Study Title: CBDV vs Placebo in Children and Adults up to Age 30 with Prader-Willi Syndrome (PWS)

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RESEARCH PLAN: CANNABIDIVARIN (CBDV) VS. PLACEBO IN CHILDREN AND YOUNG ADULTS WITH PRADER-WILLI SYNDROME (PWS)

A. SPECIFIC AIMS/ OBJECTIVES

This clinical research trial aims to study the efficacy and safety of cannabidivarin (CBDV), a naturally occurring homolog of the phytocannabinoid cannabidiol (CBD) in children and young adults with Prader-Willi Syndrome (PWS). CBDV has affects independent of CB1 and CB2 receptor activation and a good safety profile. This proposal addresses the Foundation for Prader-Willi Research's five-year PWS Research Plan- Program 1, Clinical Care Research[1]: seeks to evaluate treatments that aim to reduce behavioral symptoms, such as irritability, in order to improve the quality of life of both the individual with PWS and their families. GW Pharmaceuticals will provide the CBDV drug, matching placebo and additional funding to the site.

Primary Aim

To compare CBDV vs. placebo on change in irritability from baseline to endpoint using the Aberrant Behavior Checklist-Irritability Subscale (ABC-I).

Secondary Aims

To compare CBDV vs. placebo on changes from baseline to endpoint in:

1. Repetitive behaviors using the Repetitive Behavior Scale – Revised (RBS-R) and the Children's Yale- Brown Obsessive Compulsive Scale (CY-BOCS).
2. Hyperphagia using the Hyperphagia Scale for Clinical Trials (HQ-CT)
3. Sleep quality using ActiGraph GT9X-BT activity monitors.
4. Rigid behaviors using the Montefiore-Einstein Rigidity Scale-Revised-PWS (MERS-R-PWS)
5. Global improvement using the Clinical Global Impressions Scale-Improvement (CGI-I) and Caregiver Strain Questionnaire (CSQ).
6. ABC subscales in lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech

B. BACKGROUND and SIGNIFICANCE

There is an unmet need for therapeutics to treat the diverse symptoms of Prader-Willi Syndrome (PWS). Irritability (often manifested along with temper tantrums, anxiety and rigid behavioral patterns) is a primary characteristic of PWS that significantly disrupts the daily functioning of children and young adults with PWS and their families. Despite the substantial burden that irritability engenders, it has not been systematically examined as an outcome in clinical treatment

trials of children and young adults with PWS. The significance of reducing irritability in patients with PWS cannot be over-stated, as it would substantially improve not only the quality of life for the patient but their caregivers and family as well. CBDV is well suited to address this target symptom in PWS.

I. Key Features of PWS

PWS is a neurodevelopmental disorder caused by loss of paternally expressed genes from the 15q11-q13 region.[2] PWS symptoms include irritability, restricted and repetitive behaviors, hyperphagia, sleep disturbances and seizures. PWS individuals may also exhibit immune-inflammatory alterations[3-7] associated with GABAergic dysfunction, which contributes to hyperphagia[8]. Seizures in PWS may be associated with immune dysfunction, inflammation and altered cytokines.[9-11]

II. CBDV Mechanisms and Therapeutic Potential

CBDV is a component of cannabis and a naturally occurring homolog of cannabidiol (CBD). Unlike Δ9-THC, CBDV lacks appreciable affinity and functional activity at CB1 or CB2 receptors. Instead, it is a multi-target drug which interactions include inhibition of the equilibrative nucleoside transporter (ENT) and the orphan G-protein-coupled receptor GPR55[18]. CBDV is also an agonist of multiple transient receptor potential (TRP) channels, including TRPV1, TRPV2, TRPV4, and TRPA1 and is an antagonist of TRPM8.[19] Additionally, CBDV has anti-inflammatory effects[20] and has a potential to act as an analgesic.[21-23] In a maternal immune activation (MIA) model of neurodevelopmental disorders, repetitive behaviors are alleviated by anti- inflammatory treatment[24], suggesting that CBDV may alleviate repetitive behaviors in PWS. In PWS increased excitatory-inhibitory (E-I) ratio due to altered GABA-glutamate neurotransmission[25] can result in seizures, behavioral changes and social dysfunction. CBDV has well-established anticonvulsant effects in animal models.[26-28]

Across all GW sponsored Phase 1 and Phase 2 clinical trials with CBDV to date, CBDV was generally well tolerated in adults at doses of up to 1600 mg/day; most adverse events (AEs) were considered mild or moderate in severity and the incidence of serious treatment-emergent adverse events (TEAEs) was low[28]

The potential therapeutic mechanisms of CBDV in humans with PWS can be inferred from its neurobiological effects, and from the effects of the related compound, CBD on epilepsy, addiction, anxiety, depression and schizophrenia.[15] CBDV has the potential to be a valuable therapeutic agent for PWS by virtue of its anti- inflammatory[20,29], anti-oxidative, neuro-protective, anti-anxiety and anticonvulsant properties[28]. CBDV, similarly to CBD, may modulate sleep that is often disturbed in PWS[30] and may play a role in food regulation and hyperphagia[31]. With its effects on multiple mechanisms known to be dysfunctional in PWS and low side effect profile, CBDV is a promising treatment that needs further exploration in this population.

III. CBDV and Irritability in PWS

Individuals with PWS frequently exhibit irritability, which manifests as a consequence of emotion dysregulation, disruption of rigid behavioral patterns or excessive response to stimuli. Irritability is a well-characterized outcome that has been accepted by the FDA for the purposes of labeling in other cohorts. The FDA has approved treatments for irritability in ASD, including aripiprazole and risperidone, based on the Aberrant Behavior Checklist (ABC) – Irritability subscale.

In animal models of neurodevelopmental disorders, CBDV has been shown to reduce hyperactivity, which may be suggestive of an improvement in irritability[28].

IV. CBDV and Repetitive/Restricted Behaviors in PWS

Rigidity and repetitive behaviors (RRB) are key symptoms of PWS. RRBs are also found in other addictive and neurodevelopmental conditions[28]. CBDV reduced repetitive grooming in Valproic-Acid (VPA) treated male rats, a model of autism that is analogous to the RRB in PWS[28]. Therefore, it can be hypothesized that CBDV may also reduce RRBs in PWS. Our use of the Repetitive Behavior Scale-Revised (RBS-R), a reliable and valid scale containing six subscales (Stereotyped; Self-Injurious; Compulsive; Ritualistic; Sameness; and Restricted behaviors), will allow us to clarify the impact of CBDV on distinct subdomains of RRB.

B.1. Preliminary studies

1. **Effects of CBDV (2-200mg/kg ip) in Animal Models of Genetic Disorders**

Behavioral deficits in the MECP2 KO Mouse, a model of Rett Syndrome, were attenuated with CBDV (2, 20 and 200mg/kg i.p.). CBDV is also shown to delay neurobehavioral deficits observed in MECP2 KO mice including tremor, breathing, and general condition but appears to have limited effect on impaired motor function. CBDV also reverses short term and long term cognitive deficits observed in MECP2 KO mice. These effects of CBDV do not appear to be dose related[28].

FMR1 KO mice, a model of Fragile X Syndrome, also have attenuation of behavioral deficits with CBDV treatment. CBDV (100 and 200 mg/kg i.p.) attenuates audiogenic seizures in the FMR1 KO mouse following acute administration, while CBDV (20 and 100 mg/kg i.p.) attenuates a deficit in visual recognition memory (NOR) following sub-chronic (but not acute) administration in the FMR1 KO mouse[28].

2. **Effects of CBDV on Behavioral Deficits in the Rat Valproate (VPA) Model:**

The VPA animal model displays some of the neurobehavioral deficits and pathophysiology observed in the brains of individuals with developmental disorders[32]. Male rats prenatally exposed to VPA were treated with CBDV (2, 20, and 100 mg/kg, i.p).

3. **CBDV Clinical Studies:**

CBDV has been dosed up to 1600 mg, given as 800 mg BID in patients with focal seizures for 8 weeks. In healthy volunteers the maximum single dose administered was 20 mg/kg and the maximum daily dose 40 mg/kg[28].

Over the dose range 5 to 20 mg/kg (single dose), CBDV median t_{max} values ranged from 2.5 to 5 hours. Biphasic absorption was evident at higher doses. Exposure to CBDV and its main metabolites, 7-OH-CBDV and 7-COOH-CBDV, increased in a dose-proportional manner[28].

CBDV C_{max} and AUC $_{(0\text{-}t)}$ increased approximately 4- and 6-fold, respectively, when CBDV was taken with a high-fat/high-calorie meal, compared with fasted dosing; the AUC $_{(0\text{-}t)}$ of 7-OH-CBDV increased by approximately 3-fold and the AUC$_{(0\text{-}t)}$ of 7-COOH-CBDV remained stable.

There is limited clinical data available on CBDV. Unacceptable adverse reactions may develop at any time. With other cannabinoid medicines, AEs are typically mild in severity and resolve in a few days. Please refer to CBDV IB for further details[28]. CBDV was noted to cause an asymptomatic transaminase

increase without an increase in bilirubin in a Phase 1 healthy volunteer study. For this reason, the maximum dose of CBDV advised is 20 mg/kg/day in patient studies[28].

4. **Irritability in PWS:**
We recently completed a study comparing oxytocin vs. placebo in 23 children and adolescents with PWS. The mean ABC-I score was 17 at baseline, and 39% (9/23) had an ABC-I score of ≥18 at baseline. Improvement in the Caregiver Strain questionnaire was correlated with improvement in irritability on the ABC-I (r=.61, p=.058). Thus, our data supports high levels of irritability in children with PWS, and the impact of improvement in irritability on quality of life.

C. TREATMENT PLAN

C.1. Study design

We propose a single-site 12-week double-blind placebo-controlled pilot study of CBDV manufactured by GW Pharmaceuticals as GWP42006 in 36 children and young adults aged 5 to 30 diagnosed with PWS and have a high level of irritability (≥18 on the ABC-I). Although not expected in this population, patients who test positive for marijuana use will be excluded from the study. PWS diagnosis will be confirmed using patient medical records and previous genetic testing. Please see **Table 1** for the Schedule of Events. Albert Einstein College of Medicine-Montefiore Medical Center will be the study site. Participants in the study will be selected from the PWS network, and the site will use their current patient databases in addition to local advertising for recruitment.

C.2. Subject Selection

Inclusion Criteria

1. Male or Female outpatients aged 5 to 30 years.
2. Diagnosis of PWS confirmed by genetic testing and patient medical records and history.
3. Stable pharmacologic, educational, behavioral and/or dietary interventions for 4 weeks prior to the study start, and for the duration of the study.
4. Have a physical exam and laboratory results that are within the norms for PWS
5. Presence of a parent/caregiver/guardian that is able to consent for their participation and complete assessments regarding the patient's development and behavior throughout the study. Child Assent will be obtained if the subject is 7 years of age or older and has the mental capacity to understand and sign a written assent form and/or give verbal assent.
6. Score on the Clinical Global Impression Scale Severity (CGI-S) ≥ 4 (moderate severity) at baseline.
7. Score of ≥18 on the Aberrant Behavior Checklist-Irritability (ABC-I) at baseline.
8. Agree not to drive or operate machinery.

Exclusion Criteria

1. Exposure to any investigational agent in the 30 days prior to randomization.
2. Prior chronic treatment with CBD or CBDV.
3. Positive testing for THC or other drugs of abuse via urine testing at the screening visit or baseline visits upon repeat confirmation testing.
4. History of Drug Abuse Disorder including Cannabis Use Disorder
5. A primary psychiatric diagnosis other than PWS, including bipolar disorder, psychosis,

schizophrenia, PTSD or MDD. These patients will be excluded due to potential confounding results.

6. 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 (including but not limited to hepatic or renal impairment and cardiovascular disease).
7. Known or suspected allergy to CBDV or excipients used in the formulation (i.e. sesame).
8. ***Clinical indications of*** renal, pancreatic, or hematologic dysfunction as evidenced by values above upper limits of normal for BUN/creatinine, values twice the upper limit of normal for serum lipase and amylase, platelets <80,000 /mcL, *WBC<3.0 10^3 /mcL.* or > 2 X UNL values of AST or ALT.
9. ECG abnormality at baseline screening or clinically significant postural drop in systolic blood pressure at screening. If the initial screening ECG shows a QTcB of greater than 460 msec, then 2 additional ECGs will be conducted in the same sitting, 5 minutes apart. If not recognized at screening, then a full triplicate repeat showing an average QTcB of 460 msec or less to meet all inclusion/exclusion criteria
10. Female subjects who are pregnant will be excluded from the study. If a female subject is able to become pregnant, she will be given a pregnancy test before entry into the study. Female subjects will be informed not become pregnant while taking CBDV. Female subjects must tell the investigator and consult an obstetrician or maternal-fetal specialist if they become pregnant during the study.

C.3. Description of Study Treatments

C.3.1. Study Drug Description

CBDV is obtained from the Cannabis sativa L. plant by extraction and purification to produce an extract known as the botanical drug substance (BDS). The BDS is purified by crystallization to yield the CBDV active substance. We will use GW Pharmaceutical's formulation of CBDV, GWP42006. GWP42006 is an oral solution containing 50 mg/mL purified CBDV, dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring and β‑carotene. Placebo oral solution contains matching excipients. Purified CBDV contains a negligible quantity (less than 0.2%) of THC.

C.3.2. Study Drug Supply

CBDV will be supplied by GW Pharmaceuticals as a 50 mg/mL oral solution. GW will export CBDV as a formulated drug product directly to Dr. Hollander or through approved 3rd party. GW Pharmaceuticals will supply study drug and placebo at no cost to the study site for the duration of the study.

C.3.3. Study Drug Dosing

Enrolled patients will receive a weight-based dosing of 10 mg/kg/day of CBDV (weight-based, up to 800 mg/day) or placebo for 12 weeks, administered bid. The IMP will be administered with food.

I. Titration Phase

The total planned titration phase will be 4 weeks as tolerated up to a maximum of 10mg/kg/day up to 800 mg/day per day total.

Proposed schedule:
Week 1: 2.5 mg/kg/day
Week 2: 5 mg/kg/day week
Week 3: 7.5 mg/kg/day week
Week 4: 10 mg/kg/day week

II. Maintenance Phase (Weeks-4-12)

Subject will be maintained on maximum tolerated titrated dose up to 10 mg/kg/day (given as 5 mg/kg bid) with a maximum **of 800 mg/day (400 mg bid, if weight greater than or equal to 80 kg).**

III. Margin of Safety Calculation

The maximum dose to be administered in this trial is **10 mg/kg/day.** CBDV safety margins estimated based on the steady state clinical exposures, indicate there is an adequate margin of safety for CBDV for the recommended maximum human daily dose of 20 mg/kg/day (administered as 10 mg/kg twice daily [bid.]) in both juvenile and adult populations[28].

C.3.4. Study Drug Interruption

Dosage will be decreased or drug will be temporarily discontinued in the case of clinical or laboratory toxicity. Because of the frequency of co-morbid medical problems in this population, intolerable side effects that are symptom-based and thus subjective will be determined by the parents and investigators together on a case by case basis. The PI will make changes based on the results of side effect assessments and the physical status of the subject.

For objective measures such as weight or labs:

Measure	Toxicity criteria
1. Weight loss	>10% or excessive weight gain (determined by age, gender and familial factors) throughout the trial.
2. Clinical signs of pancreatitis and elevated lipase/amylase	2x upper limit of normal range
3. Clinical signs of liver injury with elevated bilirubin and transaminases (AST or ALT)	>8x upper limit of normal (ULN), or >5x ULN for more than 2 weeks, or >3x ULN and total bilirubin [TBL] >2x ULN, or >3x ULN and fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, and/or eosinophilia (>5%)
4. Platelets dysfunction	<80,000 /mcl
5. White blood cells dysfunction	<3.5 x 103 /mcl

Significant worsening of side effects (regardless of drug causality) (objective or subjective) for 2 consecutive visits (or phone calls) will prompt discussion with the family and may result in the discontinuation of study drug. Patient will be asked to return for a follow-up visit after early termination.

C.3.5 Study Drug Discontinuation

Investigators will consider terminating study participation for any subject due to any adverse event(s) (including clinically significant laboratory results) which, in the opinion of the investigator, would compromise the continued safe participation of the subject in the study. Significant non-compliance with the protocol requirements may also necessitate discontinuation. Pregnancy during study participation is an automatic criterion for permanent study drug discontinuation.

C.4. Potential Drug Interactions

CBDV undergoes phase 1 metabolism via CYP2C19. CYP2C8 and CYP3A4 are also capable of CBDV hydroxylation.[28]. CBDV was a potent competitive inhibitor of CYP2C19 (Ki = 0.586 μM)[28]. CBDV was a relatively potent reversible inhibitor of CYP1A2, 2B6 and 2C9 (IC50 values all < 2 μM). CBDV was a relatively weak inhibitor of CYP2D6, 2C8 and 3A4 (IC50 values between 10–30 μM), and did not inhibit CYP2E1. In a further study in HLMs, CBDV was a relatively moderate time-dependent inhibitor of CYP3A4 (KI of 14.7 μM and a K inact of 0.063 min-1)[28]. Careful titration of CBDV in patients taking concomitant medications metabolized by CYP3A4 or CYP2C19 is advised, with plasma monitoring of such medications or their metabolites to be undertaken at the investigator's discretion[28].

CBDV caused a small but significant increase in CYP2B6 mRNA levels which appeared to be concentration dependent. However, this was only observed at concentrations > 10 μM (2864 ng/mL). Hence, CBDV is unlikely to produce any significant effects at clinically relevant doses/concentrations[28]. In vitro, CBDV potently inhibited UGT1A9 (IC50 = 0.185 μM) and UGT2B7 (IC50 = 0.654 μM) respectively and weakly inhibited enzyme activity mediated by UGT1A1 (IC50 = 13.0 μM). Care should be taken when introducing CBDV to existing treatment regimens which contain medications solely or primarily metabolized by UGT1A9 and UGT2B7 [28].

CBDV inhibited P-gp and OCT1 in vitro with IC50 values of 20.4 μM (5843 ng/mL) and 6.77 μM (1939 ng/mL), respectively. The main plasma phase I metabolite of CBDV, 7-COOH-CBDV, inhibited P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1 and OAT3 with IC50 values > 25 μM (7160 ng/mL). There is potential to reach these concentrations in vivo, however, a clinically efficacious dose has yet to be established in humans[28].

As there has been limited clinical exposure to CBDV to date, the potential incidence of DDIs in humans with CBDV has not been established. In addition, the dose/exposure of CBDV required to establish/maintain efficacy also requires further evaluation. GW Pharmaceuticals advises in the IB that it would be prudent for the investigator to monitor subjects carefully in this regard, particularly if they are taking concomitant medications which undergo phase 1 metabolism via CYP2C19 or CYP3A4 or phase 2 metabolism via UGT1A9 or UGT2B7[28]. This monitoring will be done via routine drug level monitoring as described below.

C.5. Safety Assessments

Full panel of safety labs (CBC with differential, basic metabolic panel and liver function tests) and if participant is taking one or more of the anti-epileptic medications, concomitant plasma drug levels for valproic acid, lamotrigine, oxcarbazepine, phenytoin and clobazam, which are drugs metabolized by phase 1 metabolism via CYP2C19 or CYP3A4 and phase 2 metabolism via UGT1A9 or UGT2B7, will be drawn at baseline, week 4, and week 12. Additional liver function test will be drawn at week 2 to monitor response during dose escalation. Other laboratory studies may be ordered if clinically indicated. Home medications may be monitored on a patient by patient

basis if there are safety concerns suspected to be related to a drug-drug interaction. (See Appendices A and B for the lists of drugs metabolized by phase 1 via CYP2C19 or CYP3A4 and phase 2 metabolisms via UGT1A9 or UGT2B7).

While there is no formal drug-drug interaction data to demonstrate the effect of CYP2C9 inducers and inhibitors on the PK of CBDV, PK data from study GWEP1330 does not indicate an interaction of concern. In Part A of the trial, the PK and safety of CBDV was assessed when given concomitantly with inducer AEDs (including any of the following: Carbamazepine, phenobarbital, primidone or phenytoin) and inhibitor AEDs (Valproic acid). Data indicated there were no notable differences in the safety or PK results obtained for CBDV and its metabolites between the AED groups. From a safety point of view, CYP2C9 is not the sole metabolic pathway for CBDV. CBDV may also be metabolized by other cytochrome p450 enzymes including 2C8 and 3A4. Based on this indicative data we consider the exclusion of medications that are potent inhibitors or inducers of CYP2C9 is not required.

For any clinically significant (>3x ULN) elevation of ALT or AST, the following laboratory measures, at minimum, should be assessed within 72 hours: repeat ALT/AST, total bilirubin, alkaline phosphatase, and GGT.

Study drug will be discontinued in subjects who have:

1. >10% Weight gain
2. Clinical signs of pancreatitis confirmed with amylase and lipase elevation >2x ULN
3. ALT or AST >8x ULN
4. ALT or AST >5x ULN for more than 2 weeks
5. ALT or AST >3x ULN and TBL >2x ULN
6. ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All trial subjects with elevated LFTs will be followed until all abnormalities return to the baseline state as assessed by the investigator with AST/ALT < 3x ULN.

- Pregnancy test, if applicable, will be performed at screening, baseline, weeks 2, 4, and 12 via urine or blood
- ECG will be performed at baseline and week 12 or at the time of early termination should this arise.
- Columbia Suicide Severity Rating (C-SSRS) Scale -The Investigator will attempt to administer the Columbia Suicide Severity Rating Scale in the beginning and at each visit. If the C-SSRS cannot be performed then a clinical assessment of suicidality will be done

C.6. Concomitant Treatment

All concomitant conditions will be treated in accordance to prevailing medical practice. Any medications or non-drug therapies used prior and during the study will be recorded. Any changes to existing medications or addition of new medications should be discussed with the investigator. For those requiring these changes, subjects' families will be instructed to discuss these changes with study staff and staff may decide the changes are so substantial as to recommend withdrawal from the study.

C.7. Risk Benefit Analysis

This protocol is considered to involve greater than minimal risk, but it presents the prospect of

direct benefit to the individual subjects (HHS Code of Federal Regulations 45 CFR 46.405). The research is more than minimal risk because of the administration of active medication with known and unknown side effects. Participation in the study directly benefits subjects in close clinical monitoring, and families will receive feedback on the results of the cognitive and behavioral testing, which may be used to help guide educational and support services for the subject.

C.8. Definition of Primary and Secondary Outcomes/Endpoints

I. Outcome measures

Project outcomes will be determined by changes in score of parent and clinician rated measures from baseline to week 12 and comparisons of week 12 measures between active treatment and placebo groups. Assessments will be administered according to the schedule in Table 1. Future studies may incorporate additional long-term maintenance studies to provide more data on safety and efficacy. Additions measures will be completed per Schedule of Events.

II. Study Time Commitment and Reduction of Burden:

Every effort has been made to reduce the time burden on patients and caregivers. As in the case in most clinical trials, the most significant burden to the parent and child are logistics to follow study assessment procedures. To minimize patient burden and facilitate recruitment in this study that involves a rare disorder, the study will utilize remote visits in combination to in person visits. Outcome measures are selected to keep parent questionnaire between 15 to 20 minutes to complete, and child assessments are kept to a minimum. The screening visit will be conducted remotely to reduce burden of travel and minimize burdens to participants who may not meet full participation criteria.

The time commitment and study burden are similar to other studies in this population. If needed, visits can be split into two visits. Caregivers may prefer to attend a visit by themselves without their child to complete their measures. As much flexibility in scheduling as necessary will be given to the patients and families. Reimbursement for time and travel is provided at each visit ($50 at screening, $40 all subsequent visits).

C.8.1. Primary Outcomes

I. Aberrant Behavior Checklist (ABC) – Irritability Subscale

The ABC-I is a well-characterized outcome that is accepted by the FDA for the purpose of labeling, and is one of the best and most validated outcome measures in the developmental disabilities. An inclusion cutoff of 18 or higher on the ABC-I at screening was chosen based on multiple medication trials with irritability as the primary target. This includes those that led to the approval of risperidone and aripiprazole for irritability in children with ASD aged 5 to 17.[33,34] It is completed by caregivers at screening, baseline, weeks 4, 8 and 12, and takes approximately 20 minutes to complete.

The ABC-Irritability subscale consists of 15 questions that address the presence of aggression, tantrums and/or self-injury. The scores on the subscale range from 0 to 45. Subjects must score an 18 or higher at screening to be included in the study.

C.8.2. Secondary Outcomes

I. Repetitive Behavior Scale – Revised (RBS-R)

The RBS-R is a 44-item self-report questionnaire that is used to measure the breadth or repetitive behavior in children, adolescents and adults with ASD. The RBS-R provides a quantitative, continuous measure of the full spectrum of repetitive behaviors. The RBS-R consists of six subscales including: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Routine Behavior, Sameness Behavior, and Restricted Behavior that have no overlap of item content. The RBS-R is a well-validated and consistent measure of repetitive behaviors in developmental disorders.[35] It has been used in studies with adults, adolescents, and children with success. [36,37] The scale is completed by the caregivers and takes approximately 20 minutes.

II. Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)
The CY-BOCS is 10-item clinician measure designed to assess the severity of obsessive-compulsive symptoms in children and adolescents over the previous week. It consists of four primary sections including Obsessions checklist, Severity items for Obsessions, Compulsions checklist and severity items for Compulsions and a set of investigational items. Improvement on this scale was associated with improvements in caregiver quality of life in our 8-week study of intranasal oxytocin.[38]

III. Hyperphagia Questionnaire for Clinical Trials (HQ-CT)
The HQ-CT is a 9-item caregiver-reported measure of food-seeking behaviors that was used in the phase 3 beloranib trial.[39]

IV. ActiGraph GT9X-BT activity monitors
Actigraph activity monitors are a well validated activity sleep monitoring device that has been utilized widely in clinical trials and health research, measuring sleep latency, total sleep time, and sleep efficiency.[40]

V. Clinical Global Impression Scale – Improvement (CGI-I):
The CGI-I will be used as a measure of improvement and contains a 7-point scale as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. The CGI-I is a clinician rated global measure of improvement and has been used as a measure in previous clinical psychopharmacology trials that takes 5 minutes to complete.

VI. Caregiver Strain Questionnaire (CSQ).
The Caregiver Strain questionnaire is a 21-item self-report questionnaire that was developed to assess caregiver strain for families with a child living with an emotional or behavioral disorder. It is completed by the caregivers and takes approximately 15 minutes.

VII. Montefiore Einstein Rigidity Scale-Revised-PWS (MERS-R-PWS)
The Montefiore-Einstein Rigidity Scale-Revised-PWS (MERS-R-PWS) is designed to assess three domains of rigid behavior in individuals with PWS:

1. Behavioral Rigidity (e.g., Insistence on sameness, things must be done in his/her way, etc.)
2. Cognitive Rigidity (e.g., Special interests, inflexible adherence to rules, etc.)
3. Protest (in response to deviation from rigidity; e.g., tantrum, irritability, arguing)

The MERS-R-PWS is a clinician-rated scale and takes about 20 minutes to complete.

VIII. Aberrant Behavior Checklist (ABC) subscales in lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech
The ABC is an informative rating instrument that was empirically derived by principal component analysis to measure behavior in those with developmental disability and ASD. It contains 58 items that resolve into 5 subscales. The subscales and the respective number of items are as follows: (a) irritability – 15 items, (b) lethargy/social withdrawal – 16 items, (c) stereotypic behavior – 7 items, (d) hyperactivity/noncompliance – 16 items, and (e) inappropriate speech – 4 items. The ABC was designed to be completed by any adult who knows the patient well, such as a parent/caregiver or teacher. This instrument measures behavior on a four-point severity scale where 0 = no problem at all, 1 = behavior is a problem but in a slight degree, 2 = problem is moderately serious, and 3 = problem is severe in degree. The ABC has been used in multiple trials to measure changes in irritability (as seen in our preliminary data) and social withdrawal, with success. It is completed by caregivers and takes approximately 20 minutes.

C.8.3. Other Assessments

I. Clinical Global Impression-Severity (CGI-S)
The CGI-S reflects the rater's impression of the subject's current illness state on a 7-point scale ranging from no symptoms (1) to very severe (7)[41]. Whenever possible, for any individual, these assessments should be done by the same rater throughout the study.

II. IQ Test: Stanford-Binet Intelligence Scales, Fifth Edition-Abbreviated:
The Stanford-Binet will be administered to obtain data on adaptive behavior and intellectual functioning for correlation during analyses. It is a gold standard measure of intelligence used in clinical and research settings in those aged 2 to 85 years. The fifth edition has a 50/50 balance between verbal and nonverbal subtests, and the Stanford-Binet is considered the best assessment of intelligence in those with intellectual disability and mental retardation 12 [42,43]. The abbreviated version will be used for this study, which consists of 2 subtests and takes approximately 10-20 minutes to complete (administration time is approximately 5 minutes per subtest).

III. Columbia Suicide Severity Rating (C-SSRS) Scale
The assessment for suicidality in clinical trials is a requirement for CNS active molecules requested by Health Authorities. The C-SSRS (http://www.cssrs.columbia.edu) is a clinician-rated tool recommended by Health Authorities including the FDA to assess previous suicidality of a subject at screening (C-SSRS screening to be used at screening) as well as any new instances of suicidality during the clinical study (C-SSRS since last visit, to be used at subsequent visits). The C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality.

Age and capability appropriate versions of the C-SSRS will be used. The young children/cognitively impaired version will be used for children 5 – 11 years old and all cognitively impaired patients regardless of age. For participants that are unable to be directly assessed for suicidality (nonverbal, low functioning) and participants younger than 12, clinician will ask the caregiver the following additional questions:
(1). Suicidal Ideation: Has the child wished he/she were dead or wished they could go to sleep and not wake up?
(2). Suicidal Behavior: Has the child made a suicide attempt? Has he or she done anything to harm him or herself?

(3). Self-injurious Behavior: Has the child engaged in non-suicidal self-injurious behavior?

If the Investigator concludes on a suicidality risk of the subject, the Investigator must take care for further evaluation of the risk, which may involve local experts in the field of suicidality.

IV. Safety labs
CBC with differential, basic metabolic panel, liver function test, and concomitant plasma drug levels for valproic acid, lamotrigine, oxcarbazepine, phenytoin and clobazam, which are drugs metabolized by phase 1 metabolism via CYP2C19 or CYP3A4 and phase 2 metabolism via UGT1A9 or UGT2B7, will be obtained at baseline, week 4 and week 12. Additional liver function test will be drawn at week 2 to monitor response to dose escalation. Other lab studies maybe ordered if there are clinically indications that requires further investigation. Week 2 and Week 4 labs will be obtained via outpatient Quest lab.

V. Pregnancy test
For female participants reached menarche, pregnancy test will be performed at screening, baseline, week 4, and week 12. Pregnancy test (hCG) may be collected either by urine or blood.

VI. Drug testing
Drug testing will take place at screening and at baseline for all major drugs of abuse. In the case of positive urine samples, testing will be repeated for confirmation. We will adhere to all institutional/regulatory reporting requirements for any positive test results. Confirmed positive results will lead to exclusion. For patients who are unable to provide urine sample during screening visit, drug screening will be performed at first in person clinic visit via either urine or blood prior to study randomization.

VII. Menstrual Diary
Parent and participant will be asked to keep a record of menstruation throughout the study for all female subjects who have reached menarche and are having menstrual period. The diary will be reviewed monthly.

VII. Dietary Diary
Dietary intake will be assessed using the National Cancer Institute (NCI) 24-hour automated recall method, which will be completed by the primary caregiver in 15 to 20 minutes. Dietary recalls will be obtained to assess pre-treatment dietary habits at baseline, and assessed at monthly interval during in person visits at weeks 4, 8, and 12. The NCI nutritional program output will allow for secondary analyses of impact of treatment on both dietary macronutrient ratio (percent carbohydrates, proteins and fats) and caloric intake.

VIII. Actigraphy
Patient's sleep and activity levels will be assessed using actigraphy. Successfully screened patients will receive the actigraphy device prior to on site visit and will record a minimum of three days of baseline activity data prior to starting study medication. Actigraphy is captured automatically via cloud service and will be reviewed at in clinic visit.

C.9. Data Collection Methods/Assessments/Intervention/Schedule

C.9.1. Data Collection and Assessment

I. Informed Consent

We propose a 12-week double-blind, randomized, treatment trial of CBDV vs. placebo in 36 children and young adults aged 5 to 30 diagnosed with PWS and have a high level of irritability (≥18 on the ABC-I). Consent for this study will be obtained at the screening visit and repeated at first in person visit at baseline. Consent information will be given to the patient and parent/caregiver/guardian that is able to consent for their participation and complete assessments regarding the patient's development and behavior throughout the study. The study clinician will review the consent information and answer all questions prior to obtaining consent. The procedures to obtain subjects' consent/assent are as follows:

Potential Subjects under age 7

Children under 7 years old will not be asked to assent.

Potential Subjects aged 7-12

Children whose ages range from 7-12 will be asked to assent if they have the capacity. Capacity to assent will be determined by the maturity level and psychological state of the child. If the child's maturity level and psychological states allows him/her to comprehend, to the degree they are capable, what their participation in the trial would involve and what to expect during the trial, he/she will be asked to sign assent. If the child's maturity level and/or psychological state limits his/her ability to comprehend what their participation in the trial will involve and what to expect, assent will not be obtained. In this case, the investigators will document that assent has not been obtained on the consent form that will be signed by the caregiver.

Potential Subjects aged 13-17

Children ages 13-17 will be asked to sign the consent form along with the parents, if they have the capacity to do so. Capacity will be ascertained by the study team first during a brief conversation with the child to get a general sense of his/her ability to comprehend and communicate. If the child potentially has the capacity to provide consent, the team will use a talk back procedure to confirm that the prospective subject understands the required elements of consent. The research study staff will explain the consent form information and request that the child explain back the information in his/her own words, guided by the Informed Consent Feedback Tool. In particular, potential subjects will be asked to explain the purpose of the research, what the potential risks/benefits are, and what some of the study procedures are. They will also be asked questions about their understanding of volunteering (e.g., that they do not have to take part in the study and that they can change their mind at any point without consequence). The child's answers to the questions on the Informed Consent Feedback Tool will be documented and signed by the subject, caregiver and the team member reviewing consent. If the child signs the informed consent, their legal caregiver will also sign the consent form.

If the 13-17 years- old subject does not have the capacity to understand one or more of the above elements of consent, then he/she will not be able to consent. In this case, the subject's caregiver must provide informed consent and the investigators will attempt to obtain assent from the subject. To have the capacity to assent, the child's maturity level and psychological state must allow him/her to comprehend, to the degree they are capable, what their participation in the trial would involve and what to expect during the trial. If the maturity level and/or psychological state of the

child is limited so that they cannot reasonably be consulted, assent will not be obtained. The investigators will document whether or not assent is obtained on the consent form.

Potential Subjects age 18 or older
For individuals 18 years of age or older, consent and assent procedures will be followed as stated above for "Potential Subjects aged 13-17". As is the standard for research studies in adult autism populations, a caregiver will sign consent even if the potential adult subject has the capacity and also signs consent. This is done to ensure the caregiver understands the nature of the study and his/her child's involvement, and also to obtain consent from the caregiver regarding his/her own study-related responsibilities as the subject's informant (i.e., complete assessments that discuss their child's current and past behaviors and symptoms).

If a subject turn from 17 to 18 years old during the course of the study, he/she will be re-consented at the visit after his/her 18th birthday. The same method of ascertainment of ability to consent/assent will be used as described above.

Adequate time will be allowed between the review of the consent form and the signing of the consent form to allow families to decide on their participation and ask questions. Significant new findings during the course of the research would require changes to the informed consent document. Subjects would be re-consented with the new approved consent form at their next study visit, prior to any procedures being performed.

C.9.2. Study Visit Details:
Study visits are divided into remote and in-person visits. Remote visits are done via tele-medicine and utilizing patient's local Quest labs. In person visits are conducted at the Montefiore/Einstein site and on-site clinical research center.

I. Pre-screening (remote)
Potential participants will be identified via an established network of referral sources including other physicians, neurologists, psychiatrists and psychologists, as well via collaboration with patient advocacy groups and advertising. Pre-screening of potential subjects will occur over the telephone or in person to determine initial eligibility and interest in the study. During the pre-screening, the caregiver will provide general information about the subject's condition. Basic eligibility requirements will be discussed, including age, history, and current treatments. If the interviewer determines that the subject meets the pre-screen eligibility requirements, the subject will be invited to schedule a remote screening visit.

II. Screening (remote)
The screening visit will be conducted remotely and occur prior to administration of CBDV to confirm that eligibility and safety criteria are met before study entry.

The screening visit will begin with a member of the study staff going through the Informed Consent with each subject and his/her parents or guardian where they discuss the nature of the study, its requirements, and its restrictions. Subjects age 7 and older will be assessed for capacity and asked to give assent to participate if able to do so.

After obtaining informed consent, the clinician will conduct a medical and psychiatric history

interview, including confirmation of PWS diagnosis using patient medical records and previous genetic testing. The clinician will review patient and parent questionnaires to assess participant eligibility. A score of 18 or higher on the Aberrant Behavior Checklist – Irritability and 4 or more at the Clinical Global impression Scale Severity (CGI-S) are required per inclusion criteria. Also at screening, the clinician will review concomitant medications with the participants and assess stable pharmacologic, educational, behavioral and/or dietary interventions over past 4 weeks.

If patient is a good study candidate, they will be scheduled and instructed to go to a local Quest lab for drug testing, safety labs including CBC, BMP, LFT, and if applicable, pregnancy test (for female reaching menarche).

After reviewing the lab results, if the subject qualifies for enrollment based on Inclusion and Exclusion criteria, they will be informed and scheduled for an in-person baseline visit. Actigraphy device will be shipped to the selected participants to capture a minimum of 3 days of baseline activity information prior to in person baseline visit.

III. Baseline (visit 1, week 1, in-person)
At the baseline visit, subject will be re-consented. Repeat drug and pregnancy test (if applicable) will be done. In the case of positive result, testing will be repeated for confirmation. Confirmed positive results will lead to exclusion.

For subjects who continue to meet study criteria, study clinician will review concomitant medications, obtain vital signs, weight, BMI, IQ test, ABC, RBS-R. CY-BOCS, Actigraphy Remote sleep measurement, Caregiver Strain Questionnaire, CGI-S, HQ-CT, MERS-R-PWS and C-SSRS. Body composition will be assessed using bio-impedance analysis. A physical and neurological exam will be performed. ECG will be done. Safety labs including CBC, BMP, LFT, and concomitant plasma drug levels of valproic acid, lamotrigine, oxcarbazepine, phenytoin and clobazam for those patients who take them will be drawn. Dietary diary will be completed by participant and reviewed. Blood sample will be collected and preserved for biorepository for consented patients. Actigraphy data collected prior to in person visit will be reviewed.

For subject that meet all inclusion/exclusion criteria after all assessments, they may enroll and be randomized to a study group at this visit. The study pharmacist at the Clinical Research Pharmacy will use a computer-generated randomization table to randomize subjects in a 1:1 ratio.

Enrolled patients will receive a weight-based dosing up to 10 mg/kg/day of CBDV (max 800 mg/day) or placebo for 12 weeks on a titration schedule as specified in protocol, administered b.i.d with food.

IV. Visits 2 to 6 (weeks 2, 4, 6, 8 and 10, remote)
Participants will be followed remotely by the clinical team at weeks 2, 4, 6, 8 and 10. The clinicians will review with patients about any interval changes, including changes to any concomitant medications and development of any adverse events. Patient will be assessed for suicidality using C-SSRS. Menstrual diaries will be reviewed if applicable. At weeks 2 and 4, patient will be scheduled and requested to go to a local Quest lab for blood work. No lab test is required for weeks 6, 8 and 10 after patient has reached steady maintenance dose and liver function had been checked

at prior visits. Rating forms will be provided to patients in hardcopies at baseline visits and electronic copies will be provided by email. Participants would be provided Fedex labels and envelopes to return the rating forms. Drug dispensing at Week 4 and Week 8 will occur after clinician safety assessments and IP supply will be Fedex to study participants by the Investigational Drug Service Pharmacy

V. Visit 7 (weeks 12 [End of study or Early Termination], in person):
Participants will be assessed in person at 12, or sooner if patient had early termination. Patient will be assessed for interval changes including review of concomitant medication and monitor for adverse events. Patient will complete a physical/neurological exam. Safety labs including CBC with differential, BMP, LFT, and if applicable, pregnancy test, concomitant plasma drug levels for valproic acid, lamotrigine, oxcarbazepine, phenytoin and clobazam for those patients who take them, will be obtained. Vital signs, weight measurement and BMI calculation will be performed at each visit. The ABC, RBS-R. CY-BOCS, HQ-CT, Caregiver Strain Questionnaire, CGI-I, CGI-S, MERS-R-PWS, and C-SSRS will be administered. A repeat ECG will be done at week 12. Body composition will be assessed using bio-impedance analysis. Dietary diary will be collected. Blood sample will be collected and preserved for biorepository for consented patients. Actigraphy data will be reviewed.

VI. Visit 8 (week 14, Follow-up, remote):
The follow-up visit will be conducted remotely. Clinician will assess for any interval changes and monitor for potential withdraw symptoms or adverse events. Patients will be assessed using clinical scales including the CY-BOCS, HQ-CT, CGI-I, CGI-S, MERS-R-PWS, and C-SSRS. If patient didn't complete ABC assessment prior to the scheduled visit, it will be collected via clinician administration to the same reporter to ensure timely completion.

C 9.3 Special Circumstances
During special circumstances (e.g. COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. In cases where participants are not able to perform all protocol-defined assessments due to special circumstances, the investigator must discuss with the medical monitor potential mitigation approaches.

For the duration of such special circumstances, the following measures may be implemented for enrolled subjects:

- **A.** Safety follow-up may be done by a telephone call, other means of virtual contact or home visit, if appropriate.
- **B.** Patient and/or clinician-rated outcomes assessments may be done by video-conference, telephone call, and other means of virtual contact, if possible.
- **C.** An alternative approach for IMP dispensing, secure delivery and collection may be sought
- **D.** Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with documentation of the means of communication (e.g., phone call or videoconference).

E. Biological samples may be collected and analysed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.

F. If despite best efforts it is not possible to collect the biological samples or safety assessments (e.g. ECG, vital signs), the investigator must review the benefit-risk for patient continuation in the study and record this in the medical records

G. If patient is unable to attend baseline visit within 3 months of screening lab results, patient will hold off on drug administration until lab results from baseline visit has been reviewed and cleared by the study clinician, at which time the study clinician will inform the patient it is ok to start drug administration. This date will be recorded and used for drug accountability.

The rationale (e.g., the specific limitation imposed by the special circumstances that led to the inability to perform the protocol-specified assessment) and outcome of the discussion with the medical monitor will be documented in the medical record. Information on how each visit was performed will be recorded in the eCRF.

C.10. Schedule of Events

Procedure	Time Needed	Completed By			Screening (Remote)	Baseline (On Site)	Wk 2 (Remote)	Wk 4 (Remote)	Wk 6 (Remote)	Wk 8 (Remote)	Wk 10 (Remote)	Wk 12 / Early Term (On Site)	Wk 14 F/U (Remote)
		Parent	Child	Clinician									
Informed Consent	60 min	X	X	X	X	X							
I/E Criteria	10 min	X		X	X	X							
Medical Hx/Demographic	30 min	X		X	X								
Physical/Neuro Exam	20 min		X	X		X						X	
Psychiatric Interview	30 min	X	X	X	X								
IQ test (SB-5, Abbreviated)	20 min	X	X	X		X							
ECG	20 min		X	X		X						X	
Randomization	0 min					X							
Review Concomitant Medications	5 min	X		X	X	X	X	X	X	X	X	X	X
Drug Test	5 min		X		X*	X							
Pregnancy Test (if applicable)	5 min		X		X*	X		X*				X	
Vital signs, Weight, BMI	15 min		X	X		X						X	
CBC with differential and basic metabolic panel	15 min		X		X*	X		X*				X	
Liver Function Enzymes	15 min		X		X*	X	X*	X*				X	
AED drug levels (if applicable)	15 min		X			X		X				X	
Adverse Event Monitoring	10 min	X		X			X	X	X	X	X	X	X
Menstrual Diary Review (if applicable)	5 min	X				X		X		X		X	
Dispense Medication	5 min	X		X		X		X		X			

Scales	**ABC-I**	15 min	X			X	X		X		X		X	X
	RBS-R	20 min	X				X		X		X		X	
	CSQ	15 min	X				X		X		X		X	
	CY-BOCS	20 min	X		X		X		X		X		X	X
	HQ-CTx	15 min	X		X		X		X		X		X	X
	MERS-R-PWS	15 min	X		X		X		X		X		X	X
	CGI-I	5 min		X	X				X		X		X	X
	CGI-S	5 min		X	X	X	X		X		X		X	X
	C-SSRS	15 min	X	X	X		X	X	X	X	X	X	X	X
	Dietary Diary	15 mins	X				X		X		X		X	
	Actigraphy **	ongoing	X	X	X		X						X	

*Denotes visit require outpatient Quest visit
**Actigraphy device will be dispensed to participants after successful screening and prior to baseline visit, will collect minimum of 3 days of baseline data prior to randomization. Information collected continuously and reviewed at in person visit

D. ADVERSE EVENT and REPORTING PROCEDURES

D.1. Adverse Events

Information about all adverse events (AEs), whether volunteered by the subject, discovered by investigator/coordinator, or detected through physical examination, laboratory test or other means, will be collected, recorded and repeated/followed as appropriate. Required interventions required to treat the AE will be documented as well as the outcome.

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug, even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require an intervention.

Each AE should be evaluated to determine:

1. Severity grade (mild, moderate, severe) or (grade 1-4)
2. Relationship to the study drug(s) (suspected/not suspected)
3. Duration (start and end dates or if continuing at final exam)
4. Fulfillment of any serious adverse event (SAE) criteria

All AEs should be treated as clinically indicated. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an AE is identified, it should be followed until its resolution or stabilization (if permanent), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity. The investigator should determine the relationship to the study drug. The IRB will be notified about AEs in compliance with its policy.

Information about common side effects already known about the drug can be found in the Investigator's Brochure (see section D.3.1). This information is also included in the informed consent document and will be discussed with the subject during the study as needed.

D.2. Serious Adverse Events

Information about all serious adverse events (SAEs) will be collected and recorded. To ensure subject safety, any SAE must be reported to the PI as soon as possible after learning of its occurrence. An SAE is defined using the following criteria:

1. Is fatal or life-threatening.
2. Results in persistent or significant disability/incapacity.
3. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    a. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    b. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    c. treatment on an emergency outpatient basis for an event not fulfilling any

of the definitions of a SAE given above and not resulting in hospital admission

d. social reasons and respite care in the absence of any deterioration in the subject's general condition

4. Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

The Investigator will notify the GW Pharmacovigilance Department of any SAE (regardlessof causality) within 24 hours of Investigator first awareness (US toll free number for SAE reporting: 1 866 234 1751)
GW Pharmacovigilance Dept e-mail: PVD@gwpharm.com
Phone +44 1223 233410

The Investigator will report to FDA all deaths within 7 days and all serious adverse events within 15 days of discovery.

D.3. Adverse Events Specific to this Protocol
Across all GW sponsored Phase 1 and Phase 2 clinical trials with CBDV to date, CBDV was generally well tolerated[28].

D.3.1. Known Undesirable Drug Side Effects:
It should be noted that this investigational medication is in the early phases of development and the safety profile is yet to be established. An asymptomatic rise in transaminase levels (without rise in bilirubin levels) noted in a Phase 1 healthy volunteer multiple-dose study led to imposing a maximum dose cap of 20 mg/kg/day for CBDV. The maximum dose in this clinical trial is 10 mg/kg/day.[28] We will screen for any evidence of acute liver failure, teratogenicity, or the occurrence of pancreatitis. It is known that certain conditions that increase the risk of the liver toxicity including: very young age (<2 years), previous liver disease, severe mental retardation/intellectual disability, the presence of an underlying metabolic disorder (especially urea cycle disorder), or organic brain disease. Participants will be pre-screened to avoid these issues (see exclusion criterion). Given the age range (5-30) it is unlikely that the teratogenicity will be an issue in this protocol since girls will not have reached menarche. Girls with menarche will be screened with a pregnancy test and excluded if it is positive.

Recently there has been evidence of increased risk of suicidal thoughts or actions in individuals taking anticonvulsant medications. Based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drugs, there is a small elevated risk that occurs as early as 1 week after starting therapy and continued for at least 24 weeks. C-SSRS will be attempted to be given at each visit to identify those subjects at risk and they will be referred for therapy.

D.3.2. Potential Risks Associated with Study Procedures
There is the risk that the treatment may not work or may worsen symptoms or that the subject will have a reaction that is currently not known or not expected. Although all information will be kept secure, there is a minimal risk that unauthorized individuals may see this information.

I. Questionnaires.
Sometimes interviews and/or assessments could be tiring, frustrating or uncomfortable. Breaks will be provided as frequently as necessary to accommodate this. Subjects can choose not to answer

questions that make them feel uncomfortable

II. Blood Draw
Rarely, the vein where the needle is inserted will become sore or red. Sometimes, a temporary harmless "black and blue" may develop. Very rarely, fainting may occur.

III. Risks to Women Who Are or May Become Pregnant
The effect of CBDV on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are pregnant, trying to become pregnant or breastfeeding (or sharing breast milk).

IV. Allergic Reaction to Study Drug.
Any drug can cause an allergic reaction, which could be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing.

V. New Findings.
If we learn any significant new findings during the study that might influence the subjects' decision to participate, we will contact them and explain. Participants will have the option to continue with the study or stop their participation at any time.

VI. Unknown Risks.
We have described all known risks. Due to the nature of research, there exists a possibility that a subject will have an unknown reaction that we have not anticipated.

E. DATA MANAGEMENT METHODS

E.1. Data Collection, Management and Quality Control
The MediData RAVE electronic data capture (EDC) system will be used to capture data into the clinical database. The use of EDC will allow secure access to the data and provide an electronic audit trail of all data entered. It will allow a standardized method for data collection that minimizes user bias and maintains consistency. The data will be immediately and remotely accessible and can be easily summarized in a variety of real-time reports. Database programming was conducted in accordance with executed agreement with Bioforum Data Masters vendor master services agreement between Albert Einstein College of Medicine and Bioforum CDMC Ltd. Data will be encoded using unique patient identifiers, and not patient names. IDs will be assigned sequentially, in a manner unrelated to name or other easily identifiable information. Data will be entered for both screened and randomized subjects to allow analyses to assess the degree to which randomized subjects may differ from other potential subjects.

F. QUALITY CONTROL METHOD

F.1. Data and Safety Monitoring Committee
An Independent Data Safety Monitoring Committee (IDSMC) will review safety and clinical outcome data including data on adverse events (AEs) and serious adverse events (SAEs) at regular intervals. The IDSMC will be independent of the investigator and will be empowered to

recommend stopping the study due to safety concerns, but not for efficacy or futility. The IDSMC may review blinded, unblinded, or partially unblinded data, but the investigator will remain blinded until the official unblinding of the database. The IDSMC will meet three times throughout the trial to review/approve the protocol, and to monitor patient accrual and safety. The IDSMC will include within its membership a medical monitor as well as a biostatistician.
A charter will also be prepared for the IDSMC outlining the following:

1. The purpose and responsibilities of the IDSMC
2. IDSMC membership and communications
3. Issues of conflict of interest and compensation
4. Scheduling and organization of Meetings
5. Materials and protocol for IDSMC meetings
6. Reporting requirements for the Cannabidivarin (CBDV) vs. Placebo in Children with Prader-Willi Syndrome (PWS) to the IDSMC
7. Reports of IDSMC Proceedings for IRBs
8. Assessment of safety

G. DATA ANALYSIS PLAN

Subject will be randomly assigned (1:1) to CBDV or placebo and followed for 12 weeks. Analyses will be based on the intent-to-treat approach in which subjects are analyzed in the group to which they were originally assigned regardless of compliance. The demographic characteristics of all randomized patients will first be summarized using standard descriptive statistics (means, medians, standard deviations, and ranges for continuous variables and frequencies for categorical variables). Our primary analysis will examine CBDV vs. placebo on the ABC-I. Our secondary analyses will investigate changes in measures of repetitive behaviors (RBS-R, CYBOCS), hyperphagia (HQ-CT), sleep quality (ActiGraph activity monitors), rigid behaviors(MERS-R-PWS), problematic behaviors (other ABC subscales) and global improvement (CGI-I, CGI-S, CSQ). Between group differences in these measures obtained at a specific time point (e.g. 12 weeks) will be compared with the two sample t-test or Wilcoxon rank sum test. In addition, the change in outcome measures between baseline and 12 weeks will be compared between treatment groups. Exploratory analyses will first be performed to evaluate whether the magnitude of changes in these variables between the two time points depends on the baseline value. If there is no evidence that change is dependent on baseline, then two sample t- tests will be used to compare the mean change in each variable between treatment groups; otherwise, analysis of covariance models will be fit to the data where the outcome is the level measured at 12 weeks, and the main effects are treatment group and baseline value. Adjustment for any patient characteristics which appear to be imbalanced across treatment groups will be accomplished by including the relevant terms as main effects into the model. To compare longitudinal trends in outcomes between treatment groups, linear fixed effects models will be fit to all repeated measures obtained during follow-up, with main effects for time and treatment group and a time x treatment interaction term; this is a widely used statistical approach in longitudinal studies of psychiatric outcomes. Appropriate data transformations, such as the log transform, will be applied if the data deviate from the normal distribution.

In any clinical trial, some subjects will be lost to follow up but the expected rate is low given that this is only a 12-week trial. The advantage of the mixed modeling approach is that it can handle data which are missing at random and measurement times which are not evenly spaced. Analyses will also be performed to compare the characteristics of patients who were lost to follow-up and those who completed the trial to assess the degree of any selection bias. Although a number of

different outcomes will be analyzed, we will not adjust for multiple testing given the exploratory nature of this study.

H. STATISTICAL POWER and SAMPLE SIZE CONSIDERATION

Power Analysis—Sample Size Justification

Assuming a common standard deviation for data of 8.27 and using a 2-sided hypothesis test at a 0.05 α-level, a total sample size of 32 participants (16 participants per group) will provide 80% power to detect a significant result assuming a true treatment difference of -8.26 points for the ABC-I score in change from baseline to end of treatment between GWP42003-P and placebo. Allowing for a 10% drop-out rate, a minimum of 36 (i.e. 18 per group) participants need to be randomized into the study. Depending on the drop-out rate during the trial, this number may be increased to ensure a minimum of 32 evaluable participants at Week 12. The assumed SD and treatment mean difference are based on a weighted mean and a pooled standard deviation of estimates from Risperidone trials in irritability in ASD[44].

I. FUNDING

This study is supported by the Foundation for Prader-Willi Research with a budget of $108,000.00 for one year and GW Pharmaceuticals.

J. RESEARCH PROTOCOL ADHERENCE

Study activities in the first 6 months of the study include submission and receipt of IND, preparing the operations manual and regulatory documents; joint training of personnel in study procedures and outcome measures and meeting with the data management and statistical analysis teams of the ICTR to discuss study start up plans and timelines. The PI will meet regularly with the study team to review the status of the study and devise any strategies needed to meet the study goals. Planning for cross validation of all outcome measures will be part of the quality control procedures. Periodic reports on recruitment, treatment, retention and follow up will be generated and reviewed by the study team. The medical monitor, Dr. J. Battaglia, will be included on monthly calls to review study progress and safety evaluations.

The role and responsibilities of the Research Monitor, Dr. J. Battaglia includes the following:

1. May discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research.
2. Dr. Battaglia shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the her report.
3. Dr. Battaglia shall have the responsibility to promptly report her observations and findings to the IRB or other designated official.
4. Dr. Battaglia is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, Dr. Battaglia must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. He must also indicate whether she concurs with the details of the report provided by the Dr. Hollander.

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Appendix A: P450 Drug Interaction Table, Flockhart Table ™

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline	artemisinin	amodiaquine	NSAIDs:	PPIs:	tamoxifen	Anesthetics:	Macrolide antibiotics:
caffeine	bupropion	cerivastatin	diclofenac	esomeprazole		enflurane	clarithromycin
clomipramine	cyclophosphamide	paclitaxel	ibuprofen	lansoprazole	Beta Blockers:	halothane	erythromycin
clozapine	efavirenz	repaglinide	lornoxicam	omeprazole2	carvedilol	isoflurane	2 (not 3A5)
cyclobenzaprine	ifosphamide	sorafenib	meloxicam	pantoprazole	S-metoprolol	methoxyflurane	NOT
duloxetine	ketamine	torsemide	S-naproxen→		propafenone	sevoflurane	azithromycin
estradiol	meperidine		Nor piroxicam	Anti-epileptics:	timolol		telithromycin
fluvoxamine	methadone		suprofen	diazepam→Nor		acetaminophen→ NAPQI	
haloperidol	nevirapine			phenytoin(O)	Antidepressants:	aniline	Anti-arrhythmics:
imipramine N-DeMe	propafol		Oral Hypoglycemic Agents:	S-mephenytoin	amitriptyline	benzene	quinidine→3-OH (not 3A5)
mexiletine	selegiline		tolbutamide	phenobarbitone	clomipramine	chlorzoxazone	
nabumetone	sorafenib		glipizide		desipramine	ethanol	
naproxen				amitriptyline	fluoxetine	N,N-dimethylformamide	Benzodiazepines:
olanzapine			Angiotensin II Blockers:	carisoprodol	imipramine	theophylline→8-OH	alprazolam
ondansetron			losartan	citalopram	paroxetine		diazepam→3-OH
phenacetin→ acetaminophen →NAPQI			irbesartan	chloramphenicol	venlafaxine		midazolam
propranolol			Sulfonylureas:	clomipramine	Antipsychotics:		triazolam
riluzole			glyburide	clopidogrel	haloperidol		
ropivacaine			glibenclamide	cyclophosphamide	perphenazine		Immune Modulators:
tacrine			glipizide	hexobarbital	risperidone→9-OH		cyclosporine
theophylline			glimepiride	imipramine N-DeME	thioridazine		tacrolimus (FK506)
tizanidine			tolbutamide	indomethacin	zuclopenthixol		
triamterene				labetalol			HIV Antivirals:
verapamil			amitriptyline	R-mephobarbital	alprenolol		indinavir
(R)warfarin			celecoxib	moclobemide	amphetamine		nelfinavir
zileuton			fluoxetine	nelfinavir	aripiprazole		ritonavir
zolmitriptan			fluvastatin	nilutamide	atomoxetine		saquinavir
			glyburide	primidone	bufuralol1		
			nateglinide	progesterone	chlorpheniramine		Prokinetic:
			phenytoin-4-OH2	proguanil	chlorpromazine		cisapride
			rosiglitazone	propranolol	clonidine		
			tamoxifen	teniposide	codeine (→O-desMe)		Antihistamines:
			torsemide	R-warfarin→8-OH	debrisoquine		astemizole
			valproic acid	voriconazole	dexfenfluramine		chlorpheniramine
			S-warfarin		dextromethorphan		terfenadine
			zakirlukast		donepezil		
					duloxetine		Calcium Channel
					encainide		
					flecainide		
					fluvoxamine		
					lidocaine		
					metoclopramide		
					methoxyamphet		

amine
mexiletine
minaprine
nebivolol
nortriptyline
ondansetron
oxycodone
perhexiline
phenacetin
phenformin
promethazine
propafenone
propranolol
risperidone
sparteine
tramadol

Blockers:
amlodipine
diltiazem
felodipine
lercanidipine
nifedipine
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors:
atorvastatin
cerivastatin
lovastatin
NOT pravastatin
NOT rosuvastatin
simvastatin

Steroid 6beta-OH:
estradiol
hydrocortisone
progesterone
testosterone

Miscellaneous:
alfentanil
aprepitant
aripiprazole
boceprevir
buspirone
carbamazepine
cafergot
caffeine→TMU
cilostazol
cocaine
codeine-N-demethylation
dapsone
dexamethasone
dextromethorphan
docetaxel
domperidone
eplerenone
fentanyl

finasteride
gleevec
haloperidol
irinotecan
LAAM
lidocaine
methadone
nateglinide
nevirapine
ondansetron
pimozide
propranolol
quetiapine
quinine
risperidone
romidepsin
salmeterol
sildenafil
sirolimus
sorafenib
sunitinib
tamoxifen
taxol
telaprevir
terfenadine
torisel
trazodone
vemurafenib
vincristine
zaleplon
ziprasidone
zolpidem

INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.

A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

FDA preferred1 and acceptable2 inhibitors for in vitro experiments.*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine ciprofloxacin cimetidine amiodarone efavirenz fluoroquinolones fluvoxamine	clopidogrel thiotepa ticlopidine voriconazole	gemfibrozi trimethoprim glitazones montelukast quercetin	fluconazole amiodarone efavirenz fenofibrate fluconazole fluvastatin fluvoxamine isoniazid	PPIs: esomeprazole lansoprazole omeprazole pantoprazole Other: chloramphenicol cimetidine felbamate	bupropion cinacalcet fluoxetine paroxetine quinidine duloxetine sertraline terbinafine amiodarone	diethyl-dithiocarbamate disulfiram	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole

furafylline interferon methoxsalen mibefradil ticlopidine		lovastatin metronidazole paroxetine phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole1 teniposide voriconazole zafirlukast	fluoxetine fluvoxamine indomethacin isoniazid ketoconazole modafinil oral contraceptives oxcarbazepine probenicid ticlopidine2 topiramate voriconazole	cimetidine celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine haloperidol histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine promethazine ranitidine reduced-haloperidol ritonavir ticlopidine tripelennamine		nefazodone saquinavir suboxone telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine starfruit telaprevir voriconazole

INDUCERS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli brussel sprouts carbamazepine char-grilled meat insulin methylcholanthrene modafinil nafcillin beta-naphthoflavone omeprazole	artemisinin carbamazepine efavirenz nevirapine phenobarbital phenytoin rifampin	rifampin1	carbamazepine enzalutamide nevirapine phenobarbital rifampin secobarbital St. John's Wort	carbamazepine efavirenz enzalutamide norethindrone NOT pentobarbital prednisone rifampicin ritonavir St. John's Wort	dexamethasone rifampin	ethanol isoniazid	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine enzalutamide glucocorticoids modafinil oxcarbazepine phenobarbital

rifampin
tobacco

phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

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Appendix B: UGT1A9 or UGT2B7 Potential Interactions

Reaction phenotyping studies designed to identify the UGT enzymes involved in conjugating a new drug candidate must overcome certain challenges that are not evident (for the most part) in a CYP enzyme reaction phenotyping study.
UGT 1A9 is expressed in human liver, kidney, and colon. UGT 1A9 is expressed in greater amounts in kidney than in liver and is the most prevalent UGT in renal tissue. UGT 1A9 is largely responsible for the glucuronidation of a variety of bulky phenols, e.g., tert-butylphenol and the anaesthetic agent, propofol (2,6-diisopropylphenol, commonly used as a marker substrate)[45].

Propofol is a selective substrate for UGT1A8 and UGT1A9, but extrahepatic metabolism of propofol appears to be important because propofol glucuronide is formed in substantial amounts in patients during the anhepatic phase of liver transplantation. Propofol clearance is greater than liver blood flow, also suggesting that extrahepatic metabolism is important for this compound. It is glucuronidated in vitro by human kidney and small intestinal microsomes. The Vmax was 3 to 3.5 times higher in human kidney microsomes compared with liver or small intestine microsomes on a milligram per microsomal protein basis. A number of pharmacodynamic interactions have been reported between propofol and benzodiazepines or opioids such as fentanyl and alfentanil. Pharmacokinetic interaction studies in humans with fentanyl or alfentanil revealed a modest decrease in propofol clearance (20 - 50%). UGT1A9 also catalyzes the glucuronidation of clofibric acid, S-oxazepam, propranolol, raloxifene, valproic acid, cis-4-0H-tamoxifen, and several NSAIDs. These acidic drugs appear to be glucuronidated at a much faster rate by cloned, expressed UGT1A9 than by UGT2B7 on a milligram protein basis (assuming equivalent levels of expression) [45].
Selective UGT inhibitors have only been characterized for UGT1A4 (hecogenin) and UGT2B7 (fluconazole). Correlation analysis can be performed for UGT enzyme activities in individual human liver microsomes, but commercially available and specific probe drugs have been identified only for certain human UGT enzymes, including UGT1A9 (propofol), UGT2B7 [morphine 6-glucuronidation and zidovudine (AZT). Correlation analyses are somewhat limited by the fact that there is often only a three- to fivefold difference from the minimum to the maximum rate of reaction among samples of human microsomes. Formation of the phenolic ether glucuronide of MPA is catalyzed by UGT1A8 and UGT1A9, whereas the acyl glucuronide formation of MPA (a minor metabolite in HLMs) is attributable to UGT2B7. Tacrolimus and cyclosporine (agents commonly used with mycophenolate in transplant patients) have been shown to inhibit mycophenolate glucuronidation in vitro and were later shown to be substrates for intestinal UGT2B7 [45].
Morphine and codeine are metabolized by UGT2B7 and lorazepam and oxazepam by UGT2B7 and 2B15. Nicotine is a substrate for UGT1A4, 2B10, and 2B7, and cotinine for UGT1A4 and 2B10[46]. UGT1A9 and 2B7 are predominantly involved in ethanol glucuronidation (50% of the overall ethyl glucuronide formation). Ethanol can substantially inhibit UGT2B17 and 1A6. CBD is metabolized by UGT1A9, UGT2B7, and UGT2B17. CBD exhibits a strong noncompetitive inhibition of ethanol glucuronidation, which could be attributed to the inhibition of both UGT1A9 and 2B7[46]. CBDV also undergoes direct glucuronidation via uridine 5'-diphospho-

glucuronosyltransferase (UGT) 2B7. CBDV is a potent inhibitor of UGT1A9 and UGT2B7[47]. As there are limited clinical data on CBDV drug interactions, caution is advised when administering CBDV as add-on therapy to other medications.