AN EXPLORATORY, PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO INVESTIGATE THE SAFETY AND EFFICACY OF CANNABIDIOL ORAL SOLUTION (GWP42003P; CBD-OS) IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

Study Code: GWND19189

IND Number: [redacted]

EudraCT Number: 2020-002819-21

CLINICAL PROTOCOL

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol entitled "An exploratory, Phase 2, randomized, double-blind, placebo-controlled trial to investigate the safety and efficacy of cannabidiol oral solution (GWP42003-P; CBD-OS) in children and adolescents with Autism Spectrum Disorder", dated 24 November 2020 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the US FDA regulations relating to GCP and clinical trials, the EU Clinical Trials Directive (2001/20/EC), the EU GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of patients during the trial and for all trial-related medical decisions.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

Center No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: [redacted] Date: _____

Medical Director (DD Month YYYY)

[redacted]

Signature: _____

1 PROTOCOL SYNOPSIS

<table>
<tr><td>Trial Title</td><td colspan="2">An exploratory, Phase 2, randomized, double-blind, placebo-controlled trial to investigate the safety and efficacy of cannabidiol oral solution (GWP42003-P; CBD-OS) in children and adolescents with Autism Spectrum Disorder</td></tr>
<tr><td>Clinical Trial Type</td><td colspan="2">Phase 2</td></tr>
<tr><td>Indication</td><td colspan="2">Autism Spectrum Disorder</td></tr>
<tr><td>Objectives and Endpoints</td><td>Efficacy Objective</td><td>Efficacy Endpoints</td></tr>
<tr><td></td><td>• To evaluate the efficacy of GWP42003-P, compared with placebo, in reducing symptom severity in children with ASD.</td><td>Behavior
• ABC Subscales
Social Communication
• VABS-3
Overall Condition
• CGI-I
• CGI-S</td></tr>
<tr><td></td><td>Safety Objective</td><td>Safety Endpoints</td></tr>
<tr><td></td><td>• To evaluate the safety of GWP42003-P, compared with placebo, in children with ASD.</td><td>• AEs.
• Clinical laboratory parameters.
• Vital signs.
• Physical examination procedures.
• 12-lead ECG.
• C-SSRS.</td></tr>
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</table>

	[redacted]
Trial Design	This is an exploratory, Phase 2, double-blind, randomized, placebo-controlled, multisite trial, which will compare the safety and efficacy of a 10 mg/kg/day dose of GWP42003-P versus placebo in children and adolescents with ASD. Patients will be screened and if they meet eligibility criteria, they will be randomized to receive GWP42003-P or matching placebo in a 1:1 ratio. Patients will be stratified based on their age (6 to 11, 12 to 17), use of antipsychotics (on versus off), and region (North America versus Rest of the World). Patients will be administered 5 mg/kg/day GWP42003-P or matching volumes of placebo for 1 week and then 10 mg/kg/day GWP42003-P or matching volumes of placebo for 11 weeks. At the end of treatment, patients will taper the medication over 1 week. In order to facilitate trial execution in the context of infectious diseases or other transmissible conditions (e.g., COVID-19), the trial will involve a combination of clinic, remote (including a video call and a home nurse visit) and telephone visits, as specified in APPENDIX 1.
Sample Size	160 patients randomized to allow for 144 evaluable patients (72 evaluable patients per arm) at trial end.
Summary of Patient Eligibility Criteria	**Inclusion Criteria** For inclusion in the trial, patients must fulfill ALL of the following criteria: • Male or female aged 6 to 17 years (inclusive). • Patient weight is at least 12 kg. • Patients (if possessing adequate understanding, in the investigator's opinion) and their parent(s)/legal representative are willing and able to give informed assent and consent for participation in the trial. • Patient and their caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements. • Patient has a diagnosis of ASD as per DSM-5 criteria for ASD, confirmed by ADOS-2 criteria (conducted within 2 years at the trial site or at screening by a qualified assessor). *Note: During special circumstances (e.g., COVID-19 pandemic) where the ADOS-2 cannot be performed due to site restrictions (e.g., mandatory use of face masks) and an ADOS-2 conducted within 2 years at the trial site by a qualified assessor is not available, eligibility can be confirmed using: 1) an ADOS-2 performed within 2 years by a qualified assessor*

	(external to the site); 2) if 1) is not available, eligibility may be confirmed using the ADI-R at screening. • CGI-S ≥ 4 (moderately ill) at screening and randomization. • ABC-I subscale score ≥ 15 at screening. • IQ ≥ 70 at screening, or measured within 1 year of screening, using WASI-II. • All medications or interventions (including psychosocial interventions, dietary supplements, probiotics, speech therapy, etc.) for ASD related symptoms must have been stable for 4 weeks prior to screening and randomization, and the patient/caregiver should be willing to maintain a stable regimen throughout the trial. • Patients must have the ability to swallow the IMP, provided as a liquid solution. • Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law. • Patient and/or parent(s)/legal representative is/are willing to allow the patient's primary care practitioner (if they have one) and consultant (if they have one) to be notified of participation in the trial if the primary care practitioner/consultant is different from the investigator. **Exclusion Criteria** The patient may not enter the trial if ANY of the following apply: • Current diagnosis of bipolar disorder, psychosis, schizophrenia, schizoaffective disorder, or major depression (patients with depression in remission may be included). • Has a diagnosis other than ASD that dominates the clinical presentation (e.g., ADHD). • Has a progressive neurological condition. • Seizures in the past 24 weeks. • Changes in anticonvulsive therapy within the last 12 weeks. • Currently taking more than 2 AEDs. • Taking sirolimus, everolimus, temsirolimus, or tacrolimus. • Taking clobazam. • Taking omeprazole, lansoprazole, tolbutamide, or warfarin. • Taking repaglinide, pioglitazone, rosiglitazone, montelukast, bupropion, or efavirenz. • Currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex®, or Epidiolex®/Epidyolex®) within the 12 weeks prior to screening and is unwilling to abstain for the duration of the trial.

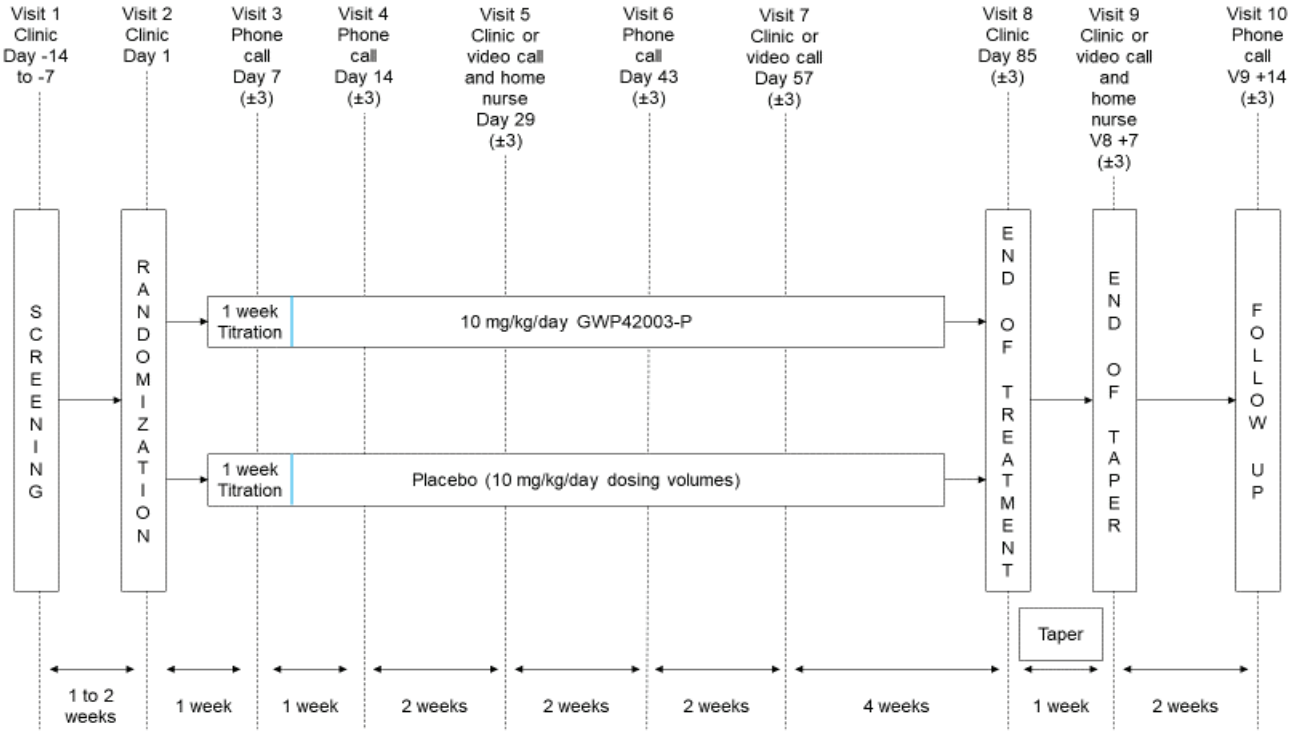
	• Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil. • Patient has moderately impaired hepatic function at screening, defined as serum ALT or AST > 2 × ULN or TBL > 2 × ULN' *This criterion can only be confirmed once the laboratory results are available; patients enrolled into the trial who are later found to meet this criterion must be screen-failed.* • Patient is male and fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) unless willing to ensure that they use male contraception (condom) or remain sexually abstinent during the trial and for 12 weeks thereafter. • Patient is female and of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless willing to ensure that they use a highly effective method of birth control (e.g., hormonal contraception, intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for 12 weeks thereafter. • Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial or within 12 weeks thereafter. • Patient has received an IMP within the 12 weeks prior to the screening visit. • Patient had brain surgery or traumatic brain injury within 1 year of screening. • Patient has any other significant disease or disorder which, in the opinion of the investigator, may either put the patient, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or may affect the patient's ability to take part in the trial. • Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they took part in the trial. • Any history of suicidal behavior (lifelong) or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 4 weeks or at screening or randomization. • Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the trial. • Patient has any known or suspected history of alcohol or substance abuse or positive drugs of abuse test at screening (not justified by a known concurrent medication).

	• Patient has previously been randomized into this trial. • Patient has plans to travel outside their country of residence during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.
Criteria for Withdrawal	The patient must be withdrawn from the trial if any of the following apply: • Administrative decision by the investigator, GW or regulatory authority. • Did not meet eligibility criteria. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient consent/assent. • Withdrawal of parent(s)/legal representative consent. • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than 2 weeks. • ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5). • Note: Prior to treatment discontinuation for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests, tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant medication with known hepatotoxicity may be reduced following discussion with the medical monitor.** • Lost to follow-up. The patient may also be withdrawn from the trial for any of the following: • Patient noncompliance. • AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial. • Patient cannot tolerate a dose level of 5 mg/kg/day. • Any evidence of use of drugs of abuse or drug diversion. • Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.

Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, ethanol (10% v/v) sweetener [sucralose], and strawberry flavoring). Mode of administration: to be taken orally b.i.d. (morning and evening) using the syringe(s) provided, preferentially with food i.e., within 30 minutes after the end of a meal/snack. The time of IMP administration in relation to food should be kept consistent throughout the trial. Volume of IMP to be determined by patient's weight.
Control Group	Placebo to match GWP42003-P oral solution containing sesame oil with anhydrous ethanol, sweetener (sucralose), strawberry flavoring, and beta carotene.
Procedures	Before undergoing any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent. In cases where the patient possesses adequate understanding, their assent will be taken, along with parental/legal representative consent. Screening (Visit 1) assessments/procedures will include: • Informed consent/assent; eligibility criteria checks; demographics; medical history. • Concomitant medications/therapies; AE/SAE review. • Test for drugs of abuse. • Full physical examinations; including height, weight, and BMI. • 12-lead ECG. • Hematology; biochemistry (including liver chemistries); and urinalysis. • Serum pregnancy test (WOCBP only). • C-SSRS. • Vital signs. • WASI-II (if required), ADOS-2 (if required, or ADI-R under special circumstances). • ABC, CGI-S. Treatment Period (Visits 2 to 8) assessments/procedures will include (please refer to APPENDIX 1 for frequency of assessments): • Randomization • Concomitant medications/therapies; AE/SAE review • Vital signs • Full physical examinations and weight • 12-lead ECG • Hematology and biochemistry (including liver chemistries) • C-SSRS

	[redacted] • [redacted] ABC, Vineland-3, [redacted] CGI-S, CGI-I, [redacted] [redacted] • IMP dispensing • IMP review Note: Visits 3, 4, 6, and 10 are to be conducted by telephone End of Taper (Visit 9) assessments/procedures will include: • Concomitant medications/therapies; AE/SAE review • C-SSRS • Vital signs • Hematology; biochemistry (including liver chemistries); and urinalysis • Serum pregnancy test (WOCBP only) • IMP review Follow-up (Visit 10) assessments/procedures will include: • Concomitant medications/therapies; AE/SAE review Additional procedures to screen for the presence of or immunity against infectious diseases (such as body temperature, sampling of nasal mucosal cells, or serology) may be conducted at screening, at the beginning of each visit, or as needed, according to local guidance and policy.
Statistical Considerations	All safety and efficacy data will be summarized and analyzed using appropriate statistical methods. Questionnaires will be summarized at each visit along with the change from baseline, where appropriate. As this is an exploratory trial, there will be no type I error adjustments with all hypothesis testing performed at a 5% significance level.
Safety Monitoring Committee	Not applicable.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Trial Design and Treatment Schematic



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List of Abbreviations

ABC	Aberrant Behavior Checklist Subscales
ABC-I	Aberrant Behavior Checklist Irritability Subscale
ADHD	Attention deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview, Revised
ADOS-2	Autism Diagnostic Observational Schedule
AE	Adverse Event
AESI	Adverse Event of Special Interest
AED	Anti-epileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
BAC	Blood alcohol content
b.i.d	Twice daily
BMI	Body mass index
[redacted]	[redacted]
BUN	Blood urea nitrogen
Ca	Calcium
[redacted]	[redacted]
CB	Cannabinoid
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	GWP42003-P, Cannabidiol oral solution
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine kinase

C_{max}	Maximum measured plasma concentration
COVID-19	Corona virus disease-19
CRF	Case report form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DS	Dravet syndrome
DMC	Data Monitoring Committee
ECG	12-Lead electrocardiogram
eCRF	Electronic case report form
ECS	Endocannabinoid system
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GPR55	G protein-coupled receptor 55
GW	GW Research Ltd
HDL	High density lipoprotein
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
LGS	Lennox-Gastaut syndrome
LS	The least squares
MDMA	3,4-Methylenedioxymethamphetamine

MMRM	Mixed-effects repeated measures model
[redacted]	[redacted]
PI	Principal Investigator
[redacted]	[redacted]
PP	Per protocol
PRN	Packaging reference number
PT/INR	Prothrombin time/International normalized ratio
PVD	Pharmacovigilance Department
[redacted]	[redacted]
RTSM	Randomization and Trial Management System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard deviation
SOC	System organ class
SRS	Social Responsiveness Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TBL	Total Bilirubin
THC	Δ^9-Tetrahydrocannabinol
TRP	Transient receptor potential
ULN	Upper limit of normal
US	United States
USA	United States of America
VABS-3	Vineland Adaptive Behavior Scales, 3rd Ed., comprehensive interview form
VAS	Visual analog scale
VPA	Valproic acid
WASI-II	Wechsler Abbreviated Scale of Intelligence Scale Second Edition
WD	Withdrawal
WOCBP	Women of childbearing potential

Definition of Terms

Term	Definition
Day 1	The day a patient first receives investigational medicinal product in this trial.
End of trial	Last patient last visit or last contact, whichever occurs last.
Enrolled patient	Any patient who has provided written informed consent/assent to take part in the trial.
International normalized ratio	A calculation made to standardize prothrombin time.
Investigational medicinal product	Term used to describe both investigational active product and reference therapy (placebo).
Investigator	Trial principal investigator or a formally delegated trial physician.

2 OBJECTIVES AND ENDPOINTS

Efficacy Objective	**Efficacy Endpoints**
• To evaluate the efficacy of GWP42003-P, compared with placebo, in reducing symptom severity in children with ASD.	Social Communication • VABS-3 Behavior • ABC Subscales Overall Condition • CGI-I • CGI-S
Safety Objective	**Safety Endpoints**
• To evaluate the safety of GWP42003-P, compared with placebo, in children with ASD.	• AEs. • Clinical laboratory parameters. • Vital signs. • Physical examination procedures. • 12-lead ECG. • C-SSRS.
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[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3 BACKGROUND AND RATIONALE

3.1 Disease

Autism Spectrum Disorder is a lifelong neurodevelopmental disorder characterized by restricted, repetitive patterns of behavior and persistent deficits in social communication and interaction. In the US, ASD is currently estimated to affect approximately 1 in every 54 children aged 8 years and is reported to occur in all racial, ethnic, and socioeconomic groups[1]. Associated comorbid symptoms can include intellectual disability, language impairment, motor abnormalities (for example, motor delay, hypotonia, catatonia and deficits in coordination), gastrointestinal problems, sleep disorders, psychiatric comorbidities (most commonly anxiety and depression) and behavioral dysregulation such as aggression, impulsivity, irritability, and self-injurious behavior[2]. Autism Spectrum Disorder is approximately 4 times more common in boys than in girls[1].

Autism Spectrum Disorder is diagnosed through developmental screening (18 and 24 months, although additional screening might be needed if a child is at high risk for ASD [e.g., an affected sibling] or if symptoms are present) and comprehensive diagnostic evaluation. Diagnostic tools usually rely on parents' or caregivers' descriptions of their child's development and a professional's observation of the child's behavior[2,3].

There is currently no single standard treatment for ASD. Current options for these patients include early intervention services, behavioral management therapy, education and school-based therapies, nutritional therapy, and medication treatment. Medications are often used to manage certain behaviors, such as irritability, aggression, and self-injury[3,4]. To date, the US FDA has approved 2 drugs for treating irritability associated with ASD (risperidone [RISPERDAL®] and aripiprazole [ABILIFY®]); however, there are no approved drugs for the treatment of the core ASD symptoms (repetitive behavior; communication and social issues). Selective serotonin reuptake inhibitors (fluoxetine [PROZAC®], fluvoxamine [LUVOX®], sertraline [ZOLOFT®], and clomipramine [ANAFRANIL®]) can help to reduce repetitive behaviors and increase social contact, yet these drugs carry an FDA black box warning regarding potential increased risk of suicidal thoughts or attempts in children and adolescents. Anti-epileptic drugs are also required in patients with seizures.

3.2 Cannabidiol Background

GWP42003-P is the substance code for the IMP, purified CBD under development by GW for the treatment of a number of conditions, including childhood onset epileptic syndromes and Rett syndrome.

GWP42003-P is extracted from *Cannabis sativa* L. plants, has a defined chemical profile, and contains consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (≥ 98%) CBD that typically contains less than 0.10% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

Cannabidiol demonstrates anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant, and anti-inflammatory activity[5]. Anti-seizure effects of GWP42003-P have been demonstrated in clinical trials of childhood onset epilepsies[6] and GWP42003-P has received FDA approval and by the EMA in the EU for the treatment of seizures associated with LGS or DS in patients 2 years of age and older (EMA approval is for treatment in conjunction with clobazam).

Cannabidiol possesses very low affinity and lacks appreciable functional activity at CB receptors; CB1 and CB2[6]. In addition, CBD does not significantly interact with enzymes responsible for the synthesis and degradation of endocannabinoids, at clinically relevant concentrations[7,8]. Other data exist describing the polypharmacology of CBD at multiple 7-transmembrane receptor systems, ion channels, transporters and enzymes[7,8] although this is often at concentrations (> 10 μM) that are unlikely to be clinically relevant.

At least 2 mechanisms of anticonvulsant action are proposed for CBD. The first is modulation of intracellular Ca^{2+} mobilization via antagonism of GPR55 and/or activation (and subsequent desensitization) of TRP channels, particularly $TRPV_1$[6]. The second is inhibition of adenosine reuptake[6].

Importantly, CBD does not produce THC-like euphoric effects.

Cannabidiol oral solution has been studied in placebo-controlled clinical trials as adjunctive treatment of seizures associated with LGS and DS and is being used on a compassionate basis, as part of a series of expanded access IND applications in variety of refractory epilepsy syndromes, mainly in pediatric patients. This meaningful clinical trial exposure has yielded safety data on over 1,419 unique patients with epilepsy, with 391 patients with more than 1 year of continuous exposure.

In general, the key risks identified from the clinical development program for LGS and DS are broadly expected to be the same for the ASD population – as the patient demographics and comorbidities have a significant amount of overlap. It is important to note that several of the key

risks for CBD-OS are dose related, as such the lower doses planned for the current trial may improve the tolerability of CBD-OS:

Hepatocellular injury is anticipated to be an important risk for CBD-OS in ASD patients, although to date the transaminase elevations observed with CBD-OS treatment have generally been asymptomatic, with no Hy's law cases reported from any source. The proposed dose level of 10 mg/kg/day may provide an improved tolerability compared to the 10 and 20 mg/kg/day doses employed in the LGS and DS program. Furthermore, the transaminase elevations in LGS and DS patients were markedly more frequent and of a greater magnitude in patients taking concomitant VPA. Of note, VPA use is expected to be less frequent in the ASD population than in the LGS and DS populations, providing an additional avenue to an improved tolerability to CBD-OS with respect to potential hepatocellular injury.

Somnolence type events are anticipated to be important risks for CBD-OS in ASD patients; however, from experience in LGS and DS patients, such events were manageable, and only a minority needed to discontinue CBD-OS. Dose adjustment should help mitigate any events of somnolence and sedation if needed. The somnolence may also diminish with repeated dosing over time.

Cannabidiol oral solution has been shown to cause loss of weight in clinical trials, however the incidence of a significant loss of weight (> 5%) was noted to be similar between the CBD-OS dose of 10 mg/kg/day and placebo in placebo-controlled trials. There was no impact on growth, as measured through BMI or height in these trials.

In DS/LGS studies, aggression was reported in 2.2% of patients in the 10 mg/kg/day group while irritability was reported in 7.2% of patients in the 10 mg/kg/day group. The majority of cases reported were of mild or moderate severity with only few cases leading to withdrawal from these trials.

A higher incidence of pneumonia was noted with CBD-OS in LGS and DS controlled trials, although incidence does not appear to be dose related, majority of patients has risk factors for pneumonia and no plausible mechanism has been identified.

Rash has been reported more often in CBD-OS patients compared with placebo patients in the controlled trials in LGS and DS. Importantly, none showed systemic involvement or involvement of mucous membranes; generally, the rash events have been self-limiting without serious outcomes.

For further information on CBD-OS and current safety information please refer to the IB[6].

3.3 Rationale

Available therapies have limited efficacy, and there is no single standard treatment for ASD. Both FDA-approved agents (risperidone [RISPERDAL in 2006] and aripiprazole [ABILIFY in 2009]) are indicated for irritability and associated with potential for neurological and metabolic adverse effects; in Europe none of these drugs are specifically approved for use in ASD. There are no approved drugs for the treatment of the core ASD symptoms.

CBD has the potential to modulate some of the pathophysiological mechanisms thought to underly ASD. CBD has also shown benefit in a range of pharmacological, brain injury-associated and genetic models of relevant medical conditions, which exhibit behavioral deficits similar to those seen in ASD, including deficits in social behavior, cognition, language, motor abnormalities, and seizures[6].

There is clinical literature on open-label investigations of cannabinoids extracts, containing CBD and THC, in ASD[9,10,11,12]. Data from these investigations suggest some positive effects on behavior however data have generally been collected using non-validated measures, flexible dosing schedules and variable cannabinoid content formulations, all of which render the results difficult to interpret. To date, data from 1 single placebo-controlled trial of a formulation containing CBD and THC in a ratio of 20:1 reported improvement in the SRS and CGI-I[9]. All these investigations have used THC-containing compounds. However, there are known potential safety issues associated with administering THC to children[13] while administration of GWP43002-P has been well tolerated in other pediatric populations. It is therefore important to investigate whether GWP43002-P improves symptom severity in children with ASD.

3.3.1 Choice of Efficacy and Exploratory Endpoints

In this trial, we will evaluate the effect of GWP42003-P on core symptoms ASD and major associated symptoms/comorbidities in children and adolescents.

Efficacy Measures

The core symptoms of autism are the symptoms required for its diagnosis. Per DSM-5, the core symptoms cover 2 domains: persistent deficits in social communication and social interaction AND restricted, repetitive patterns of behavior, interests, or activities.

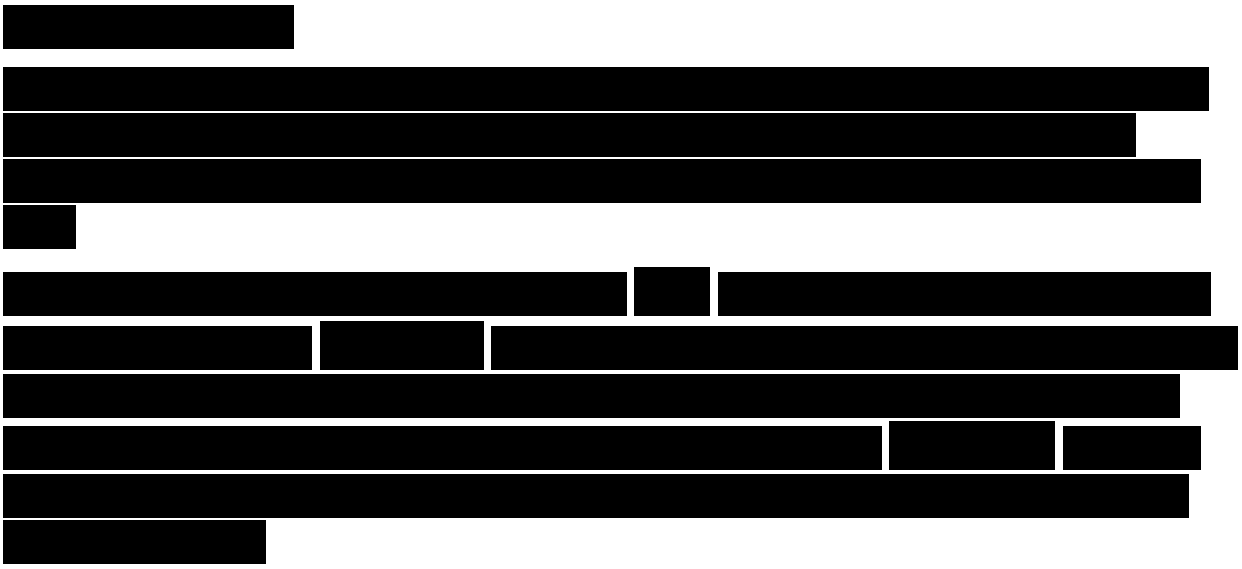
Effects on the core symptom ‘persistent deficits in social communication and social interaction’ will be evaluated using the Vineland-3. The challenges measuring social communication are well reported[14]. Measures such as the widely used SRS have been shown to be highly susceptible to placebo effect, other measures are limited in scope or age range. The Vineland is a well validated

scale with strong reliability that has been widely used in studies in children neurodevelopmental disabilities (although the majority of published studies used the previous version Vineland-2). It was identified by Anagnostou et al[14] as an appropriate measure with conditions with one of the limitations being possibly requiring a longer period to show sensitivity to change. Since, the Vineland-2, and in particular the socialization and communication domains, were reported to detect improvement over a 12-week treatment[15]. Importantly these 2 domains tackle social and communication skills relevant to the ASD population.

Behavioral aspects, such as aggressive and self-injurious behaviors are amongst the most common ASD associated conditions[2], as well as those of greatest concern to caregivers[16]. The ABC-I is a well validated questionnaire with excellent reliability[17], which will be used to evaluate effects in these problem behaviors. The ABC was designed to measure treatment effects and has been used extensively in clinical trial in autism and other neurodevelopmental disorders. The ABC-I in particular has been shown to be sensitive to treatment change, having been a primary endpoint for both risperidone and aripiprazole FDA registration studies.

The remaining subscale scores of the ABC (social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech) assess other aberrant behaviors relevant in ASD.

The CGI-S and CGI-I are widely used outcome measures in clinical trials with well accepted face validity[18]. The CGI-I in particular is known to be sensitive to treatment changes. Being a global measure, changes CGI-I reinforce the clinically meaningfulness of changes reported in symptom specific outcomes.



[redacted]

3.3.2 Choice of Dosing Regimen

Doses of up to 50 mg/kg/day GWP42003-P have been administered in the GW clinical development programs for GWP42003-P. At the time of protocol authoring, a total of approximately 4,973 subjects have received GWP42003-P from blinded and open-label GW-sponsored trials and supportive programs (expanded access and other compassionate use programs), including patients with epilepsy (data cutoff date: Feb 2020). From these data sources the following warnings and precautions were established: hepatocellular injury, somnolence and sedation, suicidal behavior and ideation, hypersensitivity reactions, and withdrawal of AEDs. Of note, routine liver monitoring is required with the use of CBD-OS. To date, the available safety data collected showed that the reported AEs were usually mild or moderate in severity and resolved. There have been few withdrawals due to AEs.

Efficacy of CBD against cognitive and social behavioral deficits in relevant animal models has been found over a range of doses from 2 to 200 mg/kg in a model and endpoint dependent manner[6], with the top dose of the tested dose range overlapping with the effective anticonvulsive dose range of 50 to 200 mg/kg/day in nonclinical models[6]. It is therefore expected that clinical anticonvulsant doses (10 mg/kg/day and 20 mg/kg/day as per studies in LGS or DS patients) should provide meaningful exposures to explore efficacy in ASD.

The doses used across the investigations reported in the literature referencing the use of CBD and THC in ASD are variable but mostly fall between 2 and 10 mg/kg/day CBD. In particular, the target dose in the randomized, placebo-controlled trial[9] was 10 mg/kg day CBD (with a maximum CBD daily dose of 420 mg and an average daily dose of 5.5 mg/kg/day).

The GWND19189 trial will evaluate the efficacy and safety of 10 mg/kg/day CBD-OS (dosed as 5 mg/kg/day b.i.d.) versus placebo. The dose of 10 mg/kg day was selected as it is within the

clinical therapeutic range for GWP42003-P in pediatric epileptic encephalopathies (LGS and DS).

The IMP solution contains 7.9% w/v anhydrous ethanol, which is required as sucralose is not soluble in sesame oil. The proposed dose of 10 mg/kg/day (administered as 5 mg/kg b.i.d.) will result in a BAC of 0.0065 g/L which equates to ethanol ingestion of 3.95 mg/kg. Both these amounts are well under the threshold for BAC of 0.125 g/L and ethanol ingestion of 75 mg/kg for patients 6 years and older. Twice daily (b.i.d) dosing is recommended for this clinical trial in accordance with the approved FDA label for CBD-OS (GWP42003-P) in the treatment of seizures associated with LGS or DS in patients 2 years of age and older. Twice daily dosing should also minimize the potential risk of acute AEs related to C_{max}. Further, peak trough ratios would be reduced, and improved patient adherence may reduce the potential clinical risks of a [redacted] patient/care psychological viewpoint.

Concomitant administration of CBD-OS with a high fat meal resulted in a predictable increase in CBD exposure and less total subject variability. The IMP will therefore be taken preferentially with food i.e., within 30 minutes after the end of a meal/snack, and the time of IMP administration in relation to food should be kept consistent throughout the trial.

3.3.3 Benefit-Risk

There are no approved medications for the core symptoms of ASD and there are limited options for the management of comorbidities.

Nonclinical and clinical data indicate that CBD-OS may benefit patients with ASD (see Section 3.3).

The key risks identified from the CBD-OS clinical development program for LGS and DS (described in Section 3.2) are broadly expected to be the same for the ASD population, as the patient demographics and comorbidities have a significant amount of overlap. Importantly, the risk of raised transaminases is reduced in the context of this ASD trial, where the lower dose of CBD-OS will be used and VPA use is expected to be lower in this population.

In the context of the anticipated benefit of CBD-OS in ASD patients, the key risks identified from the CBD-OS clinical development program in LGS and DS are acceptable given the proposed dose level of 10 mg/kg/day and the age range of 6 to 17 years. Thus, the overall benefit-risk for the development of CBD-OS in the ASD population is favorable.

3.4 Clinical Hypothesis

Treatment with GWP42003-P is associated with improvements in ASD symptom in children and adolescents as measured by the mean change in scores of the ABC-I, VABS-3 communication and socialization composite.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This is an exploratory, Phase 2, double-blind, randomized, placebo-controlled, multisite trial, which will compare the safety and efficacy of a 10/mg/kg/day dose of GWP42003-P versus placebo in children and adolescents with ASD.

Patients will be screened and if they meet eligibility criteria will be randomized to receive GWP42003-P or matching placebo in a 1:1 ratio. Patients will be stratified based on their age (6 to 11, 12 to 17), use of antipsychotics (on versus off), and region (North America versus Rest of the World). Patients will be administered 5 mg/kg/day GWP42003-P or matching volumes of placebo for 1 week and then 10 mg/kg/day GWP42003-P or matching volumes of placebo for 11 weeks. At the end of treatment, patients will taper the medication over 1 week.

A schematic (Figure 1-1), presented at the end of Section 1, depicts the overall trial design. More detailed information on treatment and trial procedures is provided in Section 8 and Section 9, respectively.

Eligible patients may be randomized 7 to 14 days after the screening visit (Visit 1), once all required assessments have been completed and laboratory results have been reviewed; if required, screening assessment may be spilt over 2 visits; however both visits must fall into the 7 to 14 day window prior to randomization (Visit 2). One week and 2 weeks following randomization, there will be 2 safety telephone visits (Visit 3 and 4). The patient will return to the clinic or video call and home nurse visit, 4 weeks after randomization (Visit 5). Six weeks after randomization, there will be another safety call (Visit 6), and then the patient will return for a clinic visit or video call visit (Visit 7) 8 weeks after randomization. The end of treatment visit will take place 12 weeks after randomization (Visit 8). If at any point it is decided to withdraw a patient from the trial, the patient should return to the clinic as soon as possible and complete Visit 8 procedures. At Visit 8, patients will commence to taper the medication (unless in case of withdrawal the medication was already discontinued or continued dosing is inadvisable, e.g., due to an AE). At the end of taper, the patient will return to the clinic or video call and home nurse visit (Visit 9). All patients will have a follow-up safety telephone visit, 14 days after Visit 9 or Visit 8 (in case the patient did not taper the medication).

Visit windows are allowed as defined in the schedule of assessment. Visit 3, 4, 5, 6, 7, and 8 days and windows are counted from the day of randomization (Visit 2). Visit 9 day and window is counted from the day of Visit 8. Visit 10 day and window is counted from the day of Visit 9, or the day of Visit 8 (if the patient did not enter the taper period).

4.2 Number of Centers

Approximately 25 centers are expected to participate in this trial. Additional centers may be used in order to supplement recruitment.

4.3 Number of Patients

It is expected that 188 patients will be screened. With an anticipated screen failure rate of 15%, it is expected that 160 patients will be randomized to allow for 144 evaluable patients (72 evaluable patients per arm) at trial end. The sample size calculation is explained fully in Section 13.1.

5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate pharmacy manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution contains 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v), with sweetener (sucralose), and strawberry flavoring (Table 5.1-1).

Table 5.1-1 Formulation of GWP42003-P Oral Solution

Ingredients	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavor	0.2 mg/mL
Refined sesame oil	make up to 1 mL

CBD = cannabidiol

5.2 Placebo

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added β-carotene, sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

Table 5.2-1 Formulation of Placebo Oral Solution

Ingredients	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavor	0.2 mg/mL
Beta Carotene*	Up to 0.1 mg/mL
Refined sesame oil	make up to 1 mL

* β-Carotene concentration can be varied up to a maximum of 0.01% w/v as required to provide a consistent yellow colored solution.

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled and/or distributed by G-Pharm or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child resistant screw caps and packed in cartons. Sufficient IMP will be dispensed at each relevant visit considering the dose group and the weight of the patient. A unique identification number will be used to identify each carton and the IMP it contains. The unique identification number together with the PRN will permit full traceability of manufacture, pack and label activities conducted at or on behalf of GW and the IMP information held on the RTSM system. GW will ensure that all IMP

provided is fully labeled and packaged. Label text will include the following information, as a minimum:

- Sponsor's name and address.
- Product identification (e.g., "GWP42003-P or Placebo").
- Dose and/or Potency (e.g., "100 mg/mL GWP42003-P").
- Trial code number.
- Expiry date.
- Storage conditions.
- Instruction: "For clinical trial use only".
- Instruction: "Keep out of the reach and sight of children".
- Any other information required by local regulatory authorities.

In addition, any local country requirements in accordance with local Drug Law or Regulatory Requirement will be included in the final label text.

Directions of use, name, address, and the telephone number of the investigator (or main contact for information about the product or the clinical trial) will be provided separately to the caregiver. Caregivers will be instructed to retain and carry this information with the patient at all times.

5.3.2 Storage

The IMP must be stored [redacted]. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities. Temperature records of the clinical center storage location must be maintained (recording a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of trial dispensing period at each center. These records must contain at least the minimum and maximum daily temperatures and must be made available to the appropriate GW personnel for review throughout the trial. Temperature during transit of IMP to the center must be checked on receipt and compliance/noncompliance to the minimum and maximum recorded.

Should storage conditions deviate from these specified requirements, the GW trial monitor must be contacted immediately to confirm if the IMP remains suitable for use. IMP must be placed under quarantine until written confirmation is received that the IMP is suitable for use.

Caregivers will be provided with instructions regarding home storage requirements for the IMP.

5.3.3 Supply and Return of Investigational Medicinal Product

At trial initiation and as needed thereafter, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator's center, who will check the amount received and condition of the drug (i.e., integrity, physical appearance, temperature during transit). Details of the IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The center will acknowledge the IMP receipt and will complete any receipt forms required. IMP will be dispensed and returned as detailed in Section 8.4. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GW/depot or destroyed at a GW-approved site if agreed in writing by the trial monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and must contain:

- Trial code.
- PRN, treatment number, date of receipt and quantity of IMP received.
- Patient's trial identification and or treatment number.
- Date and quantity of IMP dispensed.
- The initials of the dispensing/dosing party.
- Date and quantity of IMP returned to the investigator.
- IMP expiry dates.

Refer to APPENDIX 1 for when IMP will be dispensed. Patients will be asked to return all IMP (used and unused) at each relevant visit (APPENDIX 1). The site will check the returned IMP against the usage recorded in the medication diary. Any discrepancies will be discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to the relevant drug distribution depot. At the end of the trial, verification of reconciliation will be provided to GW.

These inventories must be made available for inspection by an authorized GW representative and local officials or regulatory agency inspectors.

Please refer to the separate pharmacy manual for more detailed information on the IMP.

5.3.5 Post-Trial Provision

No post-trial access to the IMP will be provided.

6 PATIENT ELIGIBILITY

Investigators are responsible for confirming patient eligibility and will be required to maintain information about all screened patients (age, sex; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

For inclusion in the trial patients must fulfill ALL of the following criteria:

6.1.1 Male or female aged 6 to 17 years (inclusive).

6.1.2 Patient weight is at least 12 kg.

6.1.3 Patients (if possessing adequate understanding, in the investigator's opinion) and their parent(s)/legal representative are willing and able to give informed consent for participation in the trial.

6.1.4 Patient is/and their caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements.

6.1.5 Patient has a diagnosis of ASD as per DSM-5 criteria for ASD, confirmed by ADOS-2 criteria (conducted within 2 years at the trial site or at screening by a qualified assessor). *Note: During special circumstances (e.g., COVID-19 pandemic) where the ADOS-2 cannot be performed due to site restrictions (e.g., mandatory use of face masks) and an ADOS-2 conducted within 2 years at the trial site by a qualified assessor is not available, eligibility can be confirmed using: 1) an ADOS-2 performed within 2 years by a qualified assessor external to the site; 2) if 1) is not available, eligibility may be confirmed using the ADI-R at screening.*

6.1.6 CGI-S ≥ 4 (moderately ill) at screening and randomization.

6.1.7 ABC-I subscale score ≥ 15 at screening.

6.1.8 IQ ≥ 70 at screening, measured within 1 year of screening, using WASI-II.

6.1.9 All medications or interventions (including psychosocial interventions, dietary supplements, probiotics, speech therapy, etc.) for ASD related symptoms must have been stable for 4 weeks prior to screening and randomization, and the patient/caregiver should be willing to maintain a stable regimen throughout the trial.

6.1.10 Patient must have the ability to swallow the IMP provided as a liquid solution.

6.1.11 Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law.

6.1.12 Patient and/or parent(s)/legal representative is/are willing to allow the patient's primary care practitioner (if they have one) and consultant (if they have one) to be notified of participation in the trial if the primary care practitioner/consultant is different from the investigator.

6.2 Exclusion Criteria

The patient may not enter the trial if ANY of the following apply:

6.2.1 Current diagnosis of bipolar disorder, psychosis, schizophrenia, schizoaffective disorder or major depression (patients with depression in remission may be included).

6.2.2 Has a diagnosis other than ASD that dominates the clinical presentation (e.g., ADHD).

6.2.3 Has a progressive neurological condition.

6.2.4 Seizures in the past 24 weeks.

6.2.5 Changes in anticonvulsive therapy within the last 12 weeks.

6.2.6 Currently taking more than 2 AEDs.

6.2.7 Taking sirolimus, everolimus, temsirolimus, or tacrolimus.

6.2.8 Taking clobazam.

6.2.9 Taking omeprazole, lansoprazole, tolbutamide, or warfarin.

6.2.10 Taking repaglinide, pioglitazone, rosiglitazone, montelukast, bupropion, or efavirenz.

6.2.11 Patient is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex®, or Epidiolex®/Epidyolex®) within the 12 weeks prior to screening and is unwilling to abstain for the duration of the trial.

6.2.12 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.

6.2.13 Patient has moderately impaired hepatic function at screening, defined as serum ALT or AST > 2 × ULN or TBL > 2 × ULN'.

6.2.14 This criterion can only be confirmed once the laboratory results are available; patients enrolled into the trial who are later found to meet this criterion must be screen-failed.

6.2.15 Patient is male and fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) unless willing to ensure that they use male contraception (condom) or remain sexually abstinent during the trial and for 12 weeks thereafter.

6.2.16 Patient is female and of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless willing to ensure that they use a highly effective method of birth control (e.g., hormonal contraception, intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for 12 weeks thereafter.

6.2.17 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial or within 12 weeks thereafter.

6.2.18 Patient has received an IMP within the 12 weeks prior to the screening visit.

6.2.19 Patient had brain surgery or traumatic brain injury within 1 year of screening.

6.2.20 Patient has any other significant disease or disorder which, in the opinion of the investigator, may either put the patient, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or may affect the patient's ability to take part in the trial.

6.2.21 Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they took part in the trial.

6.2.22 Any history of suicidal behavior (lifelong) or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 4 weeks or at screening or randomization.

6.2.23 Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the trial.

6.2.24 Patient has any known or suspected history of alcohol or substance abuse or positive drugs of abuse test at screening (not justified by a known concurrent medication).

6.2.25 Patient has previously been randomized into this trial.

6.2.26 Patient has plans to travel outside their country of residence during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.

7 PATIENT ENROLLMENT

Before patients may be entered into the trial, GW requires a copy of the relevant center's IRB/EC written approval of the protocol, informed consent/assent forms and other patient information material. Patients will be considered enrolled in the trial from the time of providing written informed consent/assent. All patients and/or parent(s)/legal representatives, where appropriate, must personally sign and date the consent/assent and, if allowed per local regulations, prior to any procedures being performed (refer to Section 9.1.1 and Section 15.2).

7.1 Treatment Assignment

At the start of Visit 1, enrolled patients will be allocated a unique patient number. After confirmation of eligibility at Visit 2, patients will be stratified and randomly allocated to GWP42003-P or matching volumes of placebo using the RTSM in a 1:1 ratio. GW will provide all IMP in a packed and labeled state and the RTSM will identify the pack number to be dispensed to the patient at each relevant visit, according to the treatment assigned in the randomization schedule.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

For details regarding IMP formulations, see Section 5.

8.1.1 Dose Administration

GWP42003-P or placebo will be administered orally b.i.d. (morning and evening) using the syringe(s) provided, preferentially with food i.e., within 30 minutes after the end of a meal/snack. The first dose of GWP42003-P or placebo is taken at home in the evening. The time of IMP administration in relation to food should be kept consistent throughout the trial. Volume of IMP to be determined by patient's weight.

The daily volumes of IMP solution to be taken will be calculated based on the patients' weight and the dosing schedule will be provided to the caregiver.

8.1.2 Dose Escalation, Adjustments, and Taper

Patients will be administered 5 mg/kg/day GWP42003-P or matching volumes of placebo for 1 week and then 10 mg/kg/day GWP42003-P or matching volumes of placebo for 11 weeks.

If an unacceptable AE develops at any time during the dose escalation or treatment periods, dosing should be reduced, at the investigator's discretion and in a blinded manner, until the event has resolved or is well tolerated. The end of treatment taper schedule should be used to guide dose adjustment. If required, dosing may be suspended. Patients whose dose has been decreased should have their dose increased again, if the tolerability improves. Patients unable to tolerate the target dose may stay at a lower dose. If a patient cannot tolerate a dose of 5 mg/kg/day, the investigator should discuss with the medical monitor whether patient continuation in the trial is recommended. Single dose volumes must be at least 0.1 mL.

Transaminase elevations should be medically managed by the investigator either by reducing the IMP dose or, following discussion with the medical monitor, by reducing concomitant medications judged to be causing the elevation (as per Section 10). For potential cases of drug-induced liver injury see Section 12.9.

Dose adjustments should be discussed with the GW medical monitor. The final decision regarding dose adjustments should be taken by the investigator.

At the end of treatment, patients will taper the medication in steps of -2.5 mg/kg/day every 2 days.

8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant medications for ASD related symptoms must have been stable for at least 4 weeks prior to screening and must remain stable throughout the blinded trial period. If there are side-effects suspected of being related to a drug-drug interaction, the investigator must contact the medical monitor to discuss best management. Decisions should be based on clinical symptoms and not plasma levels of concomitant medications. Further information on drug interactions can be found in the IB[6]. Dose reductions for concomitant medications for ASD related symptoms are permitted on clinical grounds (e.g., due to AEs or transaminase elevations **not meeting** withdrawal criteria specified in Section 10 and Section 12.8 following discussion with the medical monitor).

Any non-pharmacological therapies (e.g., psychosocial interventions, dietary supplements, probiotics, speech therapy, etc.) must also be stable up to 4 weeks prior to screening and throughout the duration of the trial.

All medications and non-pharmacological therapies, other than the IMP, taken during the trial must be recorded on the CRF.

8.3 Prohibited Therapy During Trial Period

The following medications are prohibited for the duration of the trial beginning from the date of the screening visit. However, any patients taking these medications after randomization should not be discontinued from treatment unless there are safety concerns.

Care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethylclobazam and are excluded as indicated below. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7.

- Sirolimus, everolimus, temsirolimus, or tacrolimus.
- Clobazam.
- Omeprazole or lansoprazole.
- Tolbutamide or warfarin.
- Repaglinide, pioglitazone, rosiglitazone, montelukast, bupropion, or efavirenz.
- Any new medications or interventions for ASD related symptoms or changes in dosage, within 4 weeks or during the trial.
- Recreational or medicinal cannabis or cannabinoid-based medications (including Sativex, Epidiolex/Epidyolex) within the 12 weeks prior to or during the trial.
- Any other IMP taken as part of a clinical trial within the 12 weeks prior to or during the trial.

8.4 Compliance in Investigational Medicinal Product Administration

The caregiver will record the volume of solution on each treatment day in the diary.

Patients should return all IMP (used and unused) at Visits 5, 8, and 9. The diary-reported dosing information will be checked and any discrepancies discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents.

Records of IMP accountability will be maintained according to Section 5.3.4.

8.5 Access to Blinded Treatment Assignment

The identity of IMP assigned to patients will be held by the RTSM system. The PI at each site, or his/her designee, is responsible for ensuring that information on how to access the RTSM system is available to the relevant staff in case of an emergency and unblinding is required. A patient's treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any other reason will be considered a protocol deviation.

The investigator is encouraged to contact the medical monitor to discuss the rationale for unblinding prior to doing so. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of trial medication will not be dependent upon the investigator receiving approval from the medical monitor (i.e., the investigator will be able to obtain the code break information independent of contacting the medical monitor).

If the investigator does unblind, they must contact the medical monitor within 1 working day of the event and must document the time, date and reason(s) for unblinding in the patient's medical notes and on the eCRF.

9 TRIAL PROCEDURES

In order to facilitate trial execution in the context of infectious diseases or other transmissible conditions (e.g., COVID-19), the trial will involve a combination of clinic, remote (including a video call and a home nurse visit) and telephone visits, as specified in APPENDIX 1. The investigator will determine in discussion with the caregiver by visit 2 which visits will be performed at clinic or remotely. If at any point there is motive for concern (e.g., AE of concern, a score of 4 or 5 in the C-SSRS) the patient should attend the clinic for further assessment (either for a scheduled visit or for an unscheduled visit). Unscheduled visits and assessments may be performed in the event of a safety concern, as deemed necessary by the investigator. Data from any unscheduled visits or assessments should be reported on the unscheduled visits eCRF.

When remote visits are agreed these may require (as per visit schedule):

- A home nurse visit to collect blood and urine samples (including urine dipstick), and vital signs.
- A video call with the child and the caregiver to review IMP usage, adverse events, changes in concomitant medications, perform clinical interviews (C-SSRS and Vineland-3), and patient observation for assessment of CGI-S and CGI-I.
- The caregiver to complete the caregiver questionnaires electronically (ABC and [redacted]).
- IMP review by the home nurse or over the video call and IMP secure delivery/collection.

All events must take place within the protocol window; further guidance will be provided in a site manual.

A list of the required trial procedures is provided in the subsections that follow; refer also to the schedule of assessments (APPENDIX 1).

Patient functional assessments, i.e., the WASI-II, ADOS-2, [redacted] should be performed prior to any invasive assessments being carried out. All assessments should reflect the patient's regular state; therefore, it should be ensured the patient had adequate time to settle prior to each assessment.

Assessments or tests that are not done and examinations that are not conducted must be reported as such on the electronic CRF.

The location of the source data for study procedures will be documented, per center, and filed in the trial file; for further details see Section 16.2.

9.1 Trial Procedures

9.1.1 Informed Consent

The parent(s)/legal representative of minor patients must personally sign and date the IRB/EC approved ICF before any trial-specific procedures are performed or any patient-related data is recorded for the trial. In addition, assent will be taken (if allowed per local regulations) along with parent(s)/legal representative consent, using IRB/EC-approved forms. It is expected that the majority of patients will have sufficient understanding to provide assent; if the investigator assesses the patient as not having sufficient understanding or communication ability to provide assent, this must be clearly recorded in the patient notes. The explicit wish of a minor, who is capable of forming an opinion and assessing the information provided, to refuse participation in or to be withdrawn from the clinical trial at any time must be considered by the investigator. Investigators must record in the patient notes any reason(s) why a minor is unable to sign a form.

The original signed ICF should be retained and a copy provided to the patient and/or parent(s)/legal representative. Patients/parent(s)/legal representative will be given the option of being informed about the summary outcome and results of the trial as part of the ICF. For further details, see Section 15.2.

9.1.2 Contraception Requirements

To be eligible for the trial, female patients of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must have agreed that they are willing to use highly effective contraception for the duration of the trial and for 12 weeks thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly[20]. Such methods include hormonal contraception (the use of hormonal contraception must be supplemented with a barrier method [preferably male condom]), an intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence[21].

To be eligible for the trial, male patients who are fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) must have agreed that they are willing to use male contraception (condom) or remain sexually abstinent during the trial and for 12 weeks thereafter.

Abstinence, as referenced above, is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar,

symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhea method are not acceptable methods of contraception[21].

9.1.3 Demographics

The following information will be obtained for each patient: date of birth, sex, race, and ethnicity (as allowed per local regulations). Details informing amount of time spent with main caregiver will also be collected.

9.1.4 Medical History

Relevant, significant medical history will be obtained at Screening (Visit 1) and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the trial.
- Suspected or confirmed COVID-19 infection (or other significant infectious diseases) within 1 year prior to Screening (Visit 1).
- Information on ASD history, including known etiologies, will be recorded.

9.1.5 Concomitant Medications and Interventions

Details of all current and recent medication/therapy (i.e., taken within the 14 days prior to the initial screening visit) will be recorded. All medications and interventions for ASD related symptoms must remain at stable doses throughout the trial; however, doses may be changed in response to a safety concern. Interventions would include special diets.

Any changes in concomitant medication or interventions during the trial must be recorded on the CRF at trial visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in Section 8.3.

Testing for drugs of abuse will be performed at screening (Visit 1).

9.1.6 Physical Examination

Physical examinations will include height (measured once), body weight measurements, and BMI (Visit 1 only).

9.1.7 Vital Signs

Vital sign measurements (body temperature, pulse rate, respiration rate), including blood pressure taken in a sitting position at rest for 5 minutes. Blood pressure must be recorded using the same arm throughout the trial, where possible.

9.1.8 12-Lead Electrocardiogram

A 12-lead ECG will be performed after 5 minutes in a supine position. A physician must review the ECG immediately (annotated, signed and dated) and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately on the CRF. Additional ECG measurements can be taken at any time during the trial, if clinically indicated.

9.1.9 Clinical Laboratory Sampling

The investigator should use their judgment and knowledge of the patient to determine when best to collect the blood and urine samples in order to mitigate the risk that invasive procedures may cause the patient to become stressed, thereby affecting the results of other assessments.

Laboratory tests will include hematology, biochemistry, coagulation (Visit 1 only; thereafter only as an unscheduled assessment if ALT or AST > 3 × ULN) and urinalysis (provided urine can be obtained). Blood sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

Urine samples for biochemistry will be analyzed at the trial site (or by the home nurse) by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture, and sensitivity, as applicable). In cases where urine samples cannot be analyzed at the site (or by the home nurse) due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis. Urine sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

Urine samples for drugs of abuse will be sent to the central laboratory.

The investigator and trial monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the trial and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in Table 9.1-1.

Table 9.1-1 Biochemistry, Hematology, Urinalysis, and THC					
Biochemistry (Serum)[a]	**Hematology (Whole Blood)[a]**	**Coagulation (plasma)[a,b]**	**Urinalysis (Urine)[c]**	**Pregnancy Test (Serum)[a]**	**Drugs of Abuse (Urine)[a]**
Alanine aminotransferase (ALT)	Hematocrit	Prothrombin time (PT/INR)	Bilirubin	Serum	Amphetamines
Albumin	Hemoglobin		Blood		Barbiturates
Alkaline phosphatase	Mean cell volume		Glucose		Benzodiazepine
Aspartate aminotransferase (AST)	Mean corpuscular hemoglobin		Ketones		Cannabinoids
Calcium	Platelets		Protein		Cocaine
Creatinine	Red blood cell count		Nitrites		Methadone
Creatinine clearance	White blood cell count with automated differential		pH		Opiates
Creatine kinase (CK)			Specific gravity		MDMA
Gamma-glutamyl transferase			Urobilinogen		Methamphetamines
Glucose			White blood cells		Oxycodone
HDL-cholesterol					Phencyclidine
Potassium					Tricyclic antidepressants
Prolactin					
Sodium					
Total bilirubin					
Total protein					
Triglycerides					
Urea (blood urea nitrogen [BUN])					

HDL = high density lipoprotein; INR = international normalized ratio;
MDMA = 3,4-methylenedioxymethamphetamine: THC = tetrahydrocannabidiol.

[a] Analyzed at a central laboratory.

[b] Tested at Visit 1 only; thereafter only as an unscheduled assessment only if ALT or AST > 3 × ULN

[c] Analyzed at the trial site (or by the home nurse) by use of a dipstick (if allowed per local regulations).

Investigators at trial sites will be notified of safety laboratory test results. All laboratory results will be reviewed, and the reports signed and dated by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. The results of drugs of abuse screening will be reported back to the trial center for confirmation of eligibility. All laboratory results considered to represent an AE must be documented on the CRF. For reporting and follow-up of potential cases of drug-induced liver injury, see Section 12.7.

Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that

the abnormality is not related to the IMP and needs no further investigation. Blood sample volume requirements and processing procedures will be detailed in a separate laboratory manual; the maximum amount of blood taken during the course of the trial will not exceed 3 mL/kg of body weight within any 8-week period.

[redacted]

9.1.10 Randomization and Trial Supply Management System

The RTSM system will be used to assign patients to treatment arms, manage IMP supply, and to provide treatment allocation information in the event of patient unblinding. The RTSM system information can be accessed via the eCRF. A member of the trial team must register in the eCRF at clinic visits in order to:

- Obtain a patient number.
- Randomize a patient.
- Obtain dispensing information.

Training will be given to all sites prior to the start of the trial.

9.1.11 Questionnaires and Assessments Completed at Scheduled Visits

Caregiver-completed questionnaires should be completed by an identified main caregiver, nominated at Visit 1. The main caregiver should be able to assess the patient based on daily contact and be able to attend clinic and video call visits. For both caregiver-completed and investigator-completed questionnaires, the same assessors should answer/complete the questionnaires/assessments throughout the trial to maintain consistency. Investigators must be suitably qualified to perform each assessment/administer each questionnaire. Caregiver questionnaires are to be completed electronically at site or at home. Physician interviews/assessments are to be completed at site or over a video call. Visit 2 and Visit 8 assessments should always be completed at site.

If at any point of the trial the main caregiver cannot attend a visit (and this cannot be avoided), an alternate or backup caregiver may be used. This should only be done if all other options for the primary caregiver (i.e., scheduling issues) have been exhausted. The alternative caregiver should not complete the [redacted].

9.1.11.1 Wechsler Abbreviated Scale of Intelligence Scale Second Edition

Patient direct assessment.

An IQ score ≥ 70 at screening is required for eligibility, measured using WASI-II within 1 year of screening. If a score within 1 year of screening is not available the WASI-II will be conducted at the screening visit. The WASI-II provides a brief, reliable measure of cognitive ability suitable for individuals ages 6 to 90 years. The 2-subset form will be used. It evaluates Vocabulary and Matrix Reasoning and provides an estimate of general cognitive ability.

The WASI-II (2-subset form) will be administered by and experienced and suitable qualified assessor

9.1.11.2 Autism Diagnostic Observational Schedule-2

Patient direct assessment.

The ADOS-2 provides an accurate assessment and diagnosis of ASD across all ages, developmental levels and language skills. It is a semi-structured assessment of communication, social interaction, play, and restricted and repetitive behaviors. It presents various activities that elicit behaviors directly related to a diagnosis of ASD. By observing and coding these behaviors, the test user can obtain information that informs diagnosis, treatment planning, and educational placement. The ADOS-2 consists of 5 modules, each of which is appropriate for children and

adults of differing developmental and language levels, ranging from nonverbal to verbally fluent. The individual being evaluated is given only one module. The appropriate module is selected and administered depending on the individual's verbal ability. The manual provides guidelines for selecting the most appropriate module and general instructions for administration and scoring and interpreting an individual's results. The ADOS-2 must be performed face-to-face without the use of face masks, coverings, or shields. The ADOS-2 requires 40 to 60 minutes to administer.

The ADOS-2 will be administered by an experienced and suitably qualified assessor. (Unless records of an ADOS-2 performed at the trial site within 2 years are available, in which case it does not need to be carried out at screening).

9.1.11.3 Vineland Adaptive Behavior Scales, Third Edition

The Vineland-3 measures the personal and social skills of individuals from birth through adulthood. Because adaptive behavior refers to an individual's typical performance of the day-to-day activities required for personal and social sufficiency, these scales assess what a person does, rather than what he or she can do. The Vineland-3 assesses adaptive behavior in 3 domains: Communication, Daily Living Skills, and Socialization. Each domain is comprised of 3 subdomains: receptive expression and written (communication); personal, domestic and community (daily living skills); Interpersonal relationships, play and leisure and copying skills (socialization). There are several administration formats available. In this trial, the comprehensive review form will be used. The interview will be performed by an experienced suitably trained assessor.

9.1.11.4 Aberrant Behavior Checklist

The ABC was designed to assess the presence and severity of various problem behaviors commonly observed in individuals diagnosed with intellectual and developmental[16]. It contains items that resolve onto 5 subscales: Irritability (15 items); Social Withdrawal (16 items); Stereotypic Behavior (7 items); Hyperactivity/Noncompliance (16 items); and Inappropriate Speech (4 items). Each item is scored as 0 (never a problem), 1 (slight problem), 2 (moderately serious problem), or 3 (severe problem).

The ABC will be completed by the caregiver.

9.1.11.5 Clinical Global Impressions Questionnaire

The CGI questionnaire was developed as a clinical trial measure to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a trial medication[18].

The CGI questionnaire is split into 2 scales; the CGI-S scale and the CGI-I scale. The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis. The clinician is asked: *Considering your total clinical experience with this particular population, how ill is the patient at this time?* This is rated as: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill.

The second section, the CGI-I, is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The clinician is asked: *Compared to the patient's condition at admission to the project, how much has the patient changed?* This is rated as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse.

The CGI will be completed by the investigator.

At Visits 5 and 7 the CGI-I may be performed over a video call. The investigator must ensure, in collaboration with the caregiver, that there is sufficient opportunity to observe and assess the patient over the video call. The investigator may prompt the caregiver to interact with the child to facilitate assessment, to mimic as much as possible a clinic assessment.

[redacted]

[redacted]

9.1.11.10 Columbia-Suicide Severity Rating Scale

The C-SSRS supports suicide risk assessment through a series of simple, plain-language questions which answers help users identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs. It is completed as an interview covering whether and when they have thought about suicide (ideation), what actions they have taken, and when, to prepare for suicide and whether and when they attempted suicide or began a suicide attempt that was either interrupted by another person or stopped of their own volition.

Suicidality will be assessed by using the C-SSRS via interview with the patient or, if the patient is not being cooperative, interview with the patient's caregiver assistance. If the interview is carried out with the caregiver this must be recorded and justified in the patient notes.

It is expected that some patient may engage in non-suicidal self-harming behavior. Self-harming behavior is not per se an exclusion or withdrawal criteria unless it is carried out with suicidal intent. However, if an increase in non-suicidal self-harming behavior if observed this should be reported and an adverse event and the investigator should consider if it is safe for the patient to continue in the trial.

The C-SSRS is to be completed by the investigator or a delegate who has completed the C-SSRS training within the past 2 years or has continually administered the C-SSRS assessments throughout this trial since obtaining the training certificate.

9.1.12 Investigational Medicinal Product Accountability

Records of IMP accountability will be maintained according to Section 5.3.4.

9.1.13 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent form by the caregiver, will be recorded on the eCRF as AEs, after questioning the caregiver further if necessary. All AEs occurring during the trial, whether attributed to the IMP or not, observed by the investigator, or reported by the caregiver, will be recorded in the eCRF.

Any AE which meets SAE criteria should be reported as a SAE.

SAEs must be reported to GW PVD within 24 hours of discovery or notification of the event via recording in the eCRF.

Adverse events inferring to hepatic enzymes increased, rash, pneumonia, cognitive disorders and self-injurious ideation or intentional self-injury may be considered as AESI by GW PVD and additional information may be requested during follow-up.

Refer to Section 12 for definitions, procedures and further information on AE reporting.

9.2 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 patients 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 patients:

- Where the ADOS-2 cannot be performed due to site restrictions (e.g., mandatory use of face masks), and an ADOS-2 conducted within 2 years at the trial site by a qualified assessor is not available, eligibility can be confirmed using: 1) an ADOS-2 performed within 2 years by a qualified assessor external to the site; 2) if 1) is not available, eligibility may be confirmed using the ADI-Rat screening.
- Visits or assessments may take place in a different location or by different means (e.g., by video call) than defined in the protocol.
- Biological samples may be collected and analyzed 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.
- Where required, in order to collect the biological samples, safety assessments (e.g., ECG, vital signs), or efficacy assessments as defined in the protocol, visit windows may be extended up to a maximum length of 14 days.
- If despite best efforts a safety assessment cannot be performed, the investigator must review the benefit-risk for patient continuation in the trial and record this in the medical records.

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.

10 WITHDRAWAL

In accordance with the Declaration of Helsinki[25], the ICH Tripartite Guideline for GCP Topic E6(R1)[26], the FDA regulations relating to GCP and clinical trials[27,28,29], the EU Clinical Trials Directive[30], the EU Good Clinical Practice/GCP Directive[31] and/or other applicable regulations, a patient has the right to withdraw from the trial at any time and for any reason, with no obligation to provide a reason, and without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the trial if any of the following apply:

- Administrative decision by the investigator, GW, or a regulatory authority.
- Did not meet eligibility criteria.
- Pregnancy.
- Protocol deviation that is considered to compromise potentially the safety of the patient.
- Withdrawal of patient consent/assent.
- Withdrawal of parent(s)/legal representative consent.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

Note: Prior to treatment discontinuation for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests, tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant medication with known hepatotoxicity may be reduced following discussion with the medical monitor.**

- Lost to follow-up.

Patients may also be withdrawn from the trial for any of the following:

- Patient non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial.
- Patient cannot tolerate a dose level of 5 mg/kg/day.
- Any evidence of use of drugs of abuse or drug diversion.
- Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.

Should a patient request or decide to withdraw from the trial, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported on the applicable CRF pages. A safety follow-up visit should take place 14 days after last dose of IMP. If withdrawing patients decline to give a reason for withdrawal of consent, the investigator must respect the patient's wishes.

11 URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator, they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to regulatory authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the regulatory authorities and IRB/EC within 3 days.

12 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this trial an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant), or diagnosis or worsening of a pre-existing condition, which occurs following screening and at any point up to the post-treatment, safety follow-up visit, which may or may not be considered to be related to the IMP. Any event that is the result of a trial procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-trial existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to Section 12.2).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term investigator refers to the trial PI or a formally delegated trial physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP-related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to regulatory authorities, applicable IRBs/ECs and investigators (expedited reporting) by GW.

An AE must only be classed as serious, i.e., a SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening*.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically significant**.

*The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

**Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse, or positive COVID-19 test.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the trial must be reported to GW with any other supporting information and recorded in the AE section of the eCRF. Any ongoing SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be recorded in the eCRF within 24 hours of discovery or notification of the event. GW PVD will be automatically notified that an SAE has been recorded. Any additional information required for a case (follow-up or corrections to the original case) will be requested by GW PVD through eCRF queries.

The investigator should continue to document all AEs which occur up to the last formal follow-up observational period. If the investigator subsequently becomes aware of any deaths or a new IMP-related SAE after the last formal follow-up period of the trial, these should still be reported to the GW PVD.

Any other problem discovered after the follow-up visit which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the trial must be treated as an SAE and reported to the GW PVD. Such post-trial SAEs do not need to be recorded on the patient's eCRF if editing rights to the eCRF have been removed due to final trial data lock. GW PVD may request safety follow-up information after the final trial visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the center files for all trial centers.

12.4 Pregnancy

Any patient, or patient's partner, who becomes pregnant while receiving the IMP, or within 90 days of the last dose of IMP, must be reported to the GW PVD using the GW Pregnancy Monitoring forms provided. Where possible, the investigator should provide the outcome of the pregnancy. All pregnancies must be recorded in the eCRF within 24 hours of becoming aware. The GW PVD will be automatically notified that a pregnancy has been recorded. Any additional information required for a case (follow-up or corrections to the original case) will be requested by GW PVD through eCRF queries where data is entered in EDC. The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit, then he/she should report it as above. The GW PVD will follow-up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the IMP must be reported as such. The expression *"reasonable causal relationship"* is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the IMP:

"In your opinion is there a plausible relationship to the IMP?" The answer is either "yes" or "no".

Events that start before the first dose of IMP (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of IMP, a new event record should be entered into the eCRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the IMP but also other potential contributing factors. Factors for consideration of the underlying cause may include:

- Medical and disease history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Withdrawal of IMP.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the trial will be reported on the running logs in the AE section of the eCRF. This includes all events from the time following screening up to and including the post-trial follow-up visit, whether or not attributed to IMP and observed by the investigator or patient.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if Known, or Signs and Symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the eCRF. Once a diagnosis has been determined the AE section of eCRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the eCRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated, e.g., fever and malaise due to respiratory tract infection.

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given, record as much information as possible (i.e., month and year or, in exceptional circumstances, just year). When the actual start date becomes known the eCRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered/Resolved.
- Recovered/Resolved with Sequelae.
- Not Recovered/Not Resolved.
- Fatal.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting, but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious.

The severity of an AE will be recorded as one of the following:

- Mild: easily tolerated, does not interfere with normal daily activities, does not require intervention.
- Moderate: causes some interference with daily activities; minimal, local or non-invasive intervention indicated.
- Severe: daily activities limited or completely halted; intervention indicated.

E) Causality

See Section 12.6 above.

F) Action Taken with Trial Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

- Dose Not Changed.
- Dose Reduced.
- Drug Interrupted.
- Drug Withdrawn.

12.7 Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur after a patient has finished a trial.

Additional information may also be requested by GW PVD if a patient experiences any adverse events that is considered an AESI, these include any events that may infer to hepatic enzymes increased, rash, pneumonia, cognitive disorders and self-injurious ideation or intentional self-injury.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. Further details of withdrawal are presented in Section 10. If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If a safety concern is identified following withdrawal of a patient, GW may contact the investigator for additional follow-up information.

12.8 Potential Cases of Drug-Induced Liver Injury

All investigational centers are required to submit to the GW PVD the laboratory results for any patient after randomization that meets the criteria for the selected laboratory parameters as follows:

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

These reports must be sent to the GW PVD via email for SAE reporting (see APPENDIX 2) within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to the GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol-defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational center as soon as possible

(within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase levels, detailed history and physical examination; patients should be followed in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the patient cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and IRBs/ECs

In accordance with the EU Clinical Trials Directive[30], relevant parts of the FDA Code of Federal Regulations[32] and any national regulations, GW will inform investigators, regulatory authorities and relevant IRBs/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all SUSARs.

This information will be provided through 3 sources:

1) IB[6]: a compilation of the clinical and nonclinical safety data available on the IMP that is relevant to the trial. The IB is updated annually or when important new safety information becomes available.
2) Development core safety information: this document forms the safety section of the IB[6], or is updated as an addendum to the IB[6]. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
3) CIOMS reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central ECs which have approved the trial and investigators. As required, the investigator should notify their regional IRBs/ECs of SAEs or SUSARs occurring at their center and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to report promptly to their IRBs/ECs all unanticipated problems involving risks to patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance[28] the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a trial should be considered an unanticipated problem involving risk to patients and reported to the IRB/EC, *only* if it were unexpected, serious, and would have implications for the conduct of the trial (e.g., requiring a significant, and

usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the trial cannot be understood.

The FDA guidance[32] states that, accordingly, to satisfy the investigator's obligation to notify the IRB/EC of unanticipated problems, any investigators participating in a multicenter trial may rely on the sponsor's assessment and provide to the IRB/EC a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators, regulatory authorities and relevant IRBs/ECs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the trial does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethical approval and final database lock.

13 STATISTICAL CONSIDERATIONS

Further details of the proposed statistical analysis will be documented in SAP, which will be finalized prior to unblinding of the trial. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

Approximately 160 patients will be randomized to receive GWP42003-P or matching volume of placebo on a 1:1 basis.

This is an exploratory trial with interest in multiple efficacy endpoints therefore, a formal power calculation was not performed, however a sample size was informed by data available in the literature for the 2 measures with the highest level of validation, VABS[15] and ABC-I[33].

Assuming a common standard deviation for data of 8.46 and using a 2-sided hypothesis test at a 0.05 α-level, a total sample size of 160 patients randomized to allow for 144 evaluable patients (72 patients per arm) at trial end will provide 80% power to detect a significant result assuming a true treatment difference of 4 points for the VABS-3 score in change from baseline to end of treatment between GWP42003-P and placebo. Allowing for a 10% drop-out rate, a minimum of 160 patients need to be randomized into the trial. Depending on the drop-out rate during the trial, this number may be increased to ensure a minimum of 144 evaluable patients at Week 12.

The size of this trial is more than enough to ensure > 99% power on the ABC-I scale assuming a common standard deviation for data of 8.27 with a true treatment difference in change from baseline to end of treatment between GWP42003-P and placebo of -8.26 and using a 2-sided hypothesis test at a 0.05 α-level. As this is an exploratory trial, no adjustments for the type I error were considered for these calculations.

13.2 Interim Analysis

Interim evaluations for futility and superiority may be performed as part of DMC operations (see Section 14).

Bayesian analysis of the key variables of interest may be performed to evaluate the probability that GWP42003-P is different than placebo. Details of the evaluation criteria will be provided in a separate Statistical Analysis or Simulation plan.

13.3 Analysis Sets

The following analysis sets will be used for the statistical analysis:

Full Analysis Set

All patients who are randomized and receive at least 1 dose of IMP in the trial will be included and analyzed according to their randomized treatment arm.

The FAS is the primary analysis set for all efficacy endpoints.

Safety Analysis Set

All patients who receive at least 1 dose of IMP in the trial will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set. This analysis set will be used to report the safety data.

Per Protocol Analysis Set

If there are a sufficient number of significant protocol deviations in the trial, a PP analysis set may also be presented. The PP set is defined as:

All patients that are a subset of the FAS who have no major protocol deviations deemed to compromise the assessment of efficacy. Major protocol deviations will be identified and fully defined prior to unblinding of the trial. The PP analyses will only be conducted on efficacy endpoints.

Analysis sets will be identified prior to the unblinding of the trial data.

13.3.1 Protocol Deviations

Protocol deviations will be listed and reasons for exclusion from the analysis sets (for major protocol deviations) will be summarized.

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, SD, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. Unless otherwise specified, tables will be summarized by randomized treatment group.

For clinic visit-based endpoints (unless otherwise specified), baseline is defined as the last record or measure collected prior to the first dose of IMP in the treatment period.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, randomized, withdrawn, etc.) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, race, and ethnicity (as per local data protection laws in each specific country) and any other demographic or baseline characteristics will be summarized by treatment arm, using appropriate summary statistics.

There will be no formal comparison of baseline data; that is, no statistical hypothesis testing.

13.5.3 Medical History

Previous and current medical conditions (including details of ASD history) will be summarized by SOC by treatment arm.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the trial will be summarized separately by treatment arm, medication class, and active ingredients. Non-pharmacologic therapies and therapeutic diets will be summarized by treatment arm.

13.6 Endpoints and Statistical Methods

Statistical hypothesis testing will be performed on the efficacy and exploratory endpoints as appropriate with no inferential statistical decision drawn as this is an exploratory trial. For each endpoint, GWP42003-P will be compared against placebo.

All safety data will be summarized using appropriate statistical methods.

13.6.1 Efficacy Endpoints

13.6.1.1 VABS-3

The VABS-3 social and communication composite (arithmetic mean of the social and communication domain scores), the adaptive behavior composite, and individual domain scores will be analyzed. The VABS social and communication composite score is a key interest.

The change from baseline in social and communication composite score for VABS-3 will be summarized by treatment arm and visit.

The change from baseline in social and communication composite score for VABS-3 will be analyzed in the final analysis using an MMRM model. The corresponding model will include randomization stratification factors, baseline composite score, visit, treatment arm, visit by treatment arm interaction as fixed effects, and visit repeated within each patient as a repeated effect. An unstructured covariance matrix will be used to estimate the variance-covariance structure within patients across time points. If convergence is not obtained, then other covariance structures to be used will be specified in the SAP. Objective criteria for assessing normality assumptions and proposed alternative analyses will be specified in the SAP.

A Bayesian evaluation will also be carried out on the final data (see also Section 13.2).

From this analysis the LS mean estimates for each treatment arm at each visit, along with the standard error and 95% CIs will be presented separately. In addition, estimates of the treatment difference at each visit will be presented along with standard errors of the difference and 95% CIs. The main comparison of interest is the estimate of the treatment difference at Week 12.

The change from baseline in adaptive behavior composite score and for each individual domain will be summarized and analyzed as described above for the social and communication composite score.

13.6.1.2 ABC

All ABC subscales will be analyzed. The ABC-I subscale is of key interest.

ABC-I subscale scores will be summarized by treatment arm and visit together with the corresponding change from baseline scores.

The change from baseline in ABC-I scores will be analyzed separately using a similar model as the one described for the social and communications composite endpoint.

The other ABC subscales will be summarized and analyzed as described for the ABC-I subscale.

13.6.1.3 CGI-I and CGI-S

Counts and proportion of patients within each category for the CGI-I and CGI-S scores will be produced separately by treatment arm and visit. These data will be analyzed separately using a GEE model approach. The model will include CGI-I as the dependent variable, with treatment arm and stratification factors as fixed effects and baseline response as a covariate. The model will also include a repeated statement that allows to model the correlation of the dependent variable at different time points. A similar model will be fitted to the CGI-S data.

Proportion of patients at Week 12 ‘minimally’, ‘much’ or ‘very much’ improved, as well as ‘much’ or ‘very much’ improved, on the CGI-I score will be summarized by treatment arm and

will be analyzed using a logistic regression model with responder (improved/not improved) as the dependent variable, with treatment arm and stratification factors as fixed effects and baseline response as a covariate. The associated odds ratios together with the corresponding 95% CIs and p-values will be presented.

13.6.3 Safety

The following safety endpoints are used to support the safety objective and will be evaluated based on SAS®. For each endpoint, GWP42003-P will be compared with placebo as described in the following sections:

- AEs.
- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- 12-lead ECG.
- C-SSRS.

All safety endpoints will be summarized by treatment received using appropriate statistical methods.

13.6.3.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.3.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A TEAE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of TEAEs will be given by preferred term and SOC for the safety analysis set. The number of patients reporting at least 1 TEAE will be provided. AEs will be summarized in terms of the number of patients with at least 1 event (N) and the percentage of patients with at least 1 event (%).

The following summaries will be produced as a minimum:

- All-causality TEAEs.
- Treatment-related AEs.
- All-causality TEAEs by maximal severity.
- All-causality serious TEAEs.
- Treatment-related serious TEAEs.
- TEAEs reported as leading to permanent cessation of IMP.
- Fatal TEAEs.

13.6.3.3 Clinical Laboratory Data

Clinical laboratory data will be summarized at screening, baseline, and at each time point during the treatment period using appropriate summary statistics. Categorical shift tables will be presented, showing the numbers of patients with values outside the normal range. Change from baseline will also be summarized by visit.

13.6.3.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data

Vital signs, ECG, physical examination data will be summarized for the safety analysis set, at screening, baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of treatment will also be summarized.

14 DATA MONITORING COMMITTEE

A Data Monitoring Committee will be setup for ongoing unblinded data review. The DMC will not include any members of the study team. Operations and constitution of the DMC will be detailed in a separate charter.

15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformity with the current version and subsequent amendments of the Declaration of Helsinki[34], the ICH Tripartite Guideline for GCP Topic E6(R1)[26], the EU Clinical Trials Directive[30], the EU GCP Directive[31] and the clinical trial regulations adopting European Commission Directives into national legislation[35,36,37,38].

15.2 Informed Consent

An initial generic ICF/Initial master informed consent/assent forms will be prepared by GW or delegate and provided to the investigator, who will tailor this for their center by adding the center's contact details and by using headed paper. The clinical manager or delegate will communicate updates to the template by letter. The written informed consent/assent documents should be prepared in the language(s) of the potential patient population.

Before a patient's involvement in the trial, the investigator is responsible for obtaining written informed consent/assent (if allowed per local regulations and if applicable) from the patient along with written parent(s)/legal representative consent after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial and before any trial-specific procedures are performed or any patient-related data are recorded for the trial. The patient and/or parent(s)/legal representative must have ample time to consider the information provided before giving written consent. More specific definitions of 'ample time' may be in force if required by IRBs/ECs or local regulations.

The acquisition of informed consent/assent must be documented in the patient's medical records and the ICF must be signed and personally dated by the patient and/or parent(s)/legal representative (as applicable) and by the person who conducted the informed consent/assent discussion. The original signed ICF/assent should be retained and a copy provided to the patient and/or parent(s)/legal representative.

15.3 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, master ICF, other patient information material, any proposed advertising material and any further documentation requested must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the appropriate version of the protocol and ICF before recruitment of patients into the trial and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent document. The investigator must notify the IRB/EC of deviations from the protocol, SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining annual/ongoing IRB/EC approval/renewal throughout the duration of the trial. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

15.4 Pre-trial Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent for entry into the trial:

- Signed and dated protocol signature page.
- Copy of IRB/EC-approved ICF (including version number and date) and other patient information material.
- Copy of the IRB/EC approval of the protocol, ICF forms (including version number and date) and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials[27,28,29,39], the EU Clinical Trials Directive[30], the EU GCP Directive[31], or the ICH Tripartite Guidelines for GCP Topic E6(R1)[20] where the EU Clinical Trials and GCP Directives do not apply.
- Signed and dated laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed and dated clinical trial agreement (including investigator indemnity insurance and financial agreement).
- Form FDA 1572 or equivalent, if required.
- Completed financial disclosure statements for the PI and all sub-investigators, if relevant.

GW will ensure that the center is informed of when screening of patients can commence.

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the eCRFs or other documents submitted to GW, patients should be identified by their patient number and their trial screening number only. Documents that are not for submission to GW, e.g., signed ICF, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to GCP and clinical trials[27,28,29,39] and the EU Clinical Trials Directive[30]/ICH Tripartite Guidelines for GCP Topic E6(R1)[26], it is required that the investigator and institution permit authorized representatives of the company, the regulatory authorities and the IRB/EC have direct access to review the patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the trial. The investigator is obligated to inform the patient that his/her trial-related records will be reviewed by the above-named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the trial and will not use it for any other purposes without the written consent of the company.

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Trial or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/EC and regulatory authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrational changes can be submitted to the IRB/EC for information only. The investigator must send a copy of the approval letter from the IRB/EC to GW.

Both GW and the investigator reserve the right to terminate the trial, according to the clinical trial agreement. The investigator must notify the IRB/EC in writing of the trial's completion or early termination and send a copy of the notification to GW.

16.2 Trial Documentation and Storage

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries in and/or corrections to CRFs will be included on the delegation log.

Source documents are original documents, data and records containing all protocol-specified information from which the patient's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs and correspondence. The source for each data point will be agreed with each center prior to patient recruitment. In the rare situations of data being recorded directly into the CRF in error, then the source data from the CRF should be transcribed into the patient's notes with appropriate signature and date to provide a full audit trail.

The investigator and trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related, essential documentation (as outlined in the ICH Tripartite Guidelines for GCP Topic R6[R1][26], Section 8.2), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, ICF forms and supporting copies of source documentation.
- Trial files containing the protocol with all amendments, IB, copies of pre-trial documentation (see Section 15.4) and all correspondence to and from the IRB/EC and GW.
- Enrollment log of all patients who consented to take part in the trial.
- Screening and recruitment log of all patients screened and whether or not they were recruited into the trial (i.e., randomized and/or dosed with IMP).

- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug-related correspondence.

In addition, all original source documents supporting entries in the eCRFs, and diary data must be maintained and be readily available.

Following completion or termination of a clinical trial, GW will initiate proper archive of clinical trial-related documentation and electronic records generated by the investigator and/or GW. All clinical trial-related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents must be retained until at least 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 IMP. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements[31] or if needed by GW.

GW will inform the investigators for each center in writing of the need for record retention. No trial document may be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Trial Monitoring and Data Collection

The GW representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial, e.g., CRFs and other pertinent data, provided that patient confidentiality is respected.

The GW trial monitor, or designee, is responsible for inspecting (on site or remotely) the CRFs and available diary data at regular intervals throughout the trial to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The trial monitor must have (direct or remote) access to patient medical records and other trial-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the trial monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a CRO. During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations[27,28,29,39], ICH Tripartite

Guidelines for GCP Topic E6(R1)[26] and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

16.4 Quality Assurance

In accordance with the FDA regulations[27,28,29], EU Clinical Trials Directive[30]/ICH Tripartite Guidelines for GCP Topic E6(R1)[26] and the sponsor's audit plans, representatives from GW's Clinical Quality Assurance Department may select this trial for audit. Inspection of center facilities, e.g., pharmacy, drug storage areas, laboratories, and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, the EU Clinical Trials Directive[30]/ICH Tripartite Guidelines for GCP Topic E6(R1)[26] and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the trial center in the event of any claim in respect of personal injury arising due to a patient's involvement in the trial, providing that the trial protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical trial patient would not otherwise have been exposed, providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical trial are appropriately published and disseminated. They will coordinate this dissemination and may solicit input and assistance from the chief/principal investigators. A summary of the results of this trial will be made available on http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu/ (as applicable), as required by US and EU Law.

The raw data from this trial may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analyses and are permitted to present such information along with methods and results of the clinical trial at symposia, national or regional professional meetings and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this trial, must be submitted to the GW Medical Affairs Department and, as applicable, GW Publication Committee for corporate review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserves the right to delay the submission of such information by a period of up to 6 months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

All intellectual property rights owned by or licensed to either GW or the PIs, other than those arising from the clinical trial, will remain their property. All intellectual property rights arising out of the clinical trial will vest in or be exclusively licensed to GW and, as such, the PI must promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.8 Confidential Information

GW and the PI must ensure that only personnel directly concerned with the trial are party to confidential information and that any information coming to either party about the other during the course of the trial must be kept strictly confidential and must not be disclosed to any third party or made use of without the prior written consent of the other.

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APPENDIX 1 SCHEDULE OF ASSESSMENTS

Schedule of Assessments

Period	Screening	Treatment Period							End of Taper	Follow-up[n]
Visit	Visit 1[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7	Visit 8 EoT/WD	Visit 9	Visit 10
Visit Type	Clinic	Clinic	Telephone	Telephone	Clinic or Video Call and Home Nurse*	Telephone	Clinic or Video Call	Clinic	Clinic or Video Call and Home Nurse*	Telephone
Day	-14 to -7	1	7 (± 3)	14 (± 3)	29 (± 3)	43 (± 3)	57 (± 3)	85 (± 3)	V8 + 7 (+ 3)	V9 + 14 (+ 3)
Informed consent/assent	X									
Demographics	X									
Medical history[b]	X									
Inclusion and exclusion criteria	X	X								
AE review	X	X	X	X	X	X	X	X	X	X
SAE review	X	X	X	X	X	X	X	X	X	X
Concomitant medication review[c]	X	X	X	X	X	X	X	X	X	X
Test for drugs of abuse	X									
C-SSRS	X	X			X		X	X	X	
Vital signs[d]	X	X			X			X	X	
Full physical examination	X							X		
Height	X									
Weight	X							X		
BMI	X									
12-lead ECG[e]	X							X		
Safety laboratory assessments[f]	X				X			*If not tapering*	X	
Urinalysis[g]	X							*If not tapering*	X	

Period	Screening	Treatment Period							End of Taper	Follow-up[n]
Visit	Visit 1[a]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7	Visit 8 EoT/WD	Visit 9	Visit 10
Visit Type	Clinic	Clinic	Telephone	Telephone	Clinic or Video Call and Home Nurse*	Telephone	Clinic or Video Call	Clinic	Clinic or Video Call and Home Nurse*	Telephone
Serum pregnancy test (WOCBP only)	X							*If not tapering*	X	
[redacted]					[redacted]					
Trial treatment		X	X	X	X	X	X	X	X	
Randomization[i]		X								
WASI-II (if required) [l]	X									
ADOS-2 (if required)	X									
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		
ABC[j]	X	X			X		X	X		
Vineland-3[j,k]		X			X		X	X		
[redacted]		[redacted]						[redacted]		
CGI-S[k]	X	X			X		X	X		
CGI-I[k]					X		X	X		
[redacted]		[redacted]						[redacted]		
[redacted]		[redacted]						[redacted]		
IMP dispensing[m]		X			X			X		
IMP review					X			X	X	
Dosing diary completion (daily)		X								
IMP dosing compliance review[o]			X	X	X	X		X	X	

Abbreviations: ABC = Aberrant Behavior Checklist; ADOS-2 = Autism Diagnostic Observational Schedule; AE = adverse events; [redacted] CGI-I = Clinical Global Impression Improvement; CGI-S = Clinical Global Impression Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECG = 12-lead electrocardiogram; EoT = End of Treatment; IMP = investigational medicinal product accountability; [redacted]

[redacted] RTSM = Randomization and Trial Management System; SAE = serious adverse events; WASI-II = Wechsler Abbreviated Scale of Intelligence Scale Second Edition; WD = withdrawal; WOCBP = women of childbearing potential.

* For visits carried out remotely, home nurse assessments include: collection of blood and urine samples (including urine dipstick), and vital signs.

[a] Screening procedures may be performed over 2 days, if needed; both days must fall within the -14 to -7 day window.

[b] Relevant, significant medical history will be obtained and is defined as any condition or disease that may affect the condition under study, is ongoing on entry into the trial, and information on ASD history, including known etiologies. Patient has a diagnosis of ASD as per DSM-5 criteria for ASD, confirmed by ADOS-2 criteria (conducted within 2 years at the trial site or at screening).

[c] All current and recent medication/therapy, i.e., taken within 14 days prior to the initial screening visit. All medications and interventions for ASD related symptoms must remain at stable doses throughout the trial; however, doses may be changed in response to a safety concern.

[d] Includes body temperature, pulse rate, and respiration rate and blood pressure taken in a sitting position at rest for 5 minutes.

[e] Performed after 5 minutes in a supine position and reviewed by a physician.

[f] Includes hematology and biochemistry (including liver chemistries). Coagulation only at Visit 1; thereafter only as an unscheduled assessment if ALT or AST > 3 × ULN). If the patient in not tapering (and therefore will not attend Visit 9), clinical laboratory sampling is to be carried out at Visit 8. Details are provided in Table 9.1-1.

[g] Urinalysis to be performed provided urine can be obtained. Urine samples for biochemistry will be analyzed at the trial site (or by the home nurse) by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture and sensitivity, as applicable). Details are provided in Table 9.1-1.

[h] The sample must be collected 12 hours (−3/+6 hours) since last IMP dose and before the patient's next dose. The time of sample collection, the time of previous IMP dose, and time and type of meal (snack, standard meal, high fat) consumed by the patient closest to the previous IMP dose will be collected.. To minimize discomfort samples should be collected together with the safety laboratory sample collection.

[i] The RTSM system will be used to assign patients to treatment arms, including randomization.

[j] Caregivers questionnaires are to be completed by an identified main caregiver (nominated at Visit 1. The same identified caregiver is to complete the clinical interviews (Vineland-3 and [redacted]).

[k] Investigator questionnaires/interviews are to be completed for each patient by the same investigator (CGI-S, CGI-I, Vineland-3, and [redacted]).

[l] Patients functional assessments, i.e., the WASI-II, ADOS-2, [redacted] should be performed prior to any invasive assessments being carried out. All assessments should reflect the patient's regular state; therefore, it should be ensured the patient had adequate time to settle prior to each assessment. WASI-II required if score within 1 year of screening is not available. ADOS-2 required if not performed at the trial site within 2years. During special circumstances (e.g., COVID-19 pandemic) where the ADOS-2 cannot be performed due to site restrictions (e.g., mandatory use of face masks), eligibility can be confirmed using the Autism Diagnostic Interview, Revised (ADI-R).

[m] In cases where Visits 5, or 9 are carried out at home, secure IMP delivery and collection will be organized.

[n] If the patient did not enter the Taper Period, then Safety Follow-up occurs 14 days after Visit 8.

[o] Dosing diary (completion and volumes taken) and time of IMP taken in relation to food will be reviewed

APPENDIX 2 TRIAL PERSONNEL

Appendix 2.1 Investigator Details

At the time of protocol production, the participating investigators have not been confirmed. A list of all investigators will be maintained within the GW master files (electronically and added to the trial master file at the end of the trial).

Appendix 2.2 Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:	**Fax: +44 (0)1223 233 319** **USA Toll-free Fax:** **+1-866-234-1751** Tel: +44 (0)1223 233 410
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1223 266 800 Fax: +44 (0) 1223 235 667
Medical Advisor, 24 hour Emergency Contact Number & Clinical Project Manager:	Please refer to the sponsor and Related Contact Details form in the trial center file.
Clinical Trial Supplies:	G-Pharm Ltd Tel: +44 (0) 1795 435 029 Fax: +44 (0) 1795 475 439

At the time of protocol production, the CROs, and the clinical and bioanalytical laboratories for the trial had not been confirmed. A corresponding list will be maintained within the GW master files (electronically and added to the trial master file at the end of the trial):

Medical Advisor & Clinical Project Manager:	Please refer to the sponsor and Related Contact Details form in the trial site file.
Clinical Trial Supplies:	G-Pharm Ltd Tel: +44 (0) 1795 435 029 Fax: +44 (0) 1795 475 439

Appendix 2.3 Contract Research Organizations

IQVIA Biotech LLC

Registered Address

IQVIA Biotech Ltd.

500 Brook Drive, Reading, RG2 6UU

Main Office Address

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Morrisville, NC USA 27560-8404