if and when available, from the developer, Dr. Catherine Lord, world-renown researcher and expert in autism evaluation, and her team at UCLA. This coding service as well as the coding scheme for the BOSCC are currently being established. We expect that they will become available within the next year or so while this study is still active. Because coding of videos is not absolutely necessary until the end of this trial, we are fairly confident that UCLA will have finalized this service in time to pursue expert analysis of our complete dataset. For context, seeking these services from Dr. Lord's team is essential; the BOSCC is a novel measure and evaluating change in the subtle symptoms of high-functioning autism is complex. Observational measurement of change will likely be unmanageable without their support. Further, using outside coders will allow for blinding of observers who will not be informed about whether the video they are coding is the first administration from the enrollment/baseline visit or the second administration from the final visit. This blinding would not be possible if coding was completed internally. Importantly, Dr. Lord and her team would not have access to these recordings until proper IRB-approved protocols and contracts are in place at both institutions, and the investigators on the current study will provide all documentation necessary to the NYULH IRB prior to initiating the consultative relationship with UCLA. Once the coding service has been approved and ready to be implemented, we will submit a Modification to include these intentions in the audio/visual recording consent form and informed consent form, to enable participants to consent to the recordings knowing of our intention to obtain authorized expert assistance to analyze the videos at a later date. Following the onset of the COVID-19 pandemic, we discontinued administration of the BOSCC. We will not administer the BOSCC for the remainder of the trial, as the requirement for participants and staff to have effective face masks during COVID makes it impractical to perform the BOSCC.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the NYU Child Study Center, Department of Child and Adolescent Psychiatry, Hassenfeld Children's Hospital at NYU Langone. Sample storage is not currently planned.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
F. Xavier Castellanos, MD	Melissa Nishawala, MD
Child Study Center, Department of Child and Adolescent Psychiatry, Hassenfeld Children's Hospital at NYU Langone	Child Study Center, Department of Child and Adolescent Psychiatry, Hassenfeld Children's Hospital at NYU Langone
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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Clinical Monitoring Committee (CMC), chaired by Glenn Hirsch, MD, and composed of the PI, F. X. Castellanos, MD, Co-PI Orrin Devinsky, MD, and co-I Daniel Friedman, MD. All are free of conflict of interest. The CMC will assess safety and efficacy data every third participant. Data reviewed will include all adverse event forms as well as primary and secondary outcome measures for each participant in the cohort.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements.

- The PI will conduct the monitoring, on-site, frequency early, for initial assessment and training as well as throughout the study, every three participants. Monitoring will be comprehensive (100% data verification). Monitoring reports will be maintained in the study binder.
- Reports of the Clinical Monitoring Committee will be sent to the IRB at least annually at the time of continuing review.
- Independent audits will not be conducted as this is an open trial.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

We will use a 21 CFR Part 11-compliant web application, Research Electronic Data Capture (REDCap) for data collection and management. REDCap is already implemented for several research studies across NYU Langone and can be programmed to meet the needs of this protocol.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents will be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations will be sent to the reviewing IRB per its policy.

Of note, protocol deviations resulting from mitigation strategies applied during the COVID-19 pandemic will be reported at time of next continuing review.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 6 years after the completion of the primary endpoint by contacting Francisco Xavier Castellanos.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ABC	Aberrant Behavior Checklist
ADAMS	Anxiety, Depression and Mood Scale
ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
AFEQ	Autism Family Experience Questionnaire
ASC-ASD-C	Anxiety Scale for Children – Autism Spectrum Disorder-Child Version
ASD-ASD-P	Anxiety Scale for Children – Autism Spectrum Disorder-Parent Version
ASI	Autism Symptom Interview
AE	Adverse Event
ASD	Autism Spectrum Disorder
BIS	Behavioral Inflexibility Scale
BNE	Bureau of Narcotic Enforcement
BOIN	Bayesian optimal interval
BOSCC	Brief Observation of Social Communication – Change
CARS-2-HF	Childhood Autism Rating Scale, 2nd Edition, High Functioning Version
CBD	Cannabidiol
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression Scale – Improvement
CGI-S	Clinical Global Impression Scale-Severity
Co-I	Co-Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRM	Continual Reassessment Method
C-SSRS	Columbia-Suicide Severity Rating Scale
DRE	Disease-Related Event
EI	Excitatory/Inhibitory
EC	Eyes Closed
eCRF	Electronic Case Report Forms
ECS	Endocannabinoid System
EEG	Electroencephalogram
EO	Eyes Open
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HFA	High-Functioning Autism
HSQ-ASD	Home Situations Questionnaire – Modified for ASD
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
K-SADS-COMP	Computerized Kiddie Schedule for Affective Disorders and Schizophrenia
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections

OSU Autism CGI	Ohio State University Autism Clinical Global Impressions
PI	Principal Investigator
PTSD	Post-Traumatic Stress Disorder
QC	Quality Control
RCT	Randomized Controlled Trial
RBS-R	Repetitive Behavior Scale-Revised
REDCap	Research Electronic Data Capture
RRB	Restricted and Repetitive Behaviors
SAE	Serious Adverse Event
SCARED	Screen for Child Anxiety Related Disorders
SDSC	Sleep Disturbance Scale for Children
SOA	Schedule of Activities
SOC	System Organ Class
SRS-2	Social Responsiveness Scale, Second Edition
SWAN	Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior
THC	Tetrahydrocannabinol
UP	Unanticipated Problem
US	United States
Vineland-3	Vineland Adaptive Behavior Scales, Third Edition
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
18-00250_MOD02	04/03/2019	ABI was removed; SRS-2 cutoff was changed from a t-score of 65 to 66. Typos in the ICF/Assent corrected. Two staff added to study.	The ABI covers the same constructs as another study measure (SRS-2). The SRS-2 cutoff better aligns with the clinical impairment ranges.
18-00250_MOD03	04/10/2019	A co-investigator was added to the protocol (Judith Bluvstein, MD).	N/A
18-00250_MOD04	06/04/2019	Added HSQ-ASD; changed details regarding urine drug test; added clause about discontinuing exclusionary medications to participate; provided more explicit definition of "prior chronic treatment of CBD or other cannabinoid"	HSQ-ASD is commonly used in RCTs; new drug test procedures more in line with age group studied; clause added to improve safety monitoring; more objectivity in the definition of CBD use was required.
18-00250_MOD05	07/05/2019	Added $10 stipend to cover travel costs for visits with blood draw; mechanism for determining eligibility with brief updating session in cases when the screening visit occurs >8 weeks before initiation of treatment; rate of recruitment changed	Participants have to travel several blocks from the clinic to the hospital; given the adaptive design, it is possible patients are screened more than 8 weeks prior to their enrollment/baseline visit; recruitment rate previously indicated did not correspond with study design
18-00250_MOD06	12/19/2019	Instruments were added (ASC-ASD-Parent and Child Versions; OSU Autism Clinical Global Impressions: Severity and Improvement Subscales), and one will replace a previous measure (AFEQ to replace PedsQL). We are to use the Reliable Change Index to measure change in scores on measures pre- and post-treatment. We made the supports used to increase compliance with EEG procedures less specific.	Measures will more comprehensively capture constructs of interest. Reliable change index measures clinical significance. Changes to EEG supports will allow for more flexibility to individualize our strategies.
18-00250_MOD07	01/17/2020	An additional parent-report measure was added (Behavioral Inflexibility Scale). In the EEG procedure, we will ask subjects to	The measure was added to more comprehensively assess constructs of interest. One-minute recordings reported in

		undergo a consecutive series of six two-minute, rather than one-minute recording periods. We will no longer change the instructions of the questionnaires to fit the time frame. The blood chemistry CRF was edited.	the original protocol represents an error; two-minute recordings is accurate. The blood chemistry CRF was edited to improve relevance/utility to the study.
18-00250_MOD08	01/23/2020	A research associate was added to the protocol.	---
18-00250_MOD09	02/23/2020	ASI was added. Two telephone follow-ups were added 2- and 4-weeks after participants complete the intervention phase. At 6 weeks, caregivers will be given the option to complete informant-report measures.	The ASI will provide greater standardization in the way clinicians inquire about current and past ASD symptoms. The follow-ups at 2, 4, and 6-weeks post intervention will provide information about any discontinuation effects.
18-00250_MOD11	03/27/2020	A financial disclosure section was added to the informed consent form.	Edits were made in line with instructions provided by CIMU.
18-00250_MOD12	06/23/2020	The consenting/assenting process will be completed online over WebEx.	Limit participant and staff potential exposure to COVID-19.
18-0050_MOD13	8/28/2020	Added inquiry about allergies to pre-screen; removed CCC-2; Vineland-3 only to be given at baseline	Save time if child had allergies prohibited participation in trial. Measure changes to reduce burden on parents.

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