A Randomized, Double-blind, Parallel-group Trial to Investigate the Safety and Efficacy of GWP42003-P Versus Placebo as Adjunctive Therapy in Participants with Schizophrenia Experiencing Inadequate Response to Ongoing Antipsychotic Treatment

Study Code: GWAP19030

EudraCT Number: 2019-003369-16

CLINICAL PROTOCOL GLOBAL VERSION 3

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol entitled "A Randomized, Double-blind, Parallel-group Trial to Investigate the Safety and Efficacy of GWP42003-P Versus Placebo as Adjunctive Therapy in Participants with Schizophrenia Experiencing Inadequate Response to Ongoing Antipsychotic Treatment", dated 23 March 2021 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice / GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) 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 participants during the trial and for 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.

Site No: _____

Print name: _____ Date: _____

Principal Investigator (DD Month YYYY)

Signature: _____

GW Authorization

[redacted] Date: 30-Mar-2021 | 02:13 PDT

VP of Clinical Sciences (Designee) (DD Month YYYY)

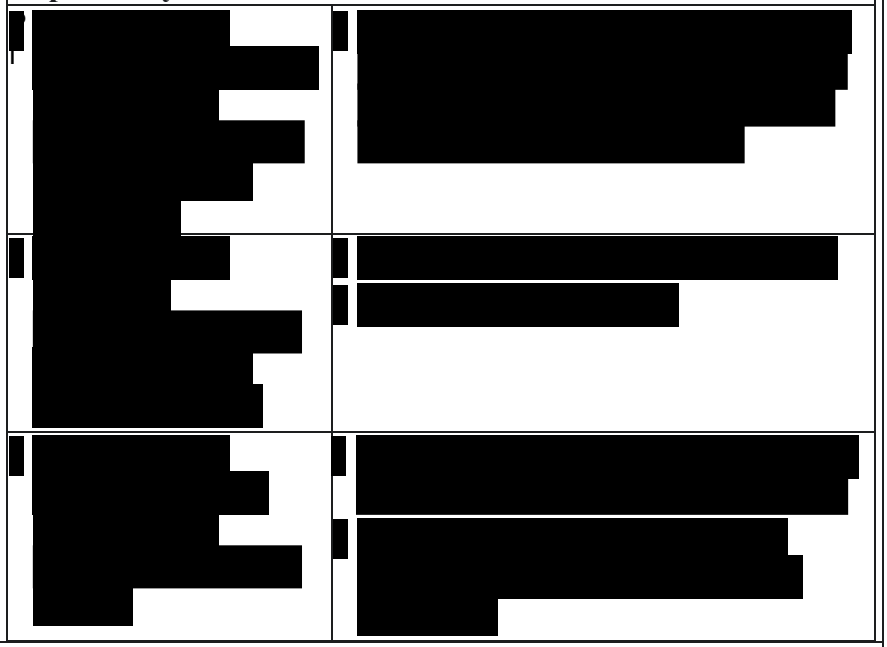
Print name: [redacted]

Signature: _____

1 PROTOCOL SYNOPSIS

<table>
<tr><td>Trial Title</td><td>A Randomized, Double-blind, Parallel-group Trial to Investigate the Safety and Efficacy of GWP42003-P Versus Placebo as Adjunctive Therapy in Participants with Schizophrenia Experiencing Inadequate Response to Ongoing Antipsychotic Treatment</td></tr>
<tr><td>Clinical Trial Type</td><td>Phase 2b</td></tr>
<tr><td>Indication</td><td>Participants with schizophrenia experiencing an inadequate response to ongoing antipsychotic treatment.</td></tr>
<tr><td>Objectives / Endpoints</td><td>
<table>
<tr><th>Objective</th><th>Endpoint</th></tr>
<tr><td colspan="2">Efficacy</td></tr>
<tr><td>• To evaluate the efficacy of GWP42003-P versus placebo after 12 weeks of treatment</td><td>• Mean change from baseline to Week 12 in the following:
– Positive and Negative Symptoms Scale (PANSS) total (PANSS-T) score
– PANSS positive subscale (PANSS-P) score
– PANSS negative subscale (PANSS-N) score
– PANSS general subscale (PANSS-G) score
– Clinical Global Impression of Severity (CGI-S) score
• Score at Week 12 in the Clinical Global Impression of Improvement (CGI-I)</td></tr>
<tr><td colspan="2">Safety</td></tr>
<tr><td>• To evaluate the safety and tolerability of GWP42003-P</td><td>• Changes in body weight, body mass index (BMI), and waist circumference
• Changes in vital sign measurements
• Adverse events (AEs) and adverse drug reactions (ADRs)
[redacted]
• Clinical laboratory test results
• 12-lead electrocardiogram (ECG) parameters
[redacted]</td></tr>
<tr><td>Objective</td><td>Endpoint</td></tr>
</table>
</td></tr>
</table>

	Safety Continued
	• Suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
	[redacted]
	[redacted]
	[redacted]
	Objective / **Endpoint**

	Exploratory Continued 
Trial Design	This is a randomized, double-blind, placebo-controlled, parallel-group, outpatient trial. The trial will compare the efficacy and safety of 2 dose levels of GWP42003-P (150 mg twice daily [b.i.d.] and 500 mg b.i.d.) versus placebo in participants with schizophrenia who are experiencing an inadequate response to ongoing antipsychotic treatment. The duration of the trial will be approximately 20 weeks, which includes a screening period (up to 4 weeks), a single-blind placebo run-in period (2 weeks), a double-blind treatment period (12 weeks), and a safety follow-up period (2 weeks). After signing the informed consent form (ICF), participants will enter the screening period (Visit 1). The investigator will submit participants' eligibility forms for clinical surveillance and training (CST) review. The CST will evaluate the eligibility of participants and provide the outcome of the evaluation to the site. Participants cannot be enrolled until site personnel have received the final CST notification. Additional details for CST will be described in the study manual. At Visit 2 screened participants who continue to meet eligibility criteria will be randomized 1:1 to receive 150 mg b.i.d. or 500 mg b.i.d. dose-matched volumes of placebo in a single-blind manner for the placebo run-in period. At Visit 3 (Day 1) participants who continue to meet the required eligibility criteria will be randomized 2:1 to receive GWP42003-P or placebo of equivalent volume to their placebo run-in allocation (see table below) in a double-blind manner for the treatment period.

<table>
<tr><td></td><td>
<table>
<tr><th>Single-blind Allocation
(Run-in Period)</th><th>Double-blind Allocation
(Treatment Period)</th></tr>
<tr><td rowspan="2">150 mg b.i.d. placebo</td><td>150 mg b.i.d. GWP42003-P</td></tr>
<tr><td>150 mg b.i.d. placebo</td></tr>
<tr><td rowspan="2">500 mg b.i.d. placebo</td><td>500 mg b.i.d. GWP42003-P</td></tr>
<tr><td>500 mg b.i.d. placebo</td></tr>
</table>

Randomization will be stratified by region (North America, Europe) and by sex (male, female).

A safety follow-up visit will be conducted 2 weeks after the last dose of investigational medicinal product (IMP). If a participant discontinues IMP prematurely (i.e., before the end of the treatment period) they are required to attend an end of treatment (EOT) visit (±3 days) and complete the safety follow-up visit 2 weeks after their last dose. Participants are encouraged to attend any outstanding visits per the trial schema. If a participant prematurely discontinues IMP and withdraws from the trial without continuing trial visits as per the trial schema, they are required to attend an early termination (ET) visit upon withdrawal and complete the safety follow-up visit 2 weeks after their last dose.</td></tr>
<tr><td>Sample Size</td><td>Approximately 366 participants will be randomized following the placebo run-in to receive 1 of 2 dose levels of GWP42003-P (150 mg b.i.d. or 500 mg b.i.d.) or dose matching volume of placebo (150 mg b.i.d. or 500 mg b.i.d.) on a 2:2:1:1 basis. The placebo groups will be pooled for the analyses of efficacy.

Assuming a common standard deviation of 11.0 and using a 2-sided hypothesis test at a 0.05 α-level, a total sample size of 366 participants (122 participants per active dose group and 61 participants per placebo group) will provide 80% power to detect a significant result assuming a true treatment difference of −4.32 points on the PANSS-T score in change from baseline to EOT between 500 mg b.i.d. of GWP42003-P and placebo. This allows for a 15% drop-out rate, with a minimum of 309 participants needed to complete the trial. Depending on the drop-out rate, during the trial, the number of randomized participants may be increased to ensure a minimum of 309 evaluable participants at Week 12.

At least 366 participants will be randomized to receive dose matching volume of placebo during the placebo run-in period (150 mg b.i.d. and 500 mg b.i.d. in a 1:1 ratio), thereafter randomized to receive GWP42003-P (150 mg b.i.d. or 500 mg b.i.d.) or dose matching volumes of placebo at a 2:1 ratio within each dose level.</td></tr>
</table>

Summary of Participant Eligibility Criteria	**Inclusion Criteria** For inclusion in the trial, the participant must fulfill ALL of the following criteria: • Male or female 18 to 55 years of age at the time of signing the ICF. • Willing and able to give informed consent for participation in the trial. • BMI of 18 to 40 kg/m^2 inclusive and a body weight ≥ 50 kg at screening. • Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of schizophrenia, confirmed by the Mini-International Neuropsychiatric Interview (MINI) for Psychotic Disorders Studies. • Clinically stable outpatient, based on the investigator's judgment and defined by no signs of exacerbation of schizophrenia (no hospital admissions or prison incarcerations), and no evidence of an increased level of psychiatric care (including cognitive behavior rehabilitation or individual psychotherapy) within 12 weeks prior to screening. • PANSS-T score of ≥ 60 and < 110 at screening and baseline visits. • Score of ≥ 4 for at least 2 of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness (P6), somatic concern (G1), or unusual thought content (G9) at screening visit. • Score ≥ 4 (at least moderately ill) on the CGI-S at screening visit. • Undergoing treatment with at least 1 antipsychotic medication with no change in dosing, supported by documentation (including pharmacy records), for at least 8 weeks prior to screening and no change in antipsychotic medication dosing planned throughout the trial. • Taking a maximum of 2 antipsychotic medications. For participants taking oral antipsychotic medications only, the sum of primary and secondary antipsychotic medications is ≤ 30 mg/day of oral olanzapine equivalents. For participants taking long-acting injectable antipsychotic medications, the dose is within the range approved and any secondary oral antipsychotic medications is ≤ 5 mg/day of oral olanzapine equivalents. • Documented response (at least partially) to treatment with current antipsychotic medications (e.g., treatment of recent exacerbation of psychotic symptoms) as assessed by the

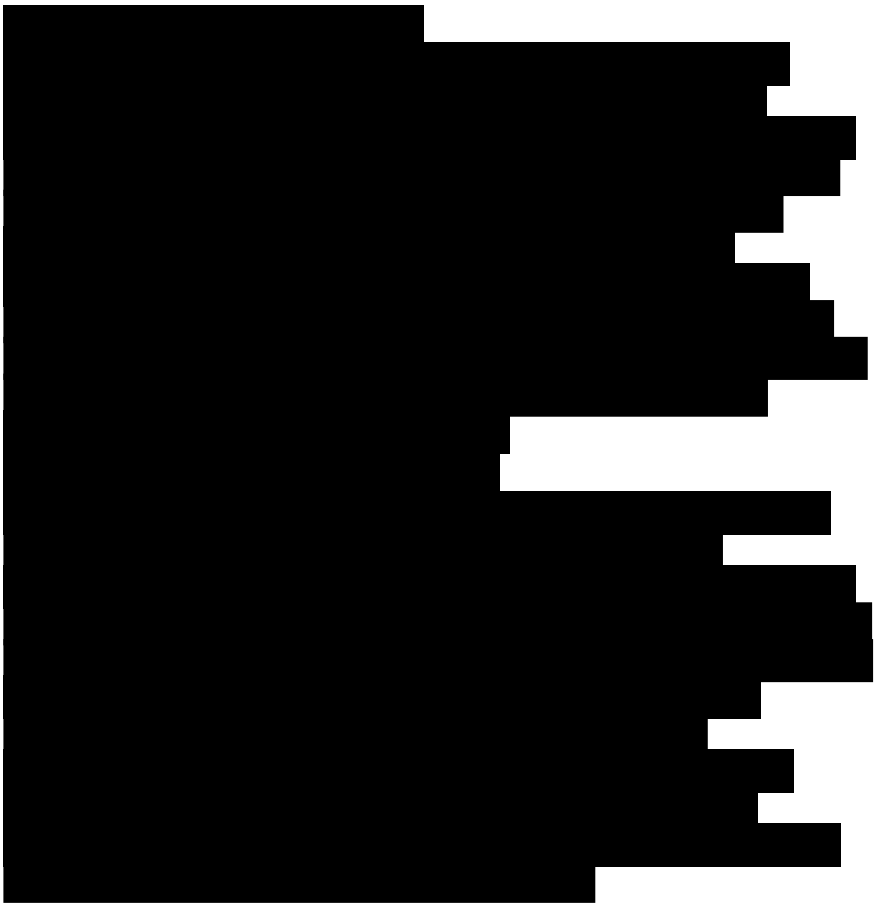
	investigator or treating physician. Documentation can include medical records, pharmacy records, or corroboration in writing by the clinician(s) currently responsible for the participant's psychiatric treatment. • On a stable dose if taking concomitant psychotropic medications and within allowed limits, including antidepressants, anxiolytics, anticholinergics and/or antiepileptics for at least 4 weeks prior to screening (dose reductions ≤ 25% of total dose are permitted) with no plans to change dosing during the trial (i.e., from screening onwards). Valproic acid or any prescribed valproate product (valproate semisodium or valproate sodium) is disallowed within 4 weeks (i.e., more than 5 half-lives) prior to the baseline visit. • Willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law. **Exclusion Criteria** The participant may not enter the trial if ANY of the following apply: ***Diagnosis and Psychiatric History*** • Recent (within the last 3 months prior to screening) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions based on the MINI for Psychotic Disorders Studies (or DSM-5) **OR** has PANSS item G6 score of ≥ 5 (depression) at screening. • Any psychiatric disorder that may interfere with the conduct of this trial, including but not limited to attention deficit hyperactivity disorder, pervasive developmental disorder, intellectual disability, personality disorder that might interfere with compliance or increase suicidal risk, manic or hypomanic episode, or any other psychotic disorder, as defined in the DSM-5. • Current diagnosis or a history of substance use disorder according to DSM-5 criteria within 6 months prior to screening or prior chronic substance abuse judged likely to recur during the trial period by the investigator. Nicotine use or occasional cannabis use (≤ 3 days per week recreational cannabis use) is acceptable. Corroboration of the participant's frequency of cannabis use by an adult informant (e.g., family member, social worker, caseworker, residential facility staff, or nurse), should be obtained if the participant has a positive urine test for Δ^9-tetrahydrocannabinol at screening. • A positive drug screen for opiates, methadone, cocaine, amphetamines (including ecstasy), or barbiturates; a repeat drug screen may be done to verify the result.

	• Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the adult C-SSRS or within 1 month prior to screening. • A ± ≥ 20% change in PANSS-T score during the placebo run-in period (Visit 2 to Visit 3). ***Treatment History*** • Treatment-resistant schizophrenia as judged by the treating physician and as defined by having previously demonstrated no response to > 2 trials of antipsychotic trial medications at therapeutic doses or required clozapine therapy due to non-response to antipsychotic therapy within the previous 6 months. • Non-compliance, as assessed by antipsychotic medication and the IMP adherence monitoring Platform: – ≤ 75% compliance of current oral antipsychotic medication during the single-blind, placebo run-in period (Visit 2 to Visit 3). – ≤ 75% compliance of current long-acting injectable antipsychotic medication as assessed by number of administrations falling more than 1 week outside of the scheduled due date of administration, in the 6 months prior to screening (Visit 1) and baseline (Visit 3). – ≤ 75% compliance of IMP during the single-blind, placebo run-in period (Visit 2 to Visit 3). • Based on the investigator assessment: – current antipsychotic medication blood levels are below the therapeutic range if therapeutic drug monitoring is available for the antipsychotic(s) prescribed for the participant; or – there is no documentation confirming the administration of long-acting injectable antipsychotic medication within the approved dose range and as prescribed by the treating physician. ***Past and Current Medical History*** • History of moderate or severe head trauma (for example, loss of consciousness for more than 15 minutes) or other neurological disorders (including epilepsy), neurodegenerative disorder (Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, etc.) or systemic medical diseases that are, in the opinion of the investigator, likely to interfere with the conduct of the trial or confound the trial assessments. • Tardive dyskinesia (TD) that is moderate to severe (i.e., a score of > 21 on the dyskinesia subscale of the ESRS at screening) or requires treatment.

	• Any other significant disease, disorder, pending court proceedings or social circumstances (e.g., homelessness) which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or may affect the participant's ability to take part in the trial. ***Other*** • Any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame seed oil. • One or more laboratory values outside the normal range, based on the blood or urine samples taken at the screening visit, that are considered by the investigator to be clinically significant; or impaired hepatic function at screening, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) **or** total bilirubin (TBL) > 1.5 × ULN **or** international normalized ratio (INR) > 1.2 (TBL ULN parameter not applicable for participants diagnosed with Gilbert's disease). Note: Out-of-range laboratory values should be confirmed on retest within the allowed screening window. • Clinically relevant abnormalities in the ECG measured at screening or randomization (including QT interval with Fridericia correction [QTcF] > 450 msec for males and > 470 msec for females, average of 3 measurements). • Positive serology panel (including hepatitis B surface antigen [HBsAg] and/or confirmed current hepatitis C infection [positive hepatitis C virus {HCV} antibody confirmed with reflex HCV RNA test]) and/or positive human immunodeficiency virus (HIV) antibody/p24 antigen screens. • Male and fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) and with a partner of childbearing potential unless agree to ensure that they use male contraception (e.g., condom) or remain sexually abstinent during the trial and for 3 months after the last dose. • Female of childbearing potential (i.e., following menarche until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless agree to use highly effective contraception (e.g., combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal or transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable or implantable], intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner [provided partner is the sole sexual

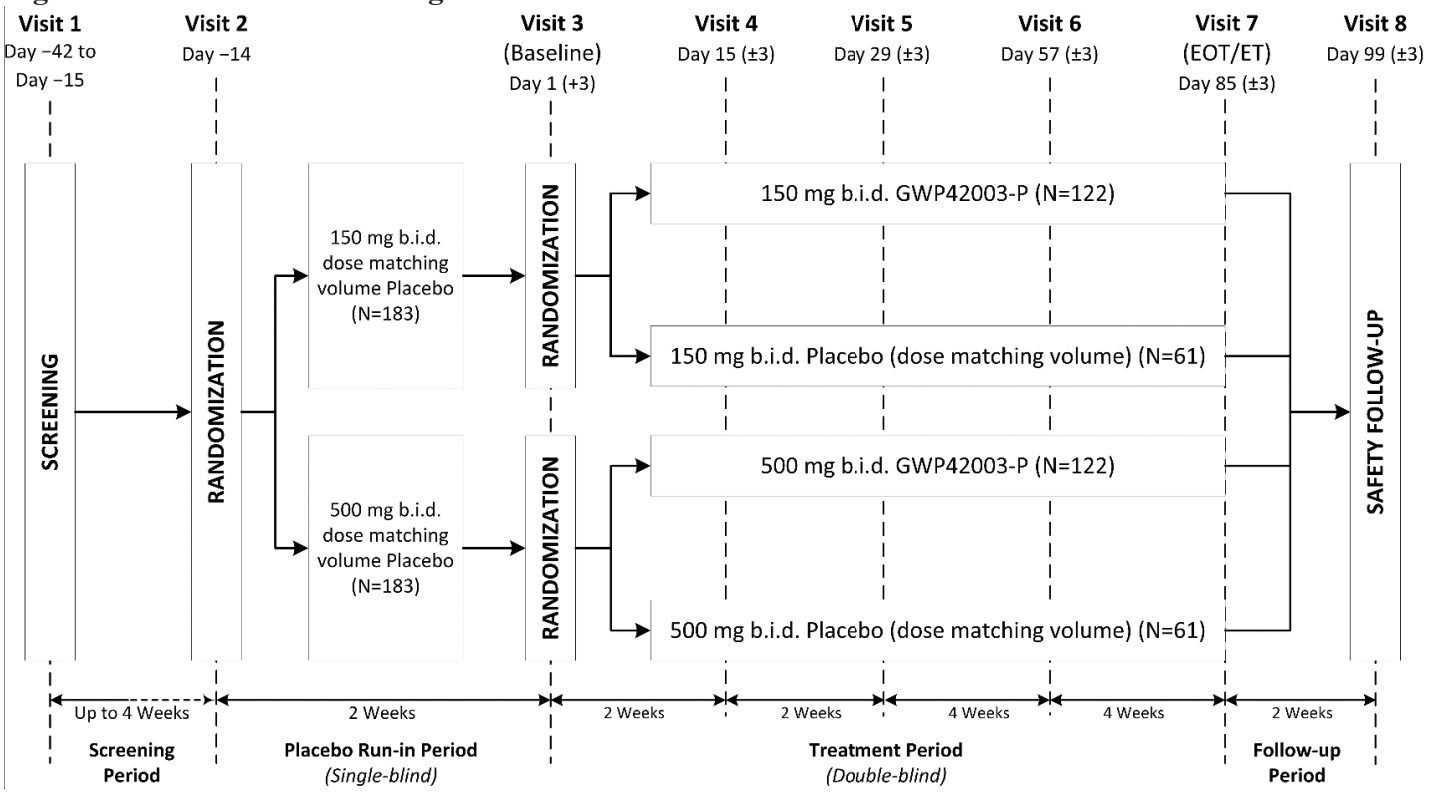
	partner and has received medical assessment of the surgical success], true sexual abstinence) during the trial (i.e., from screening) and for 3 months after the last dose. • Female who is pregnant (positive pregnancy test), lactating, or planning pregnancy during the trial or within 12 weeks after the last dose. • Received an IMP within 12 weeks prior to the screening visit. • Donated blood within 12 weeks prior to the screening visit and is unwilling to abstain from donation of blood during the trial. • Previously randomized into the placebo run-in period of this trial. • Travel outside the country of residence planned during the trial, unless the participant has confirmation that the IMP is permitted in the destination country. • Currently using or within 3 months of screening has used CBD oil or purified CBD preparations and is unwilling to abstain for the duration of the trial.
Criteria for Withdrawal/ Discontinuation of Investigational Medicinal Product	The participant must be permanently discontinued from IMP if any of the following apply: • Administrative decision by the investigator, GW, or regulatory authority. • Withdrawal of participant consent. • Lost to follow-up. • Pregnancy. • QTcF ≥ 500 msec (average of 3 measurements). • Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the adult C-SSRS or based on investigator assessment. • Protocol deviation that is considered to potentially compromise the safety of the participant or validity of the data collected. • 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 within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, and alkaline

<table>
<tr><td></td><td>phosphatase. Should the above transaminase elevation criteria be confirmed, the participant must permanently discontinue the IMP. In cases where transaminase elevation IMP discontinuation criteria are not met or confirmed, the dose of a concomitant medication with known hepatotoxicity may be reduced.</td></tr>
<tr><td>Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen</td><td>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.
Placebo oral solution contains the excipients sesame oil and anhydrous ethanol, with added β-carotene, sweetener (sucralose), and strawberry flavoring.
IMP is to be taken orally b.i.d., (e.g., morning and evening), preferably within 30 minutes of a meal using the syringe(s) provided. The dose should be swallowed.</td></tr>
<tr><td>Control Group</td><td>Matching placebo.</td></tr>
<tr><td>Procedures</td><td>All non-PK visits should be scheduled to take place at approximately the same time of day (i.e., morning or afternoon), whenever possible. Participants will be requested to abstain from recreational cannabis, alcohol, and benzodiazepines for 24 hours prior to all trial visits.
PK Assessments:
Blood sampling for PK assessments will be conducted during the screening period and the treatment period as detailed in the table below.
PK visits will be scheduled in the morning for the participant to attend prior to their morning dose of IMP. The time of the 300 kcal meal consumed at site by the participant during PK testing days will be recorded, as will the dose and dosing time of antipsychotic medications/IMP (as appropriate) relative to sampling times.
<table>
<tr><th>Analytes</th><th>Sample Time (relative to morning IMP dose)</th><th>Visit 1</th><th>Visit 4</th><th>Visit 7</th></tr>
<tr><td>Oral antipsychotic medications</td><td>Predose</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td rowspan="4">CBD
7-OH-CBD
7-COOH-CBD</td><td>Predose</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>2 to 3 hours postdose</td><td></td><td>X</td><td>X</td></tr>
<tr><td>4 to 6 hours postdose (optional)</td><td></td><td>X</td><td>X</td></tr>
<tr><td>8 to 10 hours postdose (optional)</td><td></td><td>X</td><td>X</td></tr>
</table>
</td></tr>
</table>

	 **Treatment Period Assessments:** Following the placebo run-in period, participants who continue to satisfy all inclusion criteria and none of the exclusion criteria, who did not have a ± ≥ 20% change in PANSS-T will be randomized to either GWP42003-P or placebo (150 mg b.i.d. or 500 mg b.i.d. or volume equivalent). The following assessments will be performed: eligibility criteria (recheck if required), physical examination, body weight, BMI, waist circumference, vital signs, ECG, previous and concomitant medications recorded, and AEs will be reviewed. The investigator will complete the ESRS, C-SSRS, PANSS, CGI-S, CGI-I, and CDSS. The participant will complete the cannabis use survey, PGIC, BACS, SQLS, BAS-MPsQ, and Expectation Module of Multidimensional Psychological Questionnaire (EXP-MPsQ). Clinical laboratory samples including chemistry, hematology, PK, biomarker sampling, urinalysis, drug screen, pregnancy test (for WOCBP), and optional pharmacogenomic DNA and RNA sampling will be taken. IMP will be dispensed. **Follow-up Period Assessments:** Previous and concomitant medications and AEs will be recorded by a telephone call.

Statistical Considerations	Statistical hypothesis testing will be performed on the efficacy and exploratory endpoints as appropriate. No formal adjustment of statistical significance for multiple testing on multiple endpoints will be performed, although such multiplicity should be allowed for when interpreting the results. All safety data will be summarized using appropriate statistical methods.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Trial Design and Treatment Schematic



b.i.d. = twice daily; EOT = end of treatment; ET = early termination.

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List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve calculated to the last observable concentration at time t
BACS	Brief Assessment of Cognition for Schizophrenia
BAS-MPsQ	Basic Personal Traits Module of Multidimensional Psychological Questionnaire
b.i.d.	Twice daily
BMI	Body mass index
CB	Cannabinoid
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CDSS	Calgary Depression Scale for Schizophrenia
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CIs	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum measured plasma concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CST	Clinical surveillance and training
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	12-lead electrocardiogram
EOT	End of treatment
eCRF	Electronic case report form

ePRO	Electronic participant reported outcome
ESRS	Extrapyramidal Symptom Rating Scale
ET	Early termination
EU	European Union
EXP-MPsQ	Expectation Module of Multidimensional Psychological Questionnaire
FAAH	Fatty acid amide hydrolase
FAS	Full analysis set
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GPR55	G protein-coupled receptor 55
GW	GW Research Ltd
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IQ-PANSS	Informant Questionnaire Positive and Negative Symptom Scale
IRB	Institutional review board
LPI	Lysophosphatidylinositol
LS	Least squares
MAR	Missing at random
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed-effects model repeated measures
MNAR	Missing not at random
PANSS	Positive and Negative Symptom Scale

PANSS-G	Positive and Negative Symptom Scale-General
PANSS-N	Positive and Negative Symptom Scale-Negative
PANSS-P	Positive and Negative Symptom Scale-Positive
PANSS-T	Positive and Negative Symptom Scale total
PER-MPsQ	Perception Module of Multidimensional Psychological Questionnaire
PGIC	Patient Global Impression of Change
PI	Principal investigator
PK	Pharmacokinetics
PLA2	Phospholipase A2
PP	Per protocol
PRN	Packaging reference number
PVD	Pharmacovigilance Department
QTcF	QT interval with Fridericia correction
RNA	Ribonucleic acid
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SCI-PANSS	Structured Clinical Interview Positive and Negative Symptoms Scale
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SQLS	Schizophrenia Quality of Life Scale
TBL	Total bilirubin
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
TRH	Thyrotropin-releasing hormone
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential

Definition of Terms

Term	Definition
Day 1	The day a participant first receives investigational medicinal product during the treatment period in this trial.
End of trial	Last participant last visit or last contact, whichever occurs last.
Enrolled participant	Any participant who has provided written informed consent 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.
QT interval	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

2 OBJECTIVES/ENDPOINTS

Objective	Endpoint
Efficacy	
• To evaluate the efficacy of GWP42003-P versus placebo after 12 weeks of treatment	• Mean change from baseline to Week 12 in the following: – Positive and Negative Symptoms Scale (PANSS) total (PANSS-T) score – PANSS positive subscale (PANSS-P) score – PANSS negative subscale (PANSS-N) score – PANSS general subscale (PANSS-G) score – Clinical Global Impression of Severity (CGI-S) score • Score at Week 12 in the Clinical Global Impression of Improvement (CGI-I)
Safety	
• To evaluate the safety and tolerability of GWP42003-P	• Changes in body weight, body mass index (BMI), and waist circumference • Changes in vital sign measurements • Adverse events (AEs) and adverse drug reactions (ADRs) • Extrapyramidal symptoms as assessed by the Extrapyramidal Symptom Rating Scale (ESRS) • Clinical laboratory test results • 12-lead electrocardiogram (ECG) parameters • Calgary Depression Scale for Schizophrenia (CDSS) • Suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
[redacted]	
[redacted]	[redacted]

Objective	Endpoint
[redacted]	
	[redacted]
P I	
• PI	
P I	

3 BACKGROUND AND RATIONALE

3.1 Disease

Schizophrenia, a complex neurodevelopmental syndrome, results from gradual alterations in brain connectivity which may begin *in utero*, and symptoms (distorted thinking that affects language, perception, and sense of self) present and can persist for years before psychosis emerges[1,2]. Symptoms are categorized into positive (e.g., hallucinations, delusions, and speech disturbance), negative (e.g., social withdrawal, apathy, and loss of emotional response), and cognitive domains. Worldwide over 21 million people live with schizophrenia, half of whom do not receive care[2] and individuals' ability to work and integrate socially is profoundly affected[3]. There is a slightly greater incidence in males who also experience an earlier onset[4,5]. However, regardless of sex, individuals with schizophrenia have a 2 to 3 fold increased risk of death from a range of comorbid somatic conditions (mostly cardiovascular and metabolic diseases) and suicide, the former attributable to unhealthy lifestyle, predisposition, and antipsychotic medication[4,6]. Individuals typically smoke, can be overweight or obese, suffer from hypertension, dyslipidemias, metabolic syndrome, and diabetes[7] health concerns that are exacerbated by atypical antipsychotic medications causing weight gain and metabolic abnormalities compared with the extrapyramidal and tardive side effects of typical antipsychotic medications[6].

Antipsychotic medications, effective in the treatment of psychosis in most cases, act via antagonism of central dopamine receptor D_2[1,8] however, numerous longitudinal studies have consistently noted significant heterogeneity and a high frequency of unfavorable outcomes in schizophrenia[9,10,11]. Relapse rates reach 80% to 85% during the first 5 years of illness[12,13] with three quarters of individuals discontinuing antipsychotic treatment in 18 months[14]. A chronic course characterized by residual symptoms and/or relapses occurs in 34% to 57% of individuals[11]. Treatment response is a key determinant of subsequent outcome, as it is an essential precondition for remission and recovery[15]. Sub-optimally controlled psychotic symptoms are associated with a significant reduction in quality of life and functioning[16]. There is therefore a substantial unmet need for new and effective therapies to treat schizophrenia.

Those individuals who respond to dopamine receptor blocking agents experience improvement in positive symptoms, but have little clinically significant improvement of negative symptoms and cognitive impairment[3,17].

Disruption of excitatory/inhibitory balance in the central nervous system is thought to underlie a number of neurological syndromes including schizophrenia; for example, excess dopaminergic neurotransmission in the mesolimbic and striatal brain region leads to positive symptoms whilst negative symptoms are conversely thought to arise from reduced dopaminergic transmission in prefrontal brain regions[18]. Furthermore, glutamatergic hypofunction in cortico-striatal projections is thought to affect the thalamo cortical loop to cause exaggerated sensory flooding leading to psychosis. Circuit-based frameworks in schizophrenia suggest that hypofunction of hippocampal, fast spiking, interneurons lead to excessive glutamate release from pyramidal neurons, which drives dopamine release from dopaminergic neurons[19].

The antipsychotic properties of CBD have been demonstrated in a variety of *in vitro* and *in vivo* models. The efficacy of CBD was investigated in pharmacological models of relevance to schizophrenia, including amphetamine induced hyper-locomotion[20,21], and cognitive, and social deficits induced by sub-chronic phencyclidine[22]. In addition, CBD appears to attenuate the extrapyramidal side effects induced by aripiprazole[23].

Clinically it has been shown that individuals with acute schizophrenia showed a significant improvement in PANSS-T, PANSS-P, PANSS-N, and PANSS general scores when treated with CBD; the clinical improvements were comparable with those achieved with amisulpride[24]. CBD treatment was well tolerated and compared with amisulpride, participants experienced significantly fewer extrapyramidal symptoms, less weight gain, and a lower increase of the galactorrhoea and sexual dysfunction marker, prolactin[24]. A GW sponsored trial showed participants with stable schizophrenia who had failed to optimally respond to existing antipsychotics, experienced a greater reduction from baseline in PANSS-P and a greater CGI-I after 6 weeks of adjunctive therapy with GWP42003-P compared with placebo[25].

Given that schizophrenia is a complex disorder involving dysregulation of multiple pathways and biological systems, coupled with the fact that CBD does not act through the conventional route of D_2 receptor antagonism, CBD may represent an antipsychotic with a novel mechanism of action.

3.2 Investigational Medicinal Product Background

The investigational medicinal product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield purified (> 98%) CBD that contain < 0.1% (weight

by weight) Δ^9-tetrahydrocannabinol (THC) (for oral formulations). The purified CBD is subsequently dissolved in excipients with added sweetener and flavoring.

CBD has a very low affinity and lacks appreciable functional activity at the cannabinoid (CB) receptors type 1 and 2 (CB_1 and CB_2), as well as the dopamine receptor D_2[26,27]. CBD does not significantly interact with enzymes responsible for the synthesis and degradation of endocannabinoids, at clinically relevant concentrations[28,29,30,31]. Furthermore, considerable data exist describing the polypharmacology of CBD and its modulation of non-endocannabinoid system targets. Indeed, CBD has the ability to interact with multiple 7-transmembrane receptor systems, ion channels, transporters, and enzymes, reviewed in[27,32].

Putative molecular candidates for CBD relevant to schizophrenia, based on pharmacological engagement by CBD at therapeutically relevant concentrations, include equilibrative nucleoside transporter 1 inhibition and subsequent indirect agonism of adenosine receptor A_1 (anxiolytic)[32], and antagonism at G protein-coupled receptor 55 (GPR55), and agonism of transient receptor potential vanilloid receptors[33].

GPR55 is expressed by glutamatergic principal neurons in the hippocampus at their presynaptic terminals and postsynaptic membranes[34]. Based upon the hippocampal location of GPR55 receptors within a circuit-based framework in which hippocampal, fast spiking, interneuronal hypofunction, and reduced numbers thereof in schizophrenia, lead to excessive glutamate release from pyramidal neurons and thus dopamine release from dopaminergic neurons[19], emerging data in non-clinical epilepsy models and electrophysiological recordings from brain slices *in vitro* suggests that CBD-mediated antagonism of GPR55 in the hippocampus could restore gamma-aminobutyric acid (GABA) receptor-mediated inhibition via 2 different mechanisms[34]:

1. CBD-mediated antagonism of **presynaptic** GPR55 receptors present on hippocampal principal cells prevents the endogenous ligand LPI activating GPR55 receptors and the downstream induction of calcium-induced calcium release which ultimately inhibits vesicular glutamate release, **dampening excitatory transmission**.
2. CBD-mediated antagonism of GPR55 receptors present on the **postsynaptic** membranes of hippocampal principal cells proximal to interneuron presynapses prevents LPI-mediated GPR55 activation and so the downstream,

gephyrin-mediated reduction in postsynaptic GABA receptor expression, **enhancing inhibitory transmission**.

Importantly, CBD does not produce THC-like psychoactive effects. Further to this, CBD demonstrates anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity in a range of non-clinical models and has received Food and Drug Administration (FDA) approval for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in individuals 1 year of age and older[35].

3.3 Rationale

The rationale for this Phase 2b trial is based on the initial positive efficacy findings from a previous GW sponsored trial, which investigated the use of GWP42003-P as adjunctive therapy in participants with schizophrenia with inadequate response to ongoing antipsychotic treatment (GWAP1241), by further evaluating the efficacy and safety of GWP42003-P after 12 weeks of treatment in clinically stable schizophrenia participants experiencing inadequate response to antipsychotic treatment.

3.4 Clinical Hypothesis

Treatment with GWP42003-P is associated with improvements in schizophrenia as measured by the mean change of participants' PANSS-T score from baseline to Week 12.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group, outpatient trial. The trial will compare the efficacy and safety of 2 dose levels of GWP42003-P (150 mg twice daily [b.i.d.] and 500 mg b.i.d.) versus placebo in participants with schizophrenia who are experiencing an inadequate response to ongoing antipsychotic treatment.

The duration of the trial will be approximately 20 weeks, which includes a screening period (up to 4 weeks), a single-blind placebo run-in period (2 weeks), a double-blind treatment period (12 weeks), and a safety follow-up period (2 weeks).

After signing the informed consent form (ICF), participants will enter the screening period (Visit 1). The investigator will submit participants' eligibility forms for clinical surveillance and training (CST) review. The CST will evaluate the eligibility of participants and provide the outcome of the evaluation to the site. Participants cannot be enrolled until site personnel have received the final CST notification. Additional details for CST will be described in the study manual. At Visit 2 screened participants who continue to meet eligibility criteria will be randomized 1:1 to receive 150 mg b.i.d. or 500 mg b.i.d. dose matched volumes of placebo in a single-blind manner for the placebo run-in period. At Visit 3 (Day 1), participants who continue to meet the required eligibility criteria will be randomized 2:1 to receive GWP42003-P or placebo of equivalent volume to their placebo run-in allocation (Table 7.1-1) in a double-blind manner for the treatment period.

Randomization will be stratified by region (North America, Europe) and by sex (male, female).

A safety follow-up visit will be conducted 2 weeks after the last dose of IMP. If a participant discontinues IMP prematurely (i.e., before the end of the treatment period) they are required to attend an end of treatment (EOT) visit (±3 days) and complete the safety follow-up visit 2 weeks after their last dose. Participants are encouraged to attend any outstanding visits per the trial schema. If a participant prematurely discontinues IMP and withdraws from the trial without continuing trial visits as per the trial schema, they are required to attend an early termination (ET) visit upon withdrawal and complete the safety follow-up visit 2 weeks after their last dose.

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

4.2 Number of Sites

Approximately 55 sites are expected to participate in this trial. The number of sites may be reduced or increased depending on recruitment performance.

4.3 Number of Participants

Approximately 366 participants will be randomized following the placebo run-in to receive 1 of 2 dose levels of GWP42003-P (150 mg b.i.d. or 500 mg b.i.d.) or dose matching volume of placebo on a 2:2:1:1 basis.

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

5.2 Placebo Oral Solution

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol, with added β-carotene (to color match GWP42003-P), 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
β-Carotene[a]	Up to 0.1 mg/mL
Refined sesame oil	make up to 1 mL

[a] 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 Labelling

The IMP will be manufactured, packaged, labelled and/or distributed by GW 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 of the participant. A unique identification number will be used to identify each box and the IMP it contains. The unique identification number together with the packaging reference number (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 Randomization and Trial

Supply Management (RTSM) system. GW will ensure that all IMP provided is fully labelled and packaged. The unique identification label 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 sight and reach 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 of IMP, name, address, and the telephone number of the investigator (or main contact for information about the product or the clinical trial) will be provided to each participant.

5.3.2 Storage

The IMP must be stored at room temperature (do not store above 30°C) and must not be refrigerated or frozen. 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/representative must approve storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday to Friday, excluding public holidays) from date of receipt of first shipment until end of trial dispensing period at each site. 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 site must be checked on receipt and compliance/non-compliance 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.

Participants 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 thereafter, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator's site, who will check the amount received against the shipment request 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 site 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.
- Participant'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. Participants 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 using the IMP adherence monitoring Platform (Section 5.3.5). Any discrepancies will be discussed with the

participant at the time of the visit and documented accordingly within the participant'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, a record/statement of reconciliation must be completed and 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 Investigational Medicinal Product Adherence and Reminder System

This trial will employ an IMP adherence monitoring platform ("Platform") for all participants in the trial. The Platform uses artificial intelligence on smartphones to confirm IMP ingestion and built-in reminders and a communication system allow real-time intervention in case of IMP interruptions. In addition, participants will self-report their daily compliance of their current oral antipsychotic medication(s) within the Platform.

Use of this Platform will in no way supersede or replace the prescribed IMP protocol of the participants. Because the Platform does not change the IMP protocol for the participants, but rather encourages adherence to the predefined protocol, use of this Platform presents minimal risk to the participants. Use of the Platform will be required for all participants in the trial.

The monitoring Platform requires that all participants take each dose of IMP whilst using a smartphone. The Platform will be provided to participants preloaded on a smartphone, or participants will download the Platform onto their own mobile device during the second visit to site.

When at home, participants will receive an IMP reminder at a time within a predefined window. This notification reminds participants to take their IMP dose whilst using the Platform. Participants will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the IMP. The application on the smartphone will make an automated determination of whether the participant has properly taken their IMP at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the participant takes their IMP. The amount of

guidance that the Platform provides to the participant is automatically reduced as the participant becomes more proficient at using the application.

After the Platform confirms correct IMP ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrolment. The captured data and video are reviewable through a "roles and rules" restricted system ensuring privacy of the information in accordance with United States (US) and applicable European data privacy laws, including General Data Protection Regulation European Union (EU) 2016/679.

Phone numbers of the participants may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with participants, including automated messaging from the Platform and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with participant names, nor will they be given access to participant medical records.

The Platform may provide significant benefits to trial participants as well as to the other stakeholders in the trial. Participants will benefit from rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. Healthcare providers will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent trial visits by participants. Participants who regularly fail to take IMP will be contacted by healthcare providers or other trial monitoring personnel for retraining.

The Platform Provider will protect participants' personal information to the full extent required by law. However, information from this trial, including de-identified video recording(s) of participant performance of various actions, may be submitted to the trial site, and potentially to regulatory authorities. Both information obtained by the application, and information in the participant ICF, may be examined by the trial site or the trial site's representatives, and may also be reviewed by the FDA and other regulatory agencies, Institutional Review Board(s) and or Ethics Committee(s). All parties are bound to safeguard the rights, safety and well-being of all clinical trial participants, and to maintain all information in confidence, with special consideration given to trials that may include vulnerable participants.

The results of this trial may be presented at meetings or in publications; however, participants will not be identified by name in these presentations and/or publications. Information from this trial may also be retained by the Platform Provider for the purpose of improving the Platform, to allow for future analysis of various facial and

other parameters, the reporting of high level statistical analysis of the Platform, to improve the internal workings of the system running on the smartphone device, or for regulatory filings by the Platform Provider to support future applications for the provider's product.

6 PARTICIPANT ELIGIBILITY

Investigators are responsible for confirming participant eligibility and will be required to maintain a log that includes limited information about all screened participants (e.g., initials, age, sex; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

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

6.1.1 Male or female 18 to 55 years of age at the time of signing the ICF.

6.1.2 Willing and able to give informed consent for participation in the trial.

6.1.3 BMI of 18 to 40 kg/m^2 inclusive and a body weight ≥ 50 kg at screening.

6.1.4 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of schizophrenia, confirmed by the Mini-International Neuropsychiatric Interview (MINI) for Psychotic Disorders Studies.

6.1.5 Clinically stable outpatient, based on the investigator's judgment and defined by no signs of exacerbation of schizophrenia (no hospital admissions or prison incarcerations), and no evidence of an increased level of psychiatric care (including cognitive behavior rehabilitation or individual psychotherapy) within 12 weeks prior to screening.

6.1.6 PANSS-T score of ≥ 60 and < 110 at screening and baseline visits.

6.1.7 Score of ≥ 4 for at least 2 of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness (P6), somatic concern (G1), or unusual thought content (G9) at screening visit.

6.1.8 Score ≥ 4 (at least moderately ill) on the CGI-S at screening visit.

6.1.9 Undergoing treatment with at least 1 antipsychotic medication with no change in dosing, supported by documentation (including pharmacy records), for at least 8 weeks prior to screening and no change in antipsychotic medication dosing planned throughout the trial.

6.1.10 Taking a maximum of 2 antipsychotic medications. For participants taking oral antipsychotic medications only, the sum of primary and secondary antipsychotic medications is ≤ 30 mg/day of oral olanzapine equivalents. For participants taking long-acting injectable antipsychotic medications, the dose is within the range approved and any secondary oral antipsychotic medications is ≤ 5 mg/day of oral olanzapine equivalents.

6.1.11 Documented response (at least partially) to treatment with current antipsychotic medications (e.g., treatment of recent exacerbation of psychotic symptoms) as assessed by the investigator or treating physician. Documentation can include medical records, pharmacy records, or corroboration in writing by the clinician(s) currently responsible for the participant's psychiatric treatment.

6.1.12 On a stable dose if taking concomitant psychotropic medications and within allowed limits, including antidepressants, anxiolytics, anticholinergics and/or antiepileptics for at least 4 weeks prior to screening (dose reductions ≤ 25% of total dose are permitted) with no plans to change dosing during the trial (i.e., from screening onwards). Valproic acid or any prescribed valproate product (valproate semisodium or valproate sodium) is disallowed within 4 weeks (i.e., more than 5 half-lives) prior to the baseline visit.

6.1.13 Willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law.

6.2 Exclusion Criteria

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

Diagnosis and Psychiatric History

6.2.1 Recent (within the last 3 months prior to screening) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions based on the MINI for Psychotic Disorders Studies (or DSM-5) **OR** has PANSS item G6 score of ≥ 5 (depression) at screening.

6.2.2 Any psychiatric disorder that may interfere with the conduct of this trial, including but not limited to attention deficit hyperactivity disorder, pervasive developmental disorder, intellectual disability, personality disorder that might interfere with compliance or increase suicidal risk, manic or hypomanic episode, or any other psychotic disorder, as defined in the DSM-5.

6.2.3 Current diagnosis or a history of substance use disorder according to DSM-5 criteria within 6 months prior to screening or prior chronic substance abuse judged likely to recur during the trial period by the investigator. Nicotine use or occasional cannabis use (≤ 3 days per week recreational cannabis use) is acceptable. Corroboration of the participant's frequency of cannabis use by an adult informant (e.g., family member,

social worker, caseworker, residential facility staff, or nurse) should be obtained if the participant has a positive urine test for THC at screening.

6.2.4 A positive drug screen for opiates, methadone, cocaine, amphetamines (including ecstasy), or barbiturates; a repeat drug screen may be done to verify the result.

6.2.5 Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the adult C-SSRS within 1 month prior to screening.

6.2.6 A ± ≥ 20% change in PANSS-T score during the placebo run-in period (Visit 2 to Visit 3).

Treatment History

6.2.7 Treatment-resistant schizophrenia as judged by the treating physician and as defined by having previously demonstrated no response to > 2 trials of antipsychotic trial medications at therapeutic doses or required clozapine therapy due to non-response to antipsychotic therapy within the previous 6 months.

6.2.8 Non-compliance, as assessed by antipsychotic medication and the IMP adherence monitoring Platform:

- ≤ 75% compliance of current oral antipsychotic medication during the single-blind, placebo run-in periods (Visit 2 to Visit 3).
- ≤ 75% compliance of current long-acting injectable antipsychotic medication as assessed by number of administrations falling more than 1 week outside of the scheduled due date of administration, in the 6 months prior to screening (Visit 1) and baseline (Visit 3).
- ≤ 75% compliance of IMP during the single-blind, placebo run-in period (Visit 2 to Visit 3) for current IMP.

6.2.9 Based on the investigator assessment;

- current antipsychotic medication blood levels are below the therapeutic range if therapeutic drug monitoring is available for the antipsychotic(s) prescribed for the participant; or
- there is no documentation confirming the administration of long-acting injectable antipsychotic medication within the approved dose range and as prescribed by the treating physician.

Past and Current Medical History

6.2.10 History of moderate or severe head trauma (for example, loss of consciousness for more than 15 minutes) or other neurological disorders (including epilepsy), neurodegenerative disorder (Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, etc.) or systemic medical diseases that are, in the opinion of the investigator, likely to interfere with the conduct of the trial or confound the trial assessments.

6.2.11 Tardive dyskinesia (TD) that is moderate to severe (i.e., a score of > 21 on the dyskinesia subscale of the ESRS at screening) or requires treatment.

6.2.12 Any other significant disease, disorder, pending court proceedings or social circumstances (e.g., homelessness) which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or may affect the participant's ability to take part in the trial.

Other

6.2.13 Any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame seed oil.

6.2.14 One or more laboratory values outside the normal range, based on the blood or urine samples taken at the screening visit, that are considered by the investigator to be clinically significant; or the participant has impaired hepatic function at screening, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) **or** total bilirubin (TBL) > 1.5 × ULN **or** international normalized ratio (INR) > 1.2 (TBL ULN parameter not applicable for participants diagnosed with Gilbert's disease). Note: Out-of-range laboratory values should be confirmed on retest within the allowed screening window.

6.2.15 Clinically relevant abnormalities in the ECG measured at screening or randomization (including QT interval with Fridericia correction [QTcF] > 450 msec for males and > 470 msec for females, average of 3 measurements).

6.2.16 Positive serology panel (including hepatitis B surface antigen [HBsAg] and/or confirmed current hepatitis C infection [positive hepatitis C virus {HCV} antibody confirmed with reflex HCV RNA test]) and/or positive human immunodeficiency virus (HIV) antibody/p24 antigen screens.

6.2.17 Male and fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) and with a partner of childbearing potential unless agree to ensure that they use male contraception (e.g., condom) or remain sexually abstinent during the trial and for 3 months after the last dose.

6.2.18 Female of childbearing potential (i.e., following menarche until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless agree to use highly effective contraception (e.g., combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal or transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable or implantable], intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner [provided partner is the sole sexual partner and has received medical assessment of the surgical success], true sexual abstinence) during the trial (i.e., from screening) and for 3 months after the last dose.

6.2.19 Female who is pregnant (positive pregnancy test), lactating, or planning pregnancy during the trial or within 12 weeks after the last dose.

6.2.20 Received an IMP within 12 weeks prior to the screening visit.

6.2.21 Donated blood within 12 weeks prior to the screening visit and is unwilling to abstain from donation of blood during the trial.

6.2.22 Previously randomized into the placebo run-in period of this trial.

6.2.23 Travel outside the country of residence planned during the trial, unless the participant has confirmation that the IMP is permitted in the destination country.

6.2.24 Currently using or within 3 months of screening has used CBD oil or purified CBD preparations and is unwilling to abstain for the duration of the trial.

7 PARTICIPANT ENROLMENT

Before participants enter the trial, GW requires a copy of the relevant site's institutional review board (IRB) or independent ethics committee (IEC) written approval of the protocol, ICF, and other participant information material. Participants will be considered enrolled in the trial from the time of providing written informed consent. All participants must personally sign and date the consent form prior to any procedures being performed (refer to Section 15.2).

7.1 Treatment Assignment

At the start of Visit 1, enrolled participants will be allocated a unique participant number. After completion of assessments and confirmation of eligibility at Visit 2, participants will be assigned a unique treatment number and will be randomized 1:1 to receive 150 mg b.i.d. or 500 mg b.i.d. dose matched volumes of placebo in a single-blind manner for the placebo run-in period. At Visit 3 (Day 1) participants who continue to meet the required eligibility criteria will be randomized 2:1 to receive GWP42003-P or placebo of equivalent volume to their placebo run-in allocation (Table 7.1-1) in a double-blind manner for the treatment period. GW will provide all IMP in a packed and labelled state and the RTSM system will identify the pack number to be dispensed to the participant at each relevant visit, according to the treatment assigned in the randomization schedule.

Table 7.1-1 Participant Treatment Assignment

Single-blind Allocation (Run-in Period)	Double-blind Allocation (Treatment Period)
150 mg b.i.d. placebo	150 mg b.i.d. GWP42003-P
	150 mg b.i.d. placebo
500 mg b.i.d. placebo	500 mg b.i.d. GWP42003-P
	500 mg b.i.d. placebo

b.i.d. = twice daily.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The assignment during the placebo run-in period will be single-blinded and assignment during the treatment period will be double-blinded. The randomization schedule will be held centrally and not divulged to any other person involved in the trial until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration, and Schedule

The IMP will be presented as an oral solution containing 100 mg/mL GWP42003-P or only excipients (in the case of placebo). For details regarding IMP formulations, see Section 5.

8.1.1 Dose Administration

IMP will be self-administered orally (swallowed) b.i.d. (e.g., morning and evening) preferably within 30 minutes of a meal using the syringe(s) provided. The IMP may be taken with other concomitant medications, as directed by the investigator. During the PK visits, the participants' morning dose of IMP will be administered at the trial site following predose PK blood draws, with a standardized meal of at least 300 kcal under the supervision of site staff. Staff should observe dosing and provide feedback on correct dosing methods if necessary.

8.2 Concomitant Therapy

Participants will be taking at least 1 antipsychotic medication, or a maximum of 2 antipsychotic medications. For participants taking oral antipsychotic medications only, the sum of primary and secondary antipsychotic medication is ≤ 30 mg/day of oral olanzapine equivalents. For participants taking long-acting injectable antipsychotic medications, the dose is within the range approved and any and secondary oral antipsychotic medications is ≤ 5 mg/day of oral olanzapine equivalents.

Concomitant psychotropic medications including antidepressants, anxiolytics, anticholinergics, and/or antiepileptics are allowed provided that the current dose has been unchanged for the 4 weeks prior to screening (dose reductions permitted) with no plans to change dosing during the trial (i.e., from screening onwards).

Any medication, other than the IMP, taken during the trial must be recorded in the electronic case report form (eCRF).

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. If applicable, the possible effects of these medications on the efficacy endpoints will be considered during the assessment of the evaluable period.

- Cannabis or THC-based products within 24 hours prior to Visits 1, 3, and 7.

- Valproic acid or any prescribed valproate product (valproate semisodium or valproate sodium) and psychostimulants taken within 4 weeks (i.e., more than 5 half-lives) prior to the baseline visit.
- Clozapine taken within 6 months prior to screening.

The following medications are restricted for the duration of the trial beginning from the date of the screening visit until the completion of assessments at Visit 7 or the discontinuation visit:

- Daily doses of anticholinergic drugs for the treatment of extrapyramidal side effects will be limited to 1 mg/day or less of benztropine or biperiden or 2 mg/day or less of trihexyphenidyl or equivalents.
- Daily doses of benzodiazepine receptor agonists will be limited to 2 mg/day or less of lorazepam or equivalents. Benzodiazepines will be prohibited within 24 hours prior to Visits 1, 3, and 7.
- Daily doses of hypnotics will be limited to 10 mg/day of zolpidem or zopiclone or 3 mg/day of eszopiclone. Hypnotics will be prohibited within 24 hours prior to Visits 1, 3, and 7.
- Daily doses of tricyclic antidepressants will be limited to 100 mg/day or less of amitriptyline or equivalents.
- Lithium, tricyclics, and other psychotropic medications that may affect cognition should be discussed with sponsor prior to enrolling the participant.

8.4 Compliance in Investigational Medicinal Product Administration

Refer to Appendix 1 for when IMP will be dispensed. Further guidance on IMP dispensing will be provided in a separate pharmacy manual.

Please see Section 5.3.5 for details on the IMP adherence and reminder system.

Participants should return all IMP (used and unused) at each relevant visit (Appendix 1), and participants must return placebo IMP from the placebo run-in period before randomization to the treatment period. The IMP will be checked, and any discrepancies discussed with the participant at the time of the visit and documented accordingly within the participant's source documents.

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

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

In cases where participants are not able to attend trial visits due to special circumstances (e.g., Coronavirus disease 2019 [COVID-19] pandemic), the investigator will discuss with the sponsor potential mitigation approaches for IMP dispensing, secure delivery, and collection.

8.5 Access to Blinded Treatment Assignment

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

The investigator is encouraged to contact GW 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 IMP will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).

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

9 TRIAL PROCEDURES

A list of the required trial procedures is provided in the schedule of assessments (Appendix 1). Assessments or tests that are not completed and examinations that were not conducted must be reported on the electronic eCRF.

Participants will be issued with the participant information and ICF. Following adequate time to discuss the trial with the investigator, nurse or relatives, participants who provide written informed consent will be screened for entry into the trial.

The location of the source data for the trial procedures (Appendix 1) will be documented, per site, in a signed source data verification plan; for further details see Section 16.2.

9.1 Trial Procedures

9.1.1 Informed Consent

All participants with an adequate level of understanding must personally sign and date the IRB/IEC-approved ICF before any trial-specific procedures are performed or any participant-related data are recorded for the trial. For participants with an insufficient level of understanding of what is proposed, only parent(s)/legal representative consent will be sought. If an adult participant is unable to read (illiterate or visually impaired), or is physically unable to speak or write, an impartial witness should be present during the entire informed consent discussion. After the ICF is read and explained to the participant and after the participant has orally consented to participation in the trial and has signed and dated the ICF (if capable of doing so), the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to and apparently understood by the participant and that informed consent was freely given by the participant.

If the participant cannot write, they can give consent by “making their mark” on the consent form (e.g., writing an “X”).

Informed consent should be taken in accordance with the guidance provided in ICH E6 by an appropriately trained and delegated site staff member. A physician should be available to answer any questions from the participant. The original signed ICF should be retained and a copy provided to the participant. Participants 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 Rescreening

If an individual has not met all eligibility criteria at the end of the screening period, they will be registered as a screen fail. Screen fail participants may be eligible for rescreening once. However, participants may not be rescreened if they did not meet PANSS-T or CGI-S eligibility criteria on the first screening.

Rescreened participants must first be registered as screen failures and subsequently registered as rescreens. Once the participant is registered as rescreened, a new screening window will begin. For all rescreens, all screening procedures, including ICF, must be repeated. Sites should discuss planned rescreens with the medical monitor prior to rescreening.

9.1.3 Contraception Requirements

Contraception requirements must be assessed by the investigator on a case by case basis. Where applicable, the participant or their partner must use highly effective contraception for the duration of the trial and for 3 months thereafter.

To be eligible for the trial, male participants who are fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) must agree that they are willing to use male contraception (condom) or remain sexually abstinent during the trial and for 3 months thereafter.

To be eligible for the trial, female participants of childbearing potential (i.e., fertile, following menarche and until becoming postmenopausal for ≥ 12 consecutive months unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, as per the definition of woman of childbearing potential) must agree to use highly effective birth control methods for the duration of the trial and for 3 months thereafter. Highly effective methods of birth control 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. Such methods include[36]:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine devices.
- Intrauterine hormone-releasing systems.
- Bilateral tubal occlusion.
- Vasectomized partner, provided that partner is the sole sexual partner of the participant of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence, only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the participant; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception[36].

9.1.4 Demographics

The following information will be obtained for each participant: date of birth, sex, race (as allowed per local regulations), and ethnic origin.

9.1.5 Medical History

Relevant, significant medical history will be obtained at screening (Visit 1) and is defined as any condition or disease that meets any of the following criteria:

- May affect the condition under study in this trial.
- Is ongoing on entry into the trial.
- Suspected or confirmed COVID-19 infection (or other significant infectious diseases) within 1 year prior to screening.

9.1.6 Psychiatric History

The following information will be obtained for each participant:

- Date of first diagnosis of schizophrenia.
- Details of comorbid psychiatric disorders, including dates of onset and remission.
- Date of most recent relapse or acute exacerbation of schizophrenia.
- History of prior antipsychotic medication treatments for schizophrenia, including dose, start and end dates as well as clinically significant response to treatment (yes/no).

9.1.7 Concomitant Medication

Details of all current and recent non-psychotropic medication (i.e., taken within the previous 2 weeks), will be recorded. Details of all current and recent psychotropic medication, including antipsychotic medication, antidepressants, anticholinergics, antiepileptics, and/or lithium taken within the previous 4 weeks will be recorded and reviewed at each subsequent visit. All antipsychotic medications should have been maintained at a stable dose over a period of 4 weeks prior to screening and participants must agree to maintain these at a stable dose throughout the duration of the trial; however concomitant medications may be changed if required in response to a safety concern. Any changes in concomitant medication during the trial must be recorded on the eCRF at trial visits. The time of antipsychotic medications will be collected at PK sampling visits.

Any vaccination related to COVID-19 that was received within the last 12 months prior to screening should be recorded as a concomitant medication. The information recorded should include the vaccine manufacturer and the dates of administration, with differing start and end dates if more than 1 dose is received.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.1.8 Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the schedule of assessments (Appendix 1).

9.1.9 Vital Signs

Vital signs will include systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Blood pressure should be taken after the participant has been in a

supine position in a rested and calm state for at least 5 minutes. Blood pressure must be recorded using the same arm throughout the trial, where possible.

Vital signs should be collected prior to clinical laboratory assessments and PK sampling if possible.

Body weight, BMI, waist circumference, and height (collected at Visit 1 only) will also be collected. The method for measuring waist circumference will be detailed in a separate manual.

9.1.10 12-lead Electrocardiogram

An ECG will be performed after 5 minutes in a supine position, if possible. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the eCRF. Additional ECG measurements can be taken at any time during the trial, if clinically indicated. ECG collection requirements and processing procedures will be detailed in a separate manual.

ECG should be collected prior to clinical laboratory assessments and PK sampling if possible.

9.1.11 Clinical Laboratory Sampling

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

Laboratory tests will include hematology, biochemistry, urinalysis, a drug screen, and a urine/serum pregnancy test (for women of childbearing potential [WOCBP]). Analysis of all clinical blood samples and serum pregnancy tests (for WOCBP), will be conducted at a central clinical laboratory. 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 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 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.

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 9.1.11-1.

Table 9.1.11-1 Biochemistry, Biomarkers, Hematology, Urinalysis, and Drug Screen

Biochemistry (Serum)[a]	Biomarkers	Hematology (Whole Blood)[a]	Urinalysis (Urine)[b]	Pregnancy Test	Drug Screen (Urine[a])
Alanine aminotransferase	LPI	Hematocrit	Blood	Serum[a]	Alcohol
Albumin	Phospholipase A2	Hemoglobin	Glucose	Urine[b]	Amphetamines (including ecstasy)
Alkaline phosphatase	Complement C4	Mean cell volume	Nitrites		Barbiturates
Aspartate aminotransferase	Interleukin-6	Mean corpuscular hemoglobin	pH		Benzodiazepines
Calcium	Genomic DNA[d]	Platelets	Protein		Cocaine
Creatinine	Genomic RNA[d]	Red blood cell count	White blood cells		Methadone
Creatinine clearance		White blood cell count with automated differential			Opiates
GGT					THC
HBsAg					
HCV antibody[c]					
HIV antibody					
INR					
Potassium					
Prothrombin time (plasma)					
Sodium					
Total bilirubin					
Total protein					
Urea (blood urea nitrogen)					

GGT = gamma-glutamyl-transferase; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LPI = lysophosphatidylinositol.

[a] Analyzed at a central laboratory.

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

[c] Positive HCV antibody to be confirmed with reflex HCV RNA test.

[d] Genetic analysis component of the study is optional.

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 drug screening will be reported back to the trial site for confirmation of eligibility. All laboratory results considered to represent an AE must be documented on the eCRF. For reporting and follow-up of potential cases of drug-induced liver injury, see Section 12.8. Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal EOT 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.

[redacted]

9.1.12 Randomization and Trial Management System

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

- Obtain a participant number.
- Randomize a participant.
- Obtain dispensing information.
- Provide completion/ET information.

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

9.1.13 Investigational Medicinal Product Adherence and Reminder System

The site staff will assist the participant with downloading the IMP adherence and reminder system application on their personal smartphone, or 1 will be provided to the participant.

The site staff will guide the participant through the automated registration and training steps in the application.

Throughout the trial, the site staff will regularly check IMP adherence and reminder system dashboard and monitor the communications from AiCure, the company providing the service, to identify participants who are not adherent with taking IMP. The site staff will follow-up with participants to reinforce the importance of taking the IMP as directed and work with trial participants to improve their adherence as and when necessary.

Prior to receiving IMP during Visits 2 and 3 participants will watch a training video. The aim of the training is to shape proper understanding of the clinical trial characteristics, its goals and means, in order to clarify expectations and reduce risk of placebo response in participants.

9.1.14 Questionnaires and Assessments Completed at Scheduled Visits

Investigators or his/her qualified designee must have completed the sponsor specified training for each questionnaire (where appropriate), before any questionnaires are completed, and some additional training certification may be required prior to site activation. To ensure consistency, the same staff member (where possible) should complete the questionnaires for each participant throughout the trial.

The investigator/trained delegates will complete the ESRS, adult C-SSRS, MINI for Psychotic Disorders Studies, PANSS, CGI-I, CGI-S, and CDSS. Every effort should be made to include informant information in the PANSS assessment through administration of the Informant Questionnaire (IQ)-PANSS. Informants may be contacted by phone if not able to attend every trial visit. If contact with a participant's informant cannot be made within 3-day window from the date of the study visit, either by phone or in person, then the informant interview should not be considered a barrier to visit progression. Participants' responses to the structured clinical interview (SCI)-PANSS will be audiotaped and both the PANSS assessment and recorded interview and audiotapes will be reviewed by a third party at certain visits to assess accuracy of scoring and provide feedback to investigators throughout the trial. Scores will need to be uploaded to the third-party vendor's Platform for this review to occur in a timely manner. Investigators/trained delegates who are unable to score participants in a reliable manner may have their ability to rate participants in the trial revoked by the sponsor.

Participants will complete the BACS, SQLS, PGIC, Basic Personal Traits Module of Multidimensional Psychological Questionnaire (BAS-MPsQ), Expectation Module of Multidimensional Psychological Questionnaire (EXP-MPsQ), Perception Module of

Multidimensional Psychological Questionnaire (PER-MPsQ), and the cannabis use survey.

[redacted]

9.1.14.2 Columbia-Suicide Severity Rating Scale

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia-Suicide History Form. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. At screening (Visit 1), questions will be in relation to lifetime experiences. Questioning at all subsequent visits (see Appendix 1) will be in relation to the last assessment (since last visit). The adult C-SSRS will be used for all participants.

9.1.14.3 Mini-International Neuropsychiatric Interview for Psychotic Disorders Studies

The MINI for Psychotic Disorders Studies[38] is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the US and Europe, for among others DSM-5 psychiatric disorders. With an administration time of approximately 15 minutes, it meets the need for a short but accurate structured psychiatric interview for multisite clinical trials. In order to keep it short it focuses on the existence of current disorders. For each disorder, 1 or 2 screening questions rule out the diagnosis

when answered negatively. Probes for severity, disability or medically explained symptoms are not explored symptom-by-symptom.

9.1.14.4 Positive and Negative Symptom Scale

The PANSS assessment is a medical scale used for measuring symptom severity of participants with schizophrenia or related psychotic disorder. The name denotes to the 2 types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g., hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions. It is a 30-item rating instrument that assesses the positive and negative symptoms of schizophrenia as well as symptoms of general psychopathology. A PANSS-T score is derived from the sum of the 30 items and the PANSS items are also grouped into 3 subscales: positive, negative, and general. Individual items are rated on a 7-point scale, where 1 = absent and 7 = extreme.

9.1.14.4.1 Structured Clinical Interview Positive and Negative Symptom Scale

To optimize the instrument's objectivity, the SCI-PANSS was developed to secure reliable information. The SCI-PANSS interview is used to gather information objectively prior to completing the PANSS assessment.

9.1.14.4.2 Informant Questionnaire Positive and Negative Symptom Scale

The IQ-PANSS questionnaire evaluates phenomenological presentation in a reliable and valid manner. Through item definitions, statements, and questions, the questionnaire ensures that all information related to behavioral presence, frequency, and the participant's responsiveness is obtained during interviews with family members, healthcare providers, or other informants.

9.1.14.5 Clinical Global Impressions Questionnaire

The CGI is split into 2 scales. The CGI-S and the CGI-I.

The CGI-S is a 7-point scale used to rate the severity of participants’ illness at the time of assessment. Considering total clinical experience, a participant will be assessed on severity of mental illness at the time of rating 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill.

The CGI-I, is a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. 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.

[redacted]

9.1.14.7 Brief Assessment of Cognition for Schizophrenia

The BACS is an instrument used to assess the aspects of cognition found to be the most impaired and the most strongly correlated with outcome in participants with schizophrenia or related psychotic disorder. The BACS will take about 35 minutes to complete and comprises 6 domains: verbal memory; working memory; motor speed; verbal fluency; attention and speed information processing, and executive functions. A score is obtained for each domain and a composite summary score is also calculated as the average of the scores from the 6 domains. An increase in score is indicative of an improvement in cognition.

9.1.14.8 Schizophrenia Quality of Life Scale

The SQLS was developed to measure health-related quality of life in people with schizophrenia[41]. It comprises 30 items incorporated in 3 domains: psychosocial (15 items), motivation and energy (7 items), and symptoms and side effects (8 items). All except 4 items are scored on a 5-point Likert-type scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always), with the exceptional 4 items being reverse coded (0 = always, 1 = often, 2 = sometimes, 3 = rarely, 4 = never). Individual domain and total scores are standardized by a scoring algorithm with higher scores indicating comparatively lower quality of life. The SQLS is estimated to take approximately 5 to 10 minutes to complete.

[redacted]

9.1.14.12 Patient Global Impression of Change

The PGIC comprises a question to be rated on a 7-point scale. The markers are: very much improved, much improved, slightly improved, no change, slightly worse, much worse, and very much worse.

9.1.14.13 Cannabis Use Survey

The cannabis use survey will provide the following information, at screening only:

- Age of first use.
- Duration since first regular use (years).
- Currently using/used cannabis within the last month (yes, no).
- Regularly using cannabis once per week or more (yes, no).
- Most common route of current administration (smoked, vaped, oral).

All time points thereafter:

- The number of days used in last 7 days will be collected weekly via electronic participant reported outcome (ePRO) using the IMP adherence monitoring Platform.
- Average grams per occasion will be collected weekly via ePRO using the IMP adherence monitoring Platform.

9.1.15 Investigational Medicinal Product Accountability

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

Refer to Appendix 1 for further details on when IMP will be dispensed.

Participants will be asked to return all IMP (e.g., used and unused) at relevant visits (Appendix 1). The site will check the returned IMP against the expected usage. Any discrepancies will be discussed with the participant and documented accordingly within the participant's source documents.

9.1.16 Adverse Events

All AEs will be recorded on the eCRF. All AEs occurring during the trial, whether attributed to the IMP or not, observed by the investigator or reported by the participant will be recorded in the eCRF, questioning the participant further if necessary.

Serious adverse events (SAEs) must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event via recording in the eCRF.

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 participants are not able to perform all protocol-defined assessments due to special circumstances, the investigator must discuss with the medical monitor potential mitigation approaches.

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

- Participant and/or clinician-rated outcomes assessments may be done by videoconference, telephone call, or other means of virtual contact, if possible.
- Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with documentation of the means of communication (e.g., phone call or videoconference).
- 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.
- If despite best efforts it is not possible to collect the biological samples or safety assessments (e.g., ECG or vital signs) within the interval predefined in the protocol (see Appendix 1), then the interval may be extended up to a maximum length of 14 days.
- If despite best efforts safety assessment cannot be performed, the investigator must review the benefit-risk for participant 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 INVESTIGATIONAL MEDICINAL PRODUCT DISCONTINUATION AND WITHDRAWAL

In accordance with the Declaration of Helsinki, the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2), the FDA regulations relating to GCP and clinical trials, the EU Clinical Trials Directive, the EU GCP Directive and/or other applicable regulations, a participant 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 participant must be permanently discontinued from IMP if any of the following apply:

- Administrative decision by the investigator, GW, or a regulatory authority.
- Withdrawal of participant consent.
- Lost to follow-up.
- Pregnancy.
- QTcF ≥ 500 msec (average of 3 measurements).
- Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the adult C-SSRS or based on investigator assessment.
- Protocol deviation that is considered to potentially compromise the safety of the participant or validity of data collected.
- 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 within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase (GGT), and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the participant must permanently discontinue IMP. In cases where**

transaminase elevation IMP discontinuation criteria are not met or confirmed, the dose of a concomitant medication with known hepatotoxicity may be reduced.

Should a participant 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. Participants withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported on the applicable eCRF pages. A safety follow-up visit should take place 2 weeks after last dose of IMP. If withdrawing participants decline to give a reason for withdrawal of consent, the investigator must respect the participant's wishes.

11 URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the participants 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/IEC 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 (Visit 1) and at any point up to the post-treatment, safety follow-up visit (Visit 8), 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 participant has an AE during hospitalization that prolongs their scheduled hospital stay in which case it would be considered a SAE (refer 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/IECs and investigators (expedited reporting) by GW.

An AE must only be classed as serious, i.e., an SAE, when the event falls into 1 of the following criteria:

- Results in death.
- Is life-threatening. (The term “life-threatening” in the definition of “serious” refers to an event in which the participant 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.)

- Requires inpatient hospitalization or prolongation of existing hospitalization. (AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the participant has been detained [usually involving an overnight stay] at a hospital or emergency ward for observation and/or treatment which would not have been appropriate at the trial site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.)
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is medically significant. (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 participant 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 use of drugs of 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 (Visit 8). 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 Visit 8 that is deemed to be an unexpected safety issue and is likely to have an impact on participants 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 participant'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 site files for all trial sites.

12.4 Pregnancy

Any participant, or participant's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD. 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. 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.

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 they 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 participants, 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 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 (Visit 1) up to and including the post-trial follow-up visit (Visit 8), whether attributed to IMP or not and observed by the investigator or participant.

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 as either:

- Fatal.
- Not recovered/Not resolved.
- Recovered/Resolved.
- Recovered/Resolved with sequelae.
- Recovering/Resolving.
- Unknown.

D) Severity

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

If the severity of an AE fluctuates day-to-day, for example., 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 an SAE. For example, a participant 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 1 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

Refer to Section 12.5 above.

F) Action Taken with Investigational Medicinal Product

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

- Dose increased.
- Dose not changed.
- Dose rate reduced.
- Dose reduced.
- Drug interrupted.
- Drug withdrawn.
- Not applicable.
- Unknown.

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 post Visit 8, after the trial.

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 if an AE is of sufficient severity to require the participant's removal from treatment. A participant 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 participant must undergo an EOT 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 participant, GW may contact the investigator for additional follow-up information.

12.8 Potential Cases of Drug-induced Liver Injury

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

- Serum 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 (see Appendix 2) within 24 hours of becoming aware of the results. In addition, please send a copy of the participant'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 treatment discontinuation and important medical events. The investigator will arrange for the participant to return to the investigational site as soon as possible (within 24 to 48 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase, and GGT, detailed history and physical examination. Participants should be followed in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state. However, if the above transaminase elevation criteria are confirmed by the first set of follow-up laboratory tests, the participant must be withdrawn from the trial.

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 participant cannot return to the investigational site, 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 Institutional Review Board or Independent Ethics Committee

In accordance with the EU Clinical Trials Directive, relevant parts of the FDA Code of Federal Regulations and any national regulations, GW will inform investigators, regulatory authorities and relevant IRBs/IECs of all relevant safety information. This will include the reporting of relevant SAEs and all suspected unexpected serious adverse reactions (SUSARs). This information will be provided through 2 sources:

1. Investigator's Brochure (IB)[42]: a compilation of the clinical and non-clinical 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. Council for International Organizations of Medical Sciences (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/IECs of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the US, investigators are normally required to report promptly to their IRBs all unanticipated problems involving risks to participants, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance 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 participants and reported to the IRB, *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 states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multisite trial may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators, regulatory authorities and relevant IRBs/IECs 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 a 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 366 participants will be randomized following the placebo run-in period to receive 1 of 2 dose levels of GWP42003-P (150 mg b.i.d. or 500 mg b.i.d.) or dose matching volume of placebo (150 mg b.i.d. and 500 mg b.i.d.) on a 2:2:1:1 basis. The placebo groups will be pooled for the analyses of efficacy.

Assuming a common standard deviation of 11.0 and using a 2-sided hypothesis test at a 0.05 α-level, a total sample size of 366 participants (122 participants per active dose group and 61 participants per placebo group) will provide 80% power to detect a significant result assuming a true treatment difference of −4.32 points on the PANSS-T score in change from baseline to EOT between 500 mg b.i.d. of GWP42003-P and placebo. This allows for a 15% drop-out rate, with a minimum of 309 participants needed to complete the trial. Depending on the drop-out rate, during the trial, the number of randomized participants may be increased to ensure a minimum of 309 evaluable participants at Week 12.

At least 366 participants will be randomized to receive dose matching volume of placebo during the placebo run-in period (150 mg b.i.d. and 500 mg b.i.d. in a 1:1 ratio), thereafter randomized to receive GWP42003-P (150 mg b.i.d. or 500 mg b.i.d.) or dose matching volumes of placebo at a 2:1 ratio within each dose level.

13.2 Interim Analysis

Unblinded interim evaluations, including sample size reassessment, may be performed as part of an internal Data Monitoring Committee (DMC) review (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 SAP or simulation plan.

13.3 Analysis Sets

[redacted]

[redacted]

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

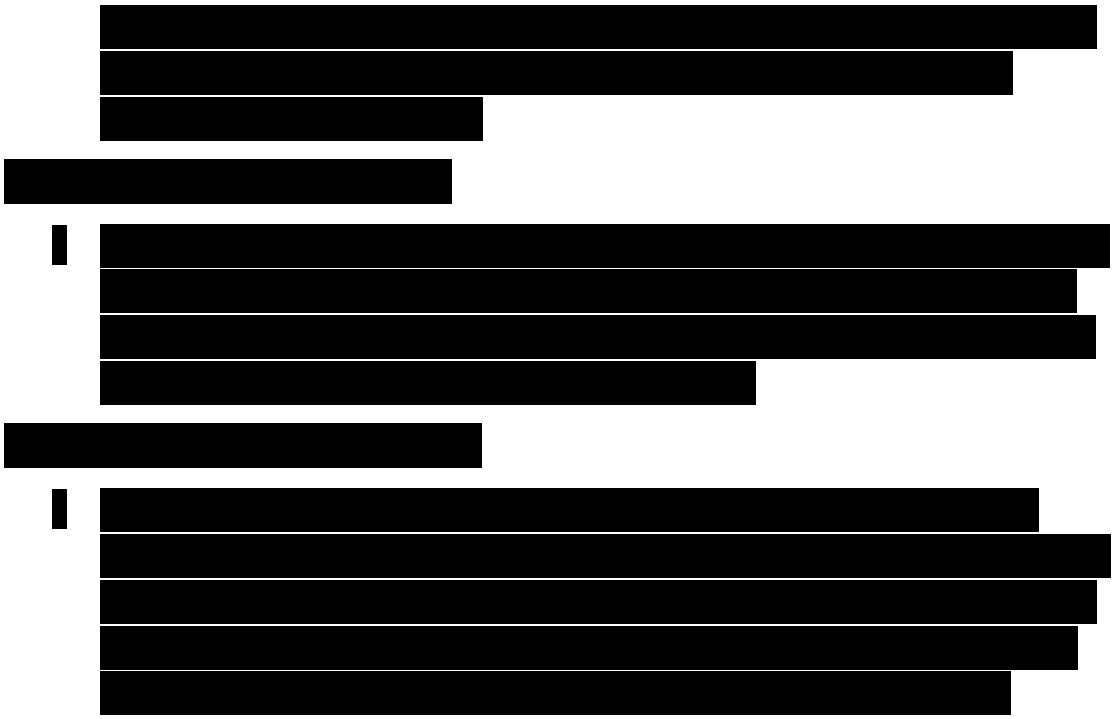
Full Analysis Set

- All participants 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 full analysis set (FAS) is the primary analysis set for all efficacy endpoints.

Safety Analysis Set

- All participants who receive at least 1 dose of IMP in the trial will be included and analyzed according to the treatment received. Only participants 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.

[redacted]



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 participants 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 Enrolment and Disposition

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

13.5.2 Baseline and Demographic Characteristics

Age, sex, race (as per local data protection laws in each specific country), ethnic origin, and any other demographic or baseline characteristics including the age of first use of cannabis, duration since first regular use (years), currently using/used cannabis within the last month (yes, no), regularly using cannabis once per week or more (yes, no), and most common route of current administration (smoked, vaped, oral) 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 schizophrenia and other comorbid psychiatric disorders) will be summarized by system organ class (SOC) by treatment arm.

13.5.4 Concomitant Medication

Concomitant medications (including antipsychotic medication treatments for schizophrenia) taken prior to and during the trial will be summarized separately by treatment arm, medication class, and active ingredients.

13.6 Endpoints and Statistical Methods

Statistical hypothesis testing will be performed on the efficacy and exploratory endpoints as appropriate. Each endpoint will have 2 comparisons against placebo (150 mg b.i.d. GWP42003-P and 500 mg b.i.d. GWP42003-P versus placebo).

All safety data will be summarized using appropriate statistical methods.

13.6.1 Efficacy Analysis

The change from baseline to Week 12 in PANSS-T, PANSS-P, PANSS-N, and PANSS-G scores will be summarized separately by treatment arm for each visit. Associated baseline scores will be taken as the last corresponding measurement prior to the first dose of IMP in the treatment period (e.g., Visit 3).

The change from baseline in each score will be analyzed separately using a mixed-effects repeated measures (MMRM) model. The corresponding model will include stratification factors, associated baseline, visit, treatment arm, visit by treatment arm interaction and visit by associated baseline interaction as fixed effects, and visit repeated within each participant as a repeated effect. An unstructured covariance matrix will be used to estimate the variance-covariance structure within

participants 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.

From this analysis the least squares (LS) mean estimates for each treatment arm at each visit, along with the standard error and 95% confidence intervals (CIs) will be presented separately for each endpoint. In addition, estimates of the treatment difference at each visit will be presented along with standard errors of the difference and 95% CIs. The primary comparison for each endpoint is the estimate of the treatment difference at Week 12.

For participants who complete the trial, regardless of whether IMP is discontinued or not, the visit effect used in the analysis will correspond to the associated score at each trial visit (e.g., Visits 4, 5, 6, and 7). However, participants who withdraw from the trial are required to complete the procedures at Visit 7 at the time of withdrawal. For these participants, Visit 7 data will be assigned to the nearest post-baseline visit (for which the assessment is scheduled to be performed), based on the trial day of the visit. Further details will be specified in the SAP.

The numeric values of CGI-S and CGI-I assessments will be analyzed separately using similar model approaches as for PANSS-T. For CGI-S, baseline score will be included as a covariate. Both values for the original categorical scale and the converted numerical scale at each visit (including change from baseline for the CGI-S numerical scale) will be summarized using standard summary statistics.

Full details of the efficacy analyses and any further analyses deemed appropriate will be provided in the SAP.

No formal adjustment of statistical significance for multiple testing on multiple endpoints will be performed, although such multiplicity should be allowed for when interpreting the results.

[redacted]

[redacted]

[redacted]

[redacted]

13.6.4 Safety

The following safety endpoints are used to support the safety objective and will be evaluated based on Statistical Analysis System (SAS®). Each endpoint will be compared with placebo at each dose level as described in the following sections:

- AEs.

- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- ECG.
- Suicidality.
- Extrapyramidal symptoms as assessed by ESRS.
- CDSS.

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

13.6.4.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.4.2 Adverse Events

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

A treatment-emergent adverse event (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 participants reporting at least 1 TEAE will be provided. AEs will be summarized in terms of the number of participants with at least 1 event (N) and the percentage of participants 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.

In the presentation of safety data, data from the GWP42003-P dose groups will be presented separately and compared with placebo. This will allow the possibility to explore any effects of the dose of IMP on safety endpoints.

Supportive summaries of ADRs will be presented.

13.6.4.3 Vital Signs, 12-lead Electrocardiogram, Physical Examination, and Other Safety Data

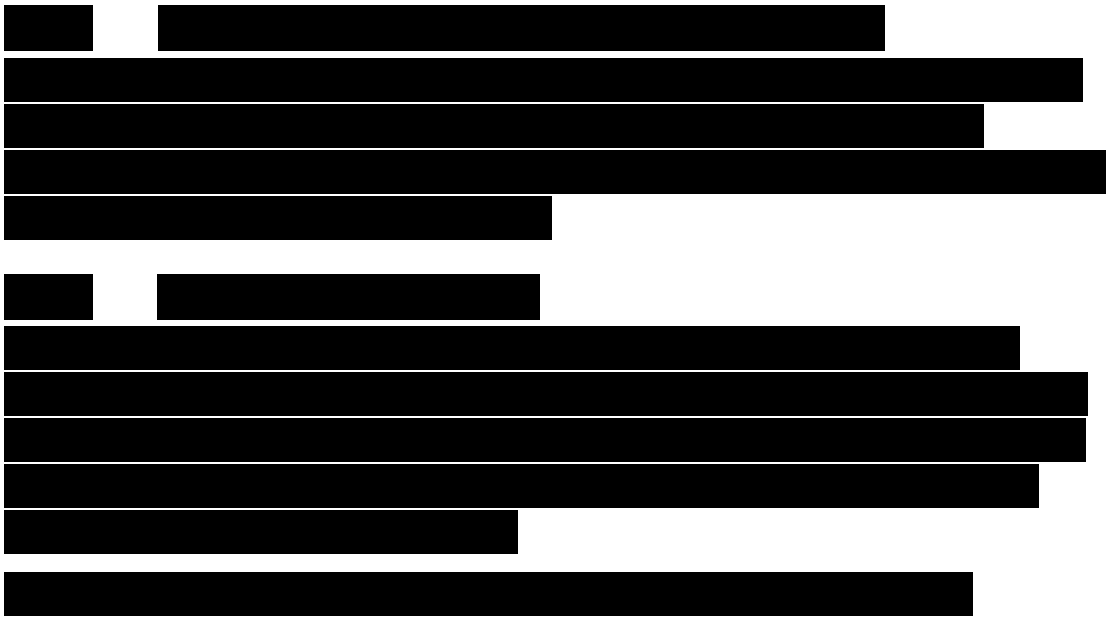
Vital signs, ECG, physical examination, CDSS, and extrapyramidal symptoms as assessed by the ESRS 45-item total score will be summarized at each time point using appropriate summary statistics. Changes in body weight, BMI, waist circumference, vital signs, ECG parameters, and the ESRS 45-item total score from baseline will be summarized by visit.

13.6.4.4 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 participants with values outside the normal range. Change from baseline will also be summarized by visit.

13.6.4.5 Suicidality

C-SSRS data will be summarized and listed as appropriate.



14 DATA MONITORING COMMITTEE

An internal DMC will be setup for 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, the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), the EU Clinical Trials Directive, the EU GCP Directive, and the clinical trial regulations adopting European Commission Directives into national legislation.

15.2 Informed Consent

An initial master ICF will be prepared by GW and provided to the investigator, who will tailor this for their site by adding the site's contact details and by using headed paper. The GW clinical manager will communicate updates to the template by letter. The written informed consent document should be prepared in the language(s) of the potential participant population.

Before a participant's involvement in the trial, the investigator or authorized delegate is responsible for obtaining written informed consent from the participant 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 participant-related data are recorded for the trial. The participant 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/IECs or local regulations.

The acquisition of informed consent must be documented in the participant's medical records and the ICF must be signed and personally dated by the participant and by the person who conducted the informed consent discussion. Informed consent should be taken in accordance with the guidance provided in ICH E6 by an appropriately trained and delegated site staff member. A physician should be available to answer any questions from the participant should they arise. The original signed ICF should be retained and a copy provided to the participant.

15.3 Institutional Review Board/Independent Ethics Committee

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

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

The investigator will be responsible for obtaining ongoing IRB/IEC approval/renewal throughout the duration of the trial. Copies of the investigator's reports and the IRB/IEC 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 participants to consent for entry into the trial:

- Signed and dated protocol signature page.
- Copy of the IRB/IEC approval of the protocol, ICF (including version number and date) and other participant information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/IEC composition and/or written statement of the IRB/IEC in compliance with the FDA regulations relating to GCP and clinical trials, the EU Clinical Trials Directive, the EU GCP Directive, or the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) 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 participant/investigator indemnity insurance and financial agreement).
- Form FDA 1572, if required.
- Completed financial disclosure statements for the PI and all sub-investigators, if relevant.

GW will ensure that the site is informed of when screening of participants can commence.

15.5 Participant Confidentiality

The investigator must ensure that the participant's anonymity is maintained. In the eCRFs or other documents submitted to GW, participants should be identified by their initials and race (if allowed per local regulations) and their trial screening number only. Documents that are not for submission to GW, e.g., signed ICFs, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to GCP and clinical trials, and the EU Clinical Trials Directive/ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), it is required that the investigator and institution permit authorized representatives of the company, the regulatory authorities and the IRB/IEC have direct access to review the participant'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 participant that his/her trial-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

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.

[redacted]

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/IEC 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/IEC for information only. The investigator must send a copy of the approval letter from the IRB/IEC 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/IEC in writing of the trial's completion or ET 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 eCRFs will be included on the GW Delegation of Authority and Signature form.

Source documents are original documents, data and records containing all protocol-specified information from which the participant's eCRF 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. A source data verification plan, identifying the source for each data point at each site, will be agreed with each site prior to participant recruitment. In the rare situations of data being recorded directly into the eCRF in error, then the source data from the eCRF should be transcribed into the participant'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 ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6[R2], Section 8.2), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Participant files containing completed eCRFs, ICFs, 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/IEC and GW.
- Enrolment log of all participants who consented to take part in the trial.
- Screening and recruitment log of all participants screened and whether they were recruited into the trial or not (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 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 or if needed by GW.

GW will inform the investigators for each site 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 (on-site or remotely) the facilities and, upon request, inspecting the various records of the trial, e.g., eCRFs and other pertinent data, provided participant confidentiality is respected.

The GW trial monitor, or designee, is responsible for inspecting the eCRFs 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 participant medical records and other trial-related records needed to verify the entries on the eCRFs.

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 participants and sites, a clinical data management review will be performed on participant data received at GW or a contract research organization (CRO). During this review, participant 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, ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and then returned to GW or the CRO, as applicable.

16.4 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive/ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) and the sponsor's audit plans, representatives from GW's Clinical Quality Assurance Department may select this trial for audit. Inspection of site 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/ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the trial site in the event of any claim in respect of personal injury arising due to a participant'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 participant 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/PIs. 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 Writing 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.

17 REFERENCES

1 MacKay MB, Paylor JW, Wong JTF, Winship IR, Baker GB, Dursun SM. Multidimensional Connectomics and Treatment-Resistant Schizophrenia: Linking Phenotypic Circuits to Targeted Therapeutics. Front Psychiatry. 2018; 9:537

2 World Health Organisation. Schizophrenia. WHO Website. https://www.who.int/mental_health/management/schizophrenia/en/ Accessed July 2019.

3 Stone JM, Raffin M, Morrison P, McGuire PK. Review: The biological basis of antipsychotic response in schizophrenia. J Psychopharmacol. 2010;24(7):953–64.

4 McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67–76.

5 Cascio MT, Cella M, Preti A, Meneghelli A, Cocchi A. Gender and duration of untreated psychosis: a systematic review and meta-analysis. Early Interv Psychiatry. 2012;6(2):115–27.

6 Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. Front Neurosci. 2015;9:297.

7 Correll CU. Balancing efficacy and safety in treatment with antipsychotics. CNS Spectr. 2007;12(10 Suppl 17):12–20, 35.

8 Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry. 2005;10(1):79–104.

9 Ram R, Bromet EJ, Eaton WW, Pato C, Schwartz JE. The natural course of schizophrenia: a review of first-admission studies. Schizophr Bull. 1992;18(2):185–207.

10 Möller HJ, Jäger M, Riedel M, Obermeier M, Strauss A, Bottlender R. The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: comparison of psychopathological and psychosocial course and outcome and prediction of chronicity. Eur Arch Psychiatry Clin Neurosci. 2010;260(5):367–84.

11 Lang FU, Kösters M, Lang S, Becker T, Jäger M. Psychopathological long-term outcome of schizophrenia - a review. Acta Psychiatr Scand. 2013;127(3):173–82.

12 Altamura AC, Bobo WV, Meltzer HY. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. Int Clin Psychopharmacol. 2007;22(5):249–67.

13 Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999;156(4):544–9.

14 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209–23.

[15] Verma S, Subramaniam M, Abdin E, Poon LY, Chong SA. Symptomatic and functional remission in patients with first-episode psychosis. Acta Psychiatr Scand. 2012;126(4):282–9.

[16] Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. CNS Drugs. 2002;16(7):473–84.

[17] Fusar-Poli P, Papanastasiou E, Stahl D, et al. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. Schizophr Bull. 2015;41(4):892–9.

[18] Lang UE, Puls I, Muller DJ, Strutz-Seebohm N, Gallinat J. Molecular mechanisms of schizophrenia. Cell Physiol Biochem. 2007;20(6):687–702.

[19] Lisman JE, Coyle JT, Green RW, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci. 2008;31(5):234–42.

[20] GWOR10133 Study Report. Evaluation of Effects of Pure Cannabidiol (CBD Pure) on D-Amphetamine-induced Hyperlocomotion. Mar 2011.

[21] GWOR10151 Study Report. Evaluation of Effects of Pure Cannabidiol (CBD Pure) on D-Amphetamine-induced Hyperlocomotion. Mar 2011.

[22] Neill JC, Barnes S, Cook S, et al. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. Pharmacol Ther. 2010;128(3):419–32.

[23] GWOR1027 Study Report. Adjunctive Effect of Cannabidiol and Tetrahydrocannabivarin on Cataleptogenic Potential of Aripiprazole in Rats. Feb 2009.

[24] Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2012; 20;2:e94.

[25] McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. Am J Psychiatry. 2018;175(3):225–231.

[26] GWTX1562 Study Report: In Vitro Pharmacology Study of Several Compounds. December 2015.

[27] Turner SE, Williams CM, Iversen L, Whalley BJ. Molecular Pharmacology of Phytocannabinoids. Prog Chem Org Nat Prod. 2017;103:61–101.

[28] GWOR0873 Study Report. An in vitro evaluation of the effect of phytocannabinoids on NAAA. Jan 2013.

[29] GWOR0885 Study Report. An in vitro evaluation of the effect of phytocannabinoids on endocannabinoid uptake. Jan 2013.

[30] GWOR0861 Study Report. An in vitro evaluation of the effect of phytocannabinoids on FAAH. Jan 2013.

[31] GWOR0849 Study Report. An in vitro evaluation of the effect of phytocannabinoids on MAGL & DAGL. Jan 2013.

[32] Ibeas Bih C, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ. Molecular Targets of Cannabidiol in Neurological Disorders. Neurotherapeutics. 2015;12(4):699-730.

[33] Ryberg E, Larsson N, Sjögren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol. 2007;152(7):1092–101.

[34] Rosenberg E, Bazelot M, Salah A, et. al. Cannabidiol (CBD) exerts anti-epileptic properties by targeting the LPI-GPR55 signaling system potentiated by seizures. American Epilepsy Society (AES) 2018 Annual Meeting. New Orleans.

[35] Epidiolex Prescribing Information. Revised October 2020. https://www.epidiolex.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf (accessed 18 March 2021)

[36] Clinical Trial Facilitation Group: Recommendations related to contraception and pregnancy testing in clinical trials. September 2014.

[37] Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res. 2005;76(2-3):247–65.

[38] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22–33;quiz 34–57.

[39] Kim SW, Kim SJ, Yoon BH, et al. Diagnostic validity of assessment scales for depression in patients with schizophrenia. Psychiatry Res. 2006;144(1):57–63.

[40] Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res. 1992;6(3):201–8.

[41] Wilkinson G, Hesdon B, Wild D, et al. Self-report quality of life measure for people with schizophrenia:the SQLS. Br J Psychiatry. 2000;177:42–6.

[42] Investigator's Brochure: CBD Medicine. GW Pharma Ltd. Edition 11. Sep 2018.

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Period	Screening Period	Placebo Run-in Period	Treatment Period					Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7 EOT/ET[a]**	**8 Telephone call**
Week	**−6**	**−2**		**2**	**4**	**8**	**12**	**14**
Day	**−42 to −15**	**−14**	**1 (Baseline)**	**15**	**29**	**57**	**85**	**99**
Visit Window (Days)			**+3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X							
Eligibility criteria	X[p]		X					
Placebo-response training video[b]		X	X				X	
Demographics	X							
Cannabis use survey[c]	X	X	X	X	X	X	X	
Medical history	X							
Psychiatric history	X							
Physical examination[d]	X		X				X	
Body weight, BMI, waist circumference and height[e]	X		X	X	X	X	X	
Vital signs[f, g]	X	X	X	X	X	X	X	
ECG[f, h]	X		X				X	
Chemistry	X		X		X		X	
Hematology	X		X		X		X	
Serology[i]	X							
PK blood sampling[j]	X			X			X[q]	
Biomarker sampling			X				X	

Period	Screening Period	Placebo Run-in Period	Treatment Period					Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7 EOT/ET[a]**	**8 Telephone call**
Week	**−6**	**−2**		**2**	**4**	**8**	**12**	**14**
Day	**−42 to −15**	**−14**	**1 (Baseline)**	**15**	**29**	**57**	**85**	**99**
Visit Window (Days)			**+3**	**±3**	**±3**	**±3**	**±3**	**±3**
Pharmacogenomic DNA sampling			X					
Pharmacogenomic RNA sampling			X				X	
Urinalysis	X		X	X		X	X	
Drug screen[k]	X		X				X	
Pregnancy test (for WOCBP)	X		X		X	X	X	
ESRS[l]	X		X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	
MINI for Psychotic Disorders Studies	X							
PANSS[m]	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	
CGI-I				X	X	X	X	
PGIC			X	X	X	X	X	
CDSS		X	X				X	
BACS	X		X				X	
SQLS		X	X				X	
BAS-MPsQ		X				X		
EXP-MPsQ			X					
PER-MPsQ		X						

Period	Screening Period	Placebo Run-in Period	Treatment Period					Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7 EOT/ET[a]**	**8 Telephone call**
Week	**−6**	**−2**		**2**	**4**	**8**	**12**	**14**
Day	**−42 to −15**	**−14**	**1 (Baseline)**	**15**	**29**	**57**	**85**	**99**
Visit Window (Days)			**+3**	**±3**	**±3**	**±3**	**±3**	**±3**
Randomization		X	X					
Dispense IMP[n, o]		X	X	X	X	X		
Return IMP			X[r]	X	X	X	X	
IMP Adherence System and Compliance Check[s]		X	X	X	X	X	X	
AEs		X	X	X	X	X	X	X
Previous and concomitant medication	X	X	X	X	X	X	X	X

Abbreviations: BACS = Brief Assessment of Cognition for Schizophrenia; BAS-MPsQ = Basic Personal Traits Module of Multidimensional Psychological Questionnaire; CDSS = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; CGI-I = Clinical Global Impression-Improvement; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = 12-lead electrocardiogram; EOT = end of treatment; ESRS= Extrapyramidal Symptom Rating Scale; ET = early termination; EXP-MPsQ = Expectation Module of Multidimensional Psychological Questionnaire; MINI = Mini-International Neuropsychiatric Interview; PER-MPsQ = Perception Module of Multidimensional Psychological Questionnaire; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; PANSS = Positive and Negative Symptoms Scale; SQLS = Schizophrenia Quality of Life Scale; WOCBP = Women of childbearing potential.

a. If a participant discontinues IMP prematurely (i.e., after Visit 3 but before the end of the treatment period) they are required to complete an EOT visit and complete the safety follow-up visit 2 weeks after their last dose. Participants who discontinue IMP prematurely should be encouraged to attend any outstanding trial visits. An ET visit should only be completed if the participant prematurely discontinues IMP and withdraws from the trial without continuing trial visits as per the trial schema.
b. Video to be watched prior to administration of PANSS.
c. Age of first use, duration since first regular use (years), current use within the last month, regular use once per week or more, and most common route of current administration (smoked, vaped, oral) will be recorded at screening. Number of days used in last 7 days and average grams used per day will be collected weekly via ePRO from Visit 2 using the IMP adherence monitoring Platform.
d. A full physical examination at screening and a symptom-directed physical examination at Visit 3 and Visit 7.
e. Height will be collected at screening only.
f. To be collected prior to clinical laboratory assessments and PK sampling.

g. Vital signs will include systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Blood pressure should be taken after the participant has been in a supine position in a rested and calm state for at least 5 minutes. Blood pressure must be recorded using the same arm throughout the trial, where possible.
h. An ECG will be performed after 5 minutes in a supine position, if possible. The ECGs should be done in triplicate at screening and baseline to ensure that QTcF < 450 msec (males)/ < 470 msec (females). Any subsequent ECG should be done once and should be repeated 2 times in cases where withdrawal criteria are met (QTcF ≥ 500 msec).
i. To include HIV, hepatitis B, and hepatitis C.
j. Plasma concentrations of the background antipsychotic medications will be assessed at Visit 1 and predose relative to the administration of IMP at Visit 4 and Visit 7.
   CBD and its major circulating metabolites will be assessed at Visit 1 and relative to the administration of IMP at Visits 4 and 7. A PK sample will be collected before the participant's morning dose of IMP and within 12 hours (−3/+6 hours) since last IMP dose (Visit 4 and Visit 7). Following collection, the IMP will be administered with a meal of at least 300 kcal to be provided. At Visit 1, only a baseline PK sample will be collected. At Visit 4 and Visit 7, samples to determine concentrations of CBD and its major circulating metabolites will be collected pre- and postdose, relative to IMP, at a timepoint between 2 to 3 hours. Thereafter optional PK sampling may be collected at postdose time points between 4 to 6 hours and 8 to 10 hours.
k. A drug screen test (urine) will include alcohol, amphetamines (including ecstasy), barbiturates, benzodiazepines, cocaine, methadone, opiates, and THC. THC will be blinded from Visit 3 to the end of the trial.
l. Assessment to be conducted prior to dosing of any regular medication prescribed for the management of extrapyramidal side effects (e.g., anticholinergics, beta-blockers etc.).
m. Every effort should be made to include informant information in the PANSS assessment through administration of the Informant Questionnaire PANSS. If contact with a participant's informant cannot be made within 3-day window from the date of the study visit, either by phone or in person, then the informant interview should not be considered a barrier to visit progression.
n. IMP is to be taken orally b.i.d., (e.g., morning and evening) preferably within 30 minutes of a meal using the syringe(s) provided. Participants will be asked to return all IMP (used and unused) at each relevant visit. The first dose of IMP at Visit 2 should be taken at the site.
o. In cases where participants are not able to attend trial visits due special circumstances (e.g., COVID-19 pandemic), the investigator will discuss with the sponsor potential mitigation approaches for IMP dispensing, secure delivery, and collection.
p. Eligibility review forms will be submitted for CST review once the diagnostic process and screening assessments are completed.
q. If the participant discontinues IMP prematurely, PK assessment will not be collected.
r. Participant must return placebo IMP prior to treatment period randomization.
s. At Visit 2, the IMP Adherence smartphone application will be demonstrated to the participant. The first dose of IMP will be taken at site to demonstrate the use of the technology correctly. At following visits, IMP compliance will be checked through measuring the contents of the returned bottles. A participant who consistently fails to dose using the smartphone application should be followed up appropriately and re-trained by the site.

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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 (UK)** **USA Toll-free Fax: +1-866-234-1751** Tel: +44 (0)1223 233 410 Email: pvd@gwpharm.com
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

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, 24-hour Emergency Contact Number, and 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
Trial Conduct	Syneos Health 1030 Sync Street Morrisville NC 27560 United States

Appendix 2.3 Contract Research Organizations

Syneos Health will monitor the trial.

Syneos Health
1030 Sync Street
Morrisville
NC 27560
United States