A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME.

Study Code: GWND18064

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol entitled 'A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome', dated 07 July 2020 and agree to abide by all provisions set forth therein.

The sponsor and I agree to comply with applicable regulatory requirement(s); the 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 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 Good Clinical Practice 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 all trial-related medical decisions.

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

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

Site No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: [redacted] Date: _____

Vice President, Clinical Sciences (or designee) (DD Month YYYY)

Signature: DocuSigned by: [redacted]
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Signing Reason: I approve this document
Signing Time: 07-Aug-2020 | 13:07 PDT
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1 PROTOCOL SYNOPSIS

Trial Title	A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome.
Clinical Trial Type	Phase 3
Indication	Rett syndrome (RTT) [typical or atypical]
Primary Objective	• To evaluate the efficacy of 15 mg/kg/day GWP42003-P, compared with placebo, at the end of 24 weeks' treatment in reducing symptom severity in patients with RTT using the Rett Syndrome Behaviour Questionnaire (RSBQ).
Secondary Objective(s)	Key Secondary Objective: • To evaluate the efficacy of 15 mg/kg/day GWP42003-P, compared with placebo, at the end of 24 weeks' treatment in reducing symptom severity in patients with RTT using the Clinical Global Impressions - Improvement (CGI-I). Other Secondary Objectives: • To evaluate the efficacy of 5 mg/kg/day GWP42003-P, compared with placebo in: o RSBQ o CGI-I • To evaluate the effect of GWP42003-P, compared with placebo, in other measures of disease severity. o RSBQ subscales. o Clinical Global Impressions - Severity (CGI-S). o 9-items Motor Behavioral Assessment (MBA-9). o Children's Sleep Habits Questionnaire (CSHQ). • To evaluate the safety of GWP42003-P, compared with placebo, in patients with RTT. Exploratory Objectives: • To evaluate the effect of GWP42003-P on caregiver and patient quality of life (QoL). o 36-item Short Form [SF-36] and Child Health Questionnaire Parent Form 50 [CHQ-PF50], respectively. • To evaluate the effect of GWP42003-P on health utilization. o Hospital Services Use Questionnaire. • Caregiver assessment of Rett symptoms (symptom diary).

	• To determine the plasma concentrations of cannabidiol (CBD) and its major metabolites with the aim of evaluating exposure versus efficacy and safety and collecting data for population pharmacokinetic (PK) analysis. • To evaluate the effect of GWP42003-P on exploratory biomarkers.
Trial Design	This multisite trial consists of a double-blind, randomized, placebo-controlled design which will compare the efficacy of GWP42003-P versus placebo over a 24-week treatment period. Patients will be randomized to receive 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volumes of placebo in a 2:2:1:1 ratio. Following screening, eligible patients will complete a 2 to 4-week baseline period (patients can be randomized as soon as they have completed at least 2 weeks of baseline and all eligibility criteria are confirmed [including review of all clinical laboratory results and, if applicable, confirmation of *MECP2* pathogenic genetic mutation]). All patients entering the trial will be stratified by severity, based on their Clinical Severity Scale (CSS) score (either a CSS score within the range of 10–22, or a CSS score within the range 23–36). Patients will be randomized and will commence the 24-week treatment period, including up to 2 weeks dose escalation. The treatment period ends at Visit 9 (Day 169), after which patients will commence a 10-day taper period followed by the 4-week follow-up period. The 10-day taper period and 4-week follow-up period may not be required for patients continuing CBD-OS treatment under a separate protocol. If a patient permanently discontinues treatment at any point during the trial, the investigational medicinal product (IMP) should be gradually reduced over 10 days (unless inadvisable due to an adverse event [AE]). Patients and caregivers will be encouraged to remain in the trial and continue to complete trial assessments and visits as per protocol. If a patient withdraws from the trial at any point during the trial, they will be required to attend a withdrawal visit, if applicable taper the IMP and attend the end of taper visit, and then complete the 4-week follow-up period.
Primary Endpoint	**Efficacy:** • RSBQ (total score) for the 15 mg/kg/day GWP42003-P dose level compared with placebo at the end of 24 weeks.
Secondary Endpoint(s)	**Key Secondary Endpoint:** • CGI-I for the 15 mg/kg/day GWP42003-P dose level compared with placebo at the end of 24 weeks.

	Other Secondary Efficacy Endpoints:
	• To compare 5 mg/kg/day GWP42003-P with placebo using:
	  o RSBQ (total score)
	  o CGI-I
	• To compare 15 mg/kg/day GWP42003-P and 5 mg/kg/day GWP42003-P with placebo using:
	  o RSBQ subscales.
	  o CGI-S.
	  o MBA-9.
	  o CSHQ.
	Exploratory Endpoints:
	• To compare 15 mg/kg/day GWP42003-P and 5 mg/kg/day GWP42003-P with placebo for the following endpoints:
	  o Caregiver QoL questionnaire (SF-36).
	  o Patient QoL questionnaire (CHQ-PF50).
	  o Hospital Services Use Questionnaire.
	  o Caregiver assessment of Rett symptoms (symptom diary).
	  o Blood levels of exploratory biomarkers.
	• Additional Exploratory Endpoints:
	  o Plasma concentrations of CBD and its main metabolites.
	Safety:
	The safety profile of GWP42003-P compared with placebo will be assessed by measuring:
	• AEs.
	• Clinical laboratory parameters.
	• Vital signs.
	• Physical examination procedures.
	• 12-lead electrocardiogram (ECG).
	• Effects on menstruation cycles.
	• Suicidality.
	• Change in growth and development by measurement of height, weight, serum insulin-like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged ≥ 7 years, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

Sample Size	Approximately 252 patients will be randomized to receive 1 of 2 dose levels of GWP42003-P (5 mg/kg/day or 15 mg/kg/day) or matching placebo (5 mg/kg/day dosing volumes or 15 mg/kg/day dosing volumes) on a 2:2:1:1 basis. The placebo data for the 2 dose groups will be pooled for analysis. Assuming a common standard deviation of 9.38 and using a 2-sided test at a 0.05 α-level, a total sample size of 252 patients (84 patients per active dose group and 42 patients per placebo group) will provide 90% power to detect a mean difference of 5 points in change from baseline to Visit 9 in RSBQ (total score) between 15 mg/kg/day of GWP42003-P and placebo, allowing for 10% withdrawals. The overall Type I error of 5% will be preserved by adopting a hierarchical testing approach where the key secondary endpoint will only be tested at the 5% significance level if the primary endpoint is statistically significant. In addition, if the key secondary endpoint is statistically significant, the α of 5% will be passed down to the secondary endpoint family.
Summary of Patient Eligibility Criteria	**Inclusion Criteria** For inclusion in the trial, patients must fulfil ALL of the following criteria: • Patient is female or male aged 2–18 years (inclusive). • Patient must weigh at least 10 kg. • Patient (if possessing adequate understanding, in the investigator's opinion) and/or the patient's parent(s)/legal representative is willing and able to give informed consent/assent for participation in the trial. • Patient and the patient's caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements (including the completion of all caregiver assessments by the same caregiver throughout the trial). • Patient must have a clinical diagnosis of RTT (typical or atypical), defined according to RettSearch Consortium criteria[a]. • Patient must have a confirmed pathogenic genetic mutation of the *MECP2* gene[b].

[a] Neul JL, Kaufmann WE, Glaze DG, et al. RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944-50

[b] For patients without a documented pathogenic *MECP2* mutation, a blood sample for pathogenic *MECP2* mutation analysis must be collected at Visit 1 or prior to Visit 1 if patient weight is < 19Kg. All patients are required to have a confirmed pathogenic mutation of the *MECP2* gene prior to randomization.

	• Patient must be post-regression (≥ 6 months since last loss of hand use or verbal language or gross motor regression). • Patient must have a disease severity of between 10 and 36, defined according to the CSS. • All medications or interventions (including antiepileptic drugs [AEDs] and non-pharmacological interventions - dietary supplements, probiotics, physical therapy, speech therapy, etc.) for RTT-related symptoms must have been stable for 4 weeks prior to screening and the patient/caregiver should be willing to maintain a stable regimen throughout the trial. • Patient must have the ability to swallow the IMP provided as a liquid solution, or the ability for IMP to be delivered via gastrostomy (G) or nasogastric (NG) feeding tube (use of G- or NG-tubes is only allowed after discussion with the Medical Monitor to confirm suitability of the tubes being used). • Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law. • Patient and/or parent(s)/legal representative is willing to allow the patient's primary care practitioner (if the patient has one) and consultant (if the patient has one) to be notified of participation in the trial, if the primary care practitioner/consultant is different to the investigator. **Exclusion Criteria** The patient may not enter the trial if ANY of the following apply: • Patient meets exclusion criteria for RTT diagnosis (traumatic brain injury, neurometabolic disease, or severe infection that causes neurological problems; grossly abnormal psychomotor development in the first 6 months of life). • Patient has clinically significant abnormal laboratory values, in the investigator's opinion. • Patient experiences more than weekly seizures (based on history over the last 2 months prior to screening), i.e., has CSS 'epilepsy/seizure' score of 4 or 5. • Patient is taking more than 2 concurrent AEDs. • Any history of suicidal behavior or any suicidal ideation in the last month or at screening.

	• Patient has clinically relevant abnormalities in the ECG measured at screening or randomization (including QT interval, corrected by Bazett's correction formula [QTcB] > 450 msec, average of 3 measurements). • Patient has any concurrent cardiovascular conditions which will, in the investigator's opinion, interfere with the ability to assess the patient's ECGs or put the patient at risk because of participation in the trial. • Patient's first or second degree relative has a history of significant ECG abnormalities, in the opinion of the investigator (e.g., premature cardiac arrest, sudden death). • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP (active and placebo), such as sesame oil. • Patient has moderately impaired hepatic function at screening, defined as serum ALT or AST > 3 × ULN **or** total bilirubin [TBL] > 2 × ULN. *This criterion can only be confirmed once the Visit 1 laboratory results are available.* • Female patient is of childbearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., combined [estrogen and progestogen containing] hormonal contraception[a] associated with inhibition of ovulation [oral, intravaginal or transdermal], progestogen-only hormonal contraception[b] associated with inhibition of ovulation [oral, injectable or implantable][c] intrauterine devices/hormone-releasing systems[b], bilateral tubal occlusion[b], vasectomized partner[b,d], sexual abstinence[e]) during the trial and for 3 months thereafter.

[a] The effect of GWP42003-P on oral contraceptives has not been investigated. GWP42003-P is not an inducer of CYP3A4 and therefore is not expected to alter the PK of hormonal contraceptives.
[b] The effect of GWP42003-P on oral contraceptives has not been investigated. GWP42003-P is not an inducer of CYP3A4 and therefore is not expected to alter the PK of hormonal contraceptives.
[c] Contraception methods that are considered to have low user dependency.
[d] Provided that partner is the sole sexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
[e] 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 patient.

	• Female patient is pregnant (positive pregnancy test) or lactating. • Male patient is fertile (i.e., after puberty unless permanently sterile by bilateral orchiectomy) 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. • Patient has received an IMP within the 3 months prior to the screening visit. • Patient has been taking felbamate for less than 1 year prior to screening. • Patient is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex®) or cannabidiol oral solutions (including CBD-OS [GWP42003-P]) within the 3 months prior to screening and is unwilling to abstain for the duration of the trial. • Patient has a positive Δ^9-tetrahydrocannabinol (THC) test at screening. • Patient has any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory) or significant disease or disorder which, in the opinion of the investigator, may either put the patient, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or the patient's ability to participate in the trial. • Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if the patient took part in the trial. • Patient has been previously randomized into this trial. • There are plans for the patient to travel outside their country of residence during the trial.
Criteria for Withdrawal/ Discontinuation of IMP	The patient must be permanently discontinued from treatment if any of the following apply: • Administrative decision by the investigator, GW Research Ltd (GW) or regulatory authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient assent.

	• Withdrawal of parent(s)/legal representative consent. • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than 2 weeks. • ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5). Note: Prior to treatment discontinuation for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests, tests within 24–48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the patient must permanently discontinue the IMP. In cases where transaminase elevation IMP discontinuation criteria are not met or confirmed, the dose of IMP or a concomitant medication with known hepatotoxicity may be reduced. Dose adjustments should be discussed with the GW medical monitor. The final decision regarding dose adjustments should be taken by the investigator.** • Lost to follow-up. The patient may also be permanently discontinued from treatment for any of the following: • Patient or caregiver non-compliance. • AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial. • Did not meet eligibility criteria. • Any evidence of use of drugs of abuse or drug diversion. • Suicidal ideation or behavior during the treatment period.
Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, sweetener [sucralose] and strawberry flavoring). Placebo oral solution (sesame oil) containing the excipients anhydrous ethanol, β-carotene, sweetener (sucralose) and strawberry flavoring. Mode of administration: to be taken orally twice daily (morning and evening) using the syringe(s) provided, preferentially with food i.e., within 30 minutes after the end of a meal and in line

	with the patients' normal feeding schedule and dietary habits. The time of IMP administration in relation to food should be kept consistent throughout the trial. The dose should be swallowed. In patients with G-or NG-tubes but where oral dosing of IMP is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should IMP be administered via G-or NG-tubes. If administration via G-or NG-tubes is planned the investigator must contact the medical monitor to review suitability of the tubes used and IMP administration guidelines. Volume of IMP to be determined by patient's weight. Patients will take their first dose of IMP in the clinic at the end of Visit 2 (Day 1) and caregivers will be instructed how to measure and administer the IMP to the patient. The investigator will observe IMP administration by the caregiver at Visit 2 and verify that IMP was correctly administered, and that the patient did not aspirate. Patients will escalate IMP to the target dose level for their dose group over a period of up to 2 weeks depending on the target dose (e.g., no titration is required to 5 mg/kg/day while titration to 15 mg/kg/day takes 2 weeks [weekly increments of 5 mg/kg/day]). Following escalation patients will remain at their assigned target dose level for the duration of the maintenance period of the trial. Patients discontinuing IMP treatment at the end the trial or at any other time if they discontinue treatment early, should undergo a 10-day taper period.
Control Group	The control group will receive matching placebo.
Procedures	Before undergoing any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent. In cases where the patient possesses adequate understanding, their assent will be taken, along with parental/legal representative consent. Due to the degree of cognitive impairment in RTT patients, patients aged 18 years of age will not be required to provide consent and will only be required to provide assent, in cases where the patient possesses adequate understanding, along with parent(s)/legal representative consent. Each visit should be scheduled to take place at approximately the same time of day (i.e., morning or afternoon), whenever possible. Visit 9 must also be booked at a time that allows the collection of a trough PK sample, i.e., the sample must be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. Preferentially, Visits 5, 6 and 7 should also be scheduled for a time that allows collection of a trough PK sample, whenever possible. Visits 3, 4, 11 (safety visits) are to be conducted by telephone.

	Screening assessments (Visit 1 [Day −28 to −14]) will include: • Demographics. • Medical history. • CSS. • RSBQ. • Eligibility check. • Genetic analysis of pathogenic *MECP2* mutation (for patients without a documented pathogenic *MECP2* mutation)[a]. • Concomitant medications review. • AE review. • Physical examination (including height and weight). • ECG. • Vital signs. • Safety labs (hematology, biochemistry, urinalysis). • Serum IGF-1 levels. • Serum pregnancy test (if appropriate). • Tanner Staging (for patients aged ≥ 7 years, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty). • Suicidality assessment. • Urine/serum THC screen[b]. • Blood sample collection for the analysis of biomarkers (if appropriate considering the patients' weight [patient must weigh ≥ 16 kg]). • Caregivers will be trained on the completion of the symptom diary to be completed weekly from screening to end of treatment. Randomization and/or post randomization assessments will include: • Eligibility check (Visit 2). • Concomitant medications review (Visits 2–11).

[a] For patients weighing < 19 kg and without a documented pathogenic *MECP2* mutation, a blood sample for pathogenic *MECP2* mutation analysis must be taken in advance of Visit 1 (following informed consent [and where applicable, patient assent]).
[b] May be carried out at site using a THC urine dipstick; otherwise a urine or blood sample may be sent to the central laboratory. Patients weighing < 12 kg must not provide a serum sample for THC screen at Visit 1, and must either provide a urine sample at Visit 1, if there are difficulties obtaining sufficient urine for THC testing at Visit 1 then a blood or urine sample must be collected at site on another day within ± 7 days of Visit 1.

	• AE review (Visits 2–11). • Physical examination (including weight) (Visits 5, 7 and 9). • Height (Visit 9). • ECG (Visits 5, 6, 7, 8 and 9). • Vital signs (Visits 2, 5, 6, 7, 8, 9 and 10). • Safety labs (hematology and biochemistry) (Visits 5, 6, 7 and 9; plus Visit 8 for patients taking concomitant valproic acid). • Urinalysis (Visit 9) • Serum IGF-1 levels (Visit 9). • Serum pregnancy test (if appropriate) (Visit 9). • PK blood samples: A blood sample for PK analysis of CBD and its main metabolites (as appropriate considering the patients weight [patient must weigh ≥ 12 kg]) will be taken as a trough sample at Visits 5, 6, 7, and 9 (PK sample must be trough at Visit 9 and preferentially trough at Visits 5, 6 and 7). The time of the patient's sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications. • Blood sample collection for the analysis of biomarkers (Visit 9). • Questionnaires: o Visits 2, 5, 6, 7, 8 and 9: RSBQ, CGI-S and CGI-I (except Visit 2 for CGI-I), Hospital Services Use Questionnaire, and CSHQ. o Visits 2, 7 and 9: MBA-9. o Visits 2 and 9: Caregiver QoL questionnaire (SF-36) and Patient QoL questionnaire (CHQ-PF50). o Visits 5, 6, 7, 8, 9 and 10: Suicidality assessment. • The weekly symptom diary is to be completed by the caregiver weekly throughout the trial and reviewed at Visits 2, 3, 4, 5, 6, 7, 8 and 9. • The daily dosing diary is to be completed by the caregiver daily throughout the trial and reviewed at Visits 3, 4, 5, 6, 7, 8, 9 and 10. • Tanner Staging (for patients aged ≥ 7 years, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) (Visit 9). • Menstruation cycle review (Visits 2 and 9).

	• IMP dispensing (Visits 2, 5, 6, 7, 8 and 9); all caregivers will be provided with a dosing schedule. • IMP collection and compliance review (Visits 5, 6, 7, 8, 9 and 10).
Statistical Considerations	**Efficacy:** Total scores and changes from baseline will be summarized by treatment arm as well as overall (where appropriate). Differences between GWP42003-P doses versus placebo will be summarized and tested using appropriate statistical models such as mixed model repeated measures or analysis of covariance using a 2-sided Type-I error of 5%. Placebo data will be pooled for efficacy analyses. **Safety:** All safety data collected during the trial will be summarized for the safety analysis set using appropriate summary statistics. **Other data:** All other data will be summarized as appropriate. A detailed statistical analysis plan will be written.
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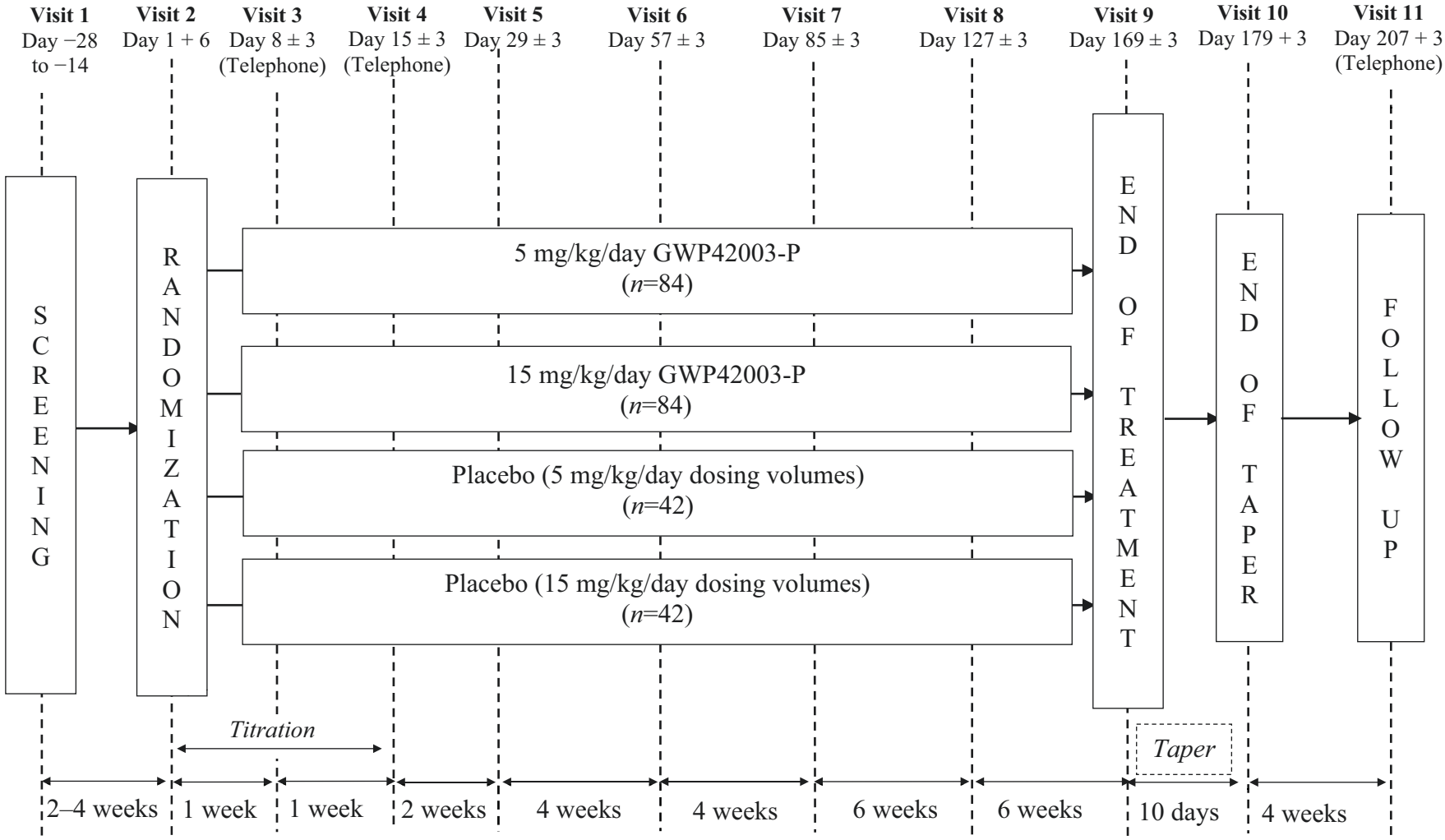
Figure 1-1 Trial Design and Treatment Schematic



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List of Abbreviations

Abbreviation or special term	Definition or Explanation
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BAC	Blood alcohol content
BDNF	Brain-derived neurotrophic factor
b.i.d.	Twice per day
CB	Cannabinoid
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CDKL5	Cyclin-dependent kinase-like
CGI	Clinical global impressions
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CHQ-PF50	Child Health Questionnaire Parent Form 50
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organization
C_{max}	Maximum measured plasma concentration
CSHQ	Children's Sleep Habits Questionnaire
CSS	Clinical Severity Scale
CYP450	Cytochrome P450
DS	Dravet syndrome
ECG	12-Lead electrocardiogram

Abbreviation or special term	Definition or Explanation
eCRF	Electronic case report form
ECS	Endocannabinoid system
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FOXG1	Forkhead box protein G1
G	Gastrostomy
GABA	γ-aminobutryic acid
GCP	Good clinical practice
GW	GW Research Ltd
i.p.	Intraperitoneal
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
KO	Knock out
LGS	Lennox-Gastaut syndrome
MBA-9	9-items Motor Behavioral Assessment
MCS	Mental health composite score
MeCP2	Methyl-CpG-binding protein 2
MMRM	Mixed model repeated measures
NG	Nasogastric
NRS	Numerical rating scale
OLE	Open-label extension

Abbreviation or special term	Definition or Explanation
PCP	Phencyclidine
PCS	Physical health composite score
PI	Principal investigator
PK	Pharmacokinetic
PP	Per protocol
PRN	Packaging reference number
PVD	Pharmacovigilance Department
QoL	Quality of life
QTcB	QT interval, corrected by Bazett's correction formula
RSBQ	Rett Syndrome Behaviour Questionnaire
RTSM	Randomization and Trial Supply Management
RTT	Rett syndrome
RTT CIA	Rett Syndrome Caregiver Inventory Assessment
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-36	36-item Short Form
SMC	Safety Monitoring Committee
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TCS	Total composite score
TEAE	Treatment emergent adverse event
Th	T helper
THC	Δ^9-tetrahydrocannabinol
TNFα	Tumor necrosis factor-alpha
TRP	Transient receptor potential
UGT	Uridine 5'-diphospho-glucuronosyltransferase

Abbreviation or special term	Definition or Explanation
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential

Definition of Terms

Term	Definition
Baseline period	The 14 to 28 (+ 3)-day period from Visit 1 (Day −14 to − 28) to the day prior to randomization (Visit 2; Day 1 [+ 6]).
Caregiver	An assigned patient's parent or designated care provider.
Day 1	The day a patient first receives investigational medicinal product in this trial.
End of treatment	Completion of the treatment period (Visit 9 [Day 169]) or withdrawal.
End of trial	Last patient last visit/call
Enrolled patient	Any patient whose parent(s)/legal representative has provided written informed consent for them to take part in the trial and, if possessing adequate understanding to do so, who has provided informed assent.
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 study physician.
Methyl-CpG-binding protein 2	Methyl-CpG-binding protein 2 is denoted differently in this document: the italicized abbreviation *MECP2* denotes the human gene; the italicized *Mecp2* denotes the mouse gene; the nonitalicized abbreviation MeCP2 denotes the protein.
Post-regression	≥ 6 months since last loss of hand use or verbal language or gross motor regression.
Status epilepticus	Any seizure lasting for 30 minutes or longer (either continuous seizure activity or repetitive seizures without return to baseline).

2 OBJECTIVES

2.1 Primary

Key objective:

- To evaluate the efficacy of 15 mg/kg/day GWP42003-P, compared with placebo, at the end of 24 weeks' treatment in reducing symptom severity in patients with Rett syndrome (RTT) using the Rett Syndrome Behaviour Questionnaire (RSBQ).

2.2 Secondary

Key Secondary Objective:

- To evaluate the efficacy of 15 mg/kg/day GWP42003-P, compared with placebo, at the end of 24 weeks' treatment in reducing symptom severity in patients with RTT using the Clinical Global Impressions - Improvement (CGI-I)

Other Secondary Objectives:

- To evaluate the efficacy of 5 mg/kg/day GWP42003-P, compared with placebo in:
  - RSBQ
  - CGI-I
- To evaluate the effect of GWP42003-P, compared with placebo, in other measures of disease severity.
  - RSBQ subscales.
  - Clinical Global Impressions - Severity (CGI-S).
  - 9-items Motor Behavioral Assessment (MBA-9).
  - Children's Sleep Habits Questionnaire (CSHQ).
- To evaluate the safety of GWP42003-P, compared with placebo, in patients with RTT.

Exploratory Objectives:

- To evaluate the effect of GWP42003-P on caregiver and patient quality of life (QoL).
  - 36-item Short Form [SF-36] and Child Health Questionnaire Parent Form 50 [CHQ-PF50], respectively.

- To evaluate the effect of GWP42003-P on health utilization.
    - Hospital Services Use Questionnaire.
- Caregiver assessment of Rett symptoms (symptom diary)
- To determine the plasma concentrations of cannabidiol (CBD) and its major metabolites with the aim of evaluating exposure versus efficacy and safety and collecting data for population pharmacokinetic (PK) analysis.
- To evaluate the effect of GWP42003-P on exploratory biomarkers.

3 BACKGROUND AND RATIONALE

3.1 Disease

RTT is a rare, non-inherited, X-linked neurodevelopmental disorder affecting approximately 1 in 10,000 live female births, resulting in abnormal neuronal development and function[1,2]. RTT is one of the leading causes of intellectual disability in young girls and is only rarely seen in males. Development of RTT is progressive, with early onset at 6–18 months characterized by a subtle slowing or regression of development. Infants/young children aged 1–4 years progress to a rapid destructive phase characterized by loss of purposeful hand skills with stereotypic hand movements, loss of spoken language, breathing irregularities such as apnea and hyperventilation, cardiac irregularities, microcephaly, and autistic-like behaviors such as social withdrawal. After a period of regression, the disorder enters a plateau phase associated with apraxia, motor problems and seizures. Over time, motor function continues to deteriorate resulting in reduced mobility, scoliosis, rigidity, muscular weakness and spasticity[3,4,5].

RTT is most commonly caused by heterozygous *de novo* mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2)[6]. MeCP2 is widely expressed in many tissues, with the highest expression in the brain[7]; MeCP2 is essential for nerve cell function, acting as a complex transcriptional modulator of genes involved in neuronal development, synaptic transmission and plasticity, including brain derived neurotrophic factor (BDNF)[8]. However, mutations in *MECP2* are not synonymous with RTT. Between 3% and 5% of individuals who strictly meet clinical criteria for RTT do not have an identified mutation in *MECP2*, and only 50–70% of patients with atypical RTT have an identified mutation in *MECP2*[9]. Moreover, cyclin-dependent kinase-like (*CDKL5*) and Forkhead box protein G1 (*FOXG1*) gene mutations are associated with 2 other variant forms of RTT. Given that *MECP2* mutations are neither necessary nor sufficient to make the diagnosis of RTT, diagnostic criteria are often utilized[9] at initial diagnosis.

A number of genetic mouse models of RTT are available where deficiency of MeCP2, globally or specifically in developing neurons, produces similar clinical features to those in humans including tremors, motor impairments, and stereotypical motions[10,11,12]. Genetic and pharmacological intervention can ameliorate or reverse behavioral deficits in *Mecp2* knockout (KO) mice, suggesting that there is significant potential for pharmacological interventions to treat RTT[13].

Aberrant synaptic plasticity and an imbalance of excitatory and inhibitory neuronal networks is thought to underlie the neurological phenotype in RTT[14]. Besides these neuronal deficits in RTT, there is also evidence that neuroinflammation and glial cells may play a role. Selective restoration of MeCP2 in astrocytes significantly improved locomotion and anxiety levels, restored respiratory functions and greatly prolonged lifespan in mice with modified astrocytes compared to control *Mecp2* KO mice. Restoration of MeCP2 in astrocytes also returned dendritic morphology to normal[15]. Microglia from *Mecp2* KO mice demonstrate enhanced release of glutamate, which is associated with neuronal toxicity, and also show impaired phagocytosis[16]. There is also increasing evidence that the immune system and inflammation may be involved in several neurodevelopmental disorders including RTT[17]. In addition, symptoms such as hyperventilation and apnea can be indicative of mitochondrial dysfunction, and before the advent of genetic testing RTT was proposed to be a metabolic disorder. Changes in morphology of mitochondria and genes associated with these structures as well as redox balance have been demonstrated in RTT patients, but it is not clear whether some of these changes are a primary cause or secondary to these mechanisms[18]. Finally mouse models have highlighted a potential role of the growth factors, BDNF and insulin-like growth factor 1 (IGF-1) in the pathology of RTT[19], an involvement that is corroborated by efficacy in clinical trials targeting these agents[20].

There is currently no curative therapy for RTT and therefore there is a critical need for treatments[21]. Medical management of RTT is essentially symptomatic and supportive. Current options for patients focus on managing the associated conditions and include the use of medications to control breathing problems, heart rhythm abnormalities, seizures, constipation, gastroesophageal reflux disease and sleep disturbances[22]. Other therapy options include physiotherapy, occupational therapy, speech therapy and feeding assistance (feeding tubes or other feeding aids)[21].

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 typically contains < 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 possesses very low affinity and lacks appreciable functional activity at cannabinoid (CB) receptors; cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2)[23]. In addition, CBD does not significantly interact with enzymes responsible for the synthesis and degradation of endocannabinoids, at clinically relevant concentrations[24,25,26,27]. Furthermore, considerable data exist describing the polypharmacology of CBD and its modulation of non-endocannabinoid system (ECS) targets. Indeed, CBD has the ability to interact with multiple 7-transmembrane receptor systems, ion channels, transporters and enzymes[28,29].

At least 2 mechanisms of anticonvulsant action are proposed for CBD. The first is modulation of intracellular Ca^{2+} mobilization via antagonism of the G protein-coupled receptor 55 (GPR55) and/or activation (and subsequent desensitization) of transient receptor potential (TRP) channels, particularly TRPV1[30,31,32]. The second is inhibition of adenosine reuptake[33,34,35].

Based upon lack of pharmacological engagement by CBD at therapeutically relevant concentrations, modulation of the following targets is considered not relevant to the anticonvulsant mechanism of action; CB_1 and CB_2 receptors, fatty acid amide hydrolase, voltage-gated sodium (Na_v) channels, benzodiazepine and γ-aminobutryic acid (GABA) binding sites of the $GABA_A$ receptor.

Importantly, CBD does not produce THC-like euphoric effects. Further to this, CBD demonstrates anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity in a range of nonclinical models and has received Food and Drug Administration (FDA) approval for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older[36].

3.2.1 Non-clinical Studies

3.2.1.1 Efficacy Pharmacology

In a subchronic phencyclidine (PCP) model in rats where there is disruption of cognition and deficits in social behavior, CBD reversed the PCP-induced recognition memory

deficit at doses of 2, 20 and 100 mg/kg intraperitoneal (i.p.)[37] and significantly reduced the sub-chronic PCP-induced increase in avoidance behavior at 2, 10, 20 and 100 mg/kg, i.p.[38] In addition, CBD improved cognitive deficits in other nonclinical models including *Fmr1* KO mice, a model of Fragile X syndrome, at 100 mg/kg and 200 mg/kg i.p. and improved bicuculline induced memory impairments in neonatal rats at 100 mg/kg i.p.[39]. CBD also improved hypoxic ischemia in rats (1 mg/kg subcutaneous)[40] and piglets (1 mg/kg i.v.)[41] when CBD was given post hypoxia-ischemia injury.

Cellular mechanisms which are thought to be involved in the neurobehavioral deficits present in RTT include aberrant synaptic plasticity[14], neuroinflammation[15,16], and immune[17] and metabolic malfunction[18,42,42]. A number of studies demonstrate that CBD may have the potential to modulate each of these basic pathophysiological mechanisms[43] albeit not in RTT models. For example, CBD has the potential to modulate excitatory/inhibitory imbalance as demonstrated by its anticonvulsant activity[44,45,46,47,48]. CBD also shows anti-inflammatory and antioxidant actions in a number of accepted animal models of inflammation, notably of the gut and the joints, where it inhibits tissue production of chemical mediators of inflammation, such as tumor necrosis factor alpha (TNFα) and interleukin-2[49]. CBD (1 mg/kg i.v.) also reverses hypoxic-ischemia induced neuroinflammation, reactive oxygen species production and excitatory and metabolic derangement in rats[40] and piglets[41] after a hypoxic ischemic insult.

Loss of language and ability to communicate is also a feature of RTT[4]. In a songbird model of vocal learning, damage to a cortical-like pre-motor region of the zebra finch brain results in a temporary disruption of vocal patterns that recovers over about 7 days and is dependent upon the ability of birds to hear as part of sensorimotor learning. CBD 10 mg/kg and 100 mg/kg (intramuscular) improved the phonology and syntax of the zebra finch song over the first 6–9 days post lesion[50].

Finally, there is evidence that cannabidivarin, a cannabinoid structurally similar to CBD that shares molecular and behavioral pharmacology, rescued behavioral and brain alterations in MeCP2-308 male mice[51], a validated RTT model, including improvement of general health status, sociability and brain weight, with partial restoration of motor coordination.

3.2.1.2 Mechanism of Action

CBD has micromolar affinity/potency at several molecular targets, whose relevance to RTT is unclear. How CBD interacts with signaling pathways and cellular processes modulated by MeCP2, that are important in RTT, is a matter of active investigation and is yet to be fully elucidated.

3.2.2 Clinical Studies

Human efficacy data from 3 positive Phase 3 trials in patients (predominantly pediatric patients) with treatment-resistant epilepsies support a role for GWP42003-P as a treatment for central nervous system disorders. Overall, GWP42003-P was generally well tolerated at doses up to 20 mg/kg/day; adverse events (AEs) were usually mild to moderate in severity and transient. Elevated liver enzymes (particularly transaminases alanine aminotransferase [ALT] and aspartate aminotransferase [AST], and less commonly reported terms of liver function tests abnormal and hepatotoxicity) have been reported in some patients receiving GWP42003-P for severe, refractory epilepsies, notably in patients taking concomitant valproic acid. None of the cases fulfilled the Hy's Law criteria for potential severe liver injury. There were no cases with a concomitant increase in bilirubin > 2 × upper limit of normal (ULN). Monitoring of the blood levels of enzymes that are markers of liver function is advised, particularly at the start of treatment and with dose increases of GWP42003-P, as well as at the time of initiation or dose increase of concomitant medication.

3.3 Rationale

A number of studies across a range of nonclinical behavioral paradigms, as discussed above, suggest that CBD has the potential to treat some of the core symptoms of RTT such as cognition, language, social behavior, and motor function (see Section 3.2.1.1). Indeed, there are suggestions from clinical studies that, as well as treating seizures, CBD may have beneficial effects on cognition and behavior as well as on patient QOL[52,53].

This Phase 3 trial will evaluate the safety and efficacy of GWP42003-P in patients with RTT who carry an *MECP2* gene mutation. In order to minimize confounders, this trial is focused on a subpopulation of RTT patients with ≤ weekly seizures.

3.3.1 Choice of Endpoints

Overall, the range of assessments cover the key symptom domains: behavior and emotion, motor function, breathing abnormalities and sleep.

GW Research Ltd (GW) has received input from caregivers of patients with RTT via a family empowerment round table organized by Rettsyndrome.org. Overall the group agreed that the RTT symptoms being explored are important and cover key aspects of the condition. Caregiver input was accounted for in the development of this protocol.

3.3.1.1 Choice of Primary Endpoints

Trial endpoints, scales and assessments were selected to evaluate a wide range of symptoms observed in RTT patients.

The RSBQ, selected as a primary efficacy endpoint, is a caregiver-completed assessment that has been specifically developed for use in RTT patients[54]. The RSBQ total score is used as a global measure to assess the patient's overall condition, while subscales of the RSBQ (as a secondary endpoint) allow evaluation of more specific domains (behavior and emotion, motor function and breathing abnormalities).

3.3.1.2 Choice of Secondary Endpoints

The CGI-I scale, the key secondary endpoint, is a clinician-rated assessment that has been used extensively in neuropsychiatric disorders in both clinical practice and clinical trial settings[55,56,57], and reported to have successfully been implemented in the RTT patient population[58]. The CGI-I is a global measure used to assess the patient's overall condition. The CGI-I assesses change in symptoms relative to the baseline CGI-S, a secondary endpoint.

Other secondary endpoints selected to evaluate additional specific RTT domains include the following (in addition to RSBQ subscales and CGI-S as described above):

- The MBA-9. This scale was selected as it provides a clinician assessment of a set of motor and behavior items of the original MBA[59,60] that are deemed amenable to change.
- The CSHQ. This questionnaire was selected as sleep problems are reported for the majority of RTT patients. CSHQ has been used to characterize sleep in other developmental disability populations (e.g., autism spectrum disorder[61]) and in a sample of patients with RTT[62].

3.3.1.3 Choice of Exploratory Endpoints

The required constant care and supervision of RTT patients places a significant burden on parent(s)/caregiver, as such, effects on caregiver QoL will be assessed as an exploratory

endpoint using the SF-36 questionnaire. In addition, caregiver reported patient QoL will also be assessed using CHQ-PF50. Information on health utilization will be assessed using the Hospital Services Use Questionnaire and aims to analyze the frequency of patient hospitalizations and hospital visits.

The caregiver assessment of RTT symptoms assessment has been specifically developed for the proposed clinical trial with the intent of obtaining weekly data on the patient's condition and aims to provide additional information on selected key areas of interest: breathing, hand stereotypies, interactions, problem behaviors, sleep, constipation, seizures and global function.

Additional exploratory endpoints also include determination of the plasma concentrations of CBD and its main metabolites in the patient population, and evaluation of plasma levels of potential disease biomarkers to inform future research.

3.3.2 Choice of Dosing Regimen

Doses of up to 51 mg/kg/day GWP42003-P have been well tolerated in the GW clinical development programs for GWP42003-P. At the time of protocol authoring, a total of 1808 subjects have received GWP42003-P from blinded and open-label GW-sponsored trials and supportive programs (expanded access and other compassionate use programs), including 1419 patients with epilepsy (data cut-off date: 01 May 2017). The available safety data collected from these patients showed that the reported AEs were usually mild or moderate in severity and resolved. There have been few withdrawals due to AEs.

Non-clinical data have demonstrated that CBD is active on cognition and behavioral endpoints over a range of doses from 2 to 200 mg/kg depending on the model, with the top dose of the tested dose range overlapping with the effective anticonvulsive dose range of 50 to 200 mg/kg/day in nonclinical models. Clinical data in patients with LGS or DS have demonstrated anticonvulsant efficacy at 10 mg/kg/day and 20 mg/kg/day. Therefore, while it is acknowledged that RTT differs from these treatment-resistant epilepsies, doses of GWP42003-P that are safe and effective in the treatment of epilepsies (15 mg/kg/day), and potentially a lower dose (5 mg/kg/day), may be effective in RTT. The 15 mg/kg/day dose of GWP42003-P is within the anticipated effective range and will be used to assess efficacy for the primary and key secondary endpoints; the 5 mg/kg/day GWP42003-P dose is evaluated as a potentially efficacious dose that could have improved tolerability. Patients in the higher dose group will titrate the medication starting at 5 mg/kg/day

(2.5 mg/kg twice per day [b.i.d.]) and weekly increments of 5 mg/kg/week (2.5 mg/kg b.i.d.).

The IMP solution contains 7.9% w/v anhydrous ethanol, which is required as sucralose is not soluble in sesame oil. The proposed maximum dose of 15 mg/kg/day (administered as 7.5 mg/kg b.i.d.) will result in a blood alcohol content (BAC) of 0.0098 g/L which equates to ethanol ingestion of 5.93 mg/kg. Both these amounts are well under the threshold for BAC of 0.125 g/L and ethanol ingestion of 75 mg/kg for patients 6 years and older, and also under the maximum BAC levels of 0.01 g/L and ethanol ingestion of 6 mg/kg for children less than 6 years old[63].

Twice daily (b.i.d) dosing is recommended for this clinical trial (GWND18064) in accordance with the approved FDA label for cannabidiol oral solution (CBD-OS) in the treatment of seizures associated with LGS or DS in patients 2 years of age and older. Twice daily dosing should also minimize the potential risk of acute AEs related to maximum measured plasma concentration (C_{max}). Further, peak trough ratios would be reduced, and improved patient adherence may reduce the potential clinical risks of a missed dose from a PK perspective and a patient/care psychological viewpoint.

Please refer to the investigator's brochure (IB) and Development Core Safety Information for the most current safety data.

3.3.3 Benefit-risk Analysis

There are no approved medications for RTT, neither disease modifying nor for symptomatic therapy. Nonclinical and clinical data indicate that CBD-OS may benefit patients with RTT (see Section 3.2.1.1, Section 3.2.2, and Section 3.3).

The key risks identified from the CBD-OS clinical development program for LGS and DS (described in Section 3.2.2) are broadly expected to be the same for the RTT population - as the patient demographics and comorbidities have a significant amount of overlap. Importantly, the risk of raised transaminases is reduced in the context of this RTT trial where lower doses of CBD-OS are planned and valproic acid use is expected to be lower in this population.

In the context of the anticipated benefit of CBD-OS in RTT patients, the key risks identified from the CBD OS clinical development program in LGS and DS are acceptable given the proposed dose levels of 5 and 15 mg/kg/day and the age range of 2–18 years.

Thus, the overall benefit-risk for the development of CBD-OS in the RTT population is favorable.

3.4 Clinical Hypothesis

The primary clinical hypothesis is that treatment with GWP42003-P is associated with improvements in RTT as measured by the RSBQ.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This multisite trial will consist of a double-blind, randomized, placebo-controlled design which will compare the efficacy of GWP42003-P versus placebo over a 24-week treatment period.

Patients will be randomized to receive 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volumes of placebo in a 2:2:1:1 ratio.

Following screening, eligible patients will complete a 2 to 4-week baseline period (patients can be randomized as soon as they have completed at least 2 weeks of baseline and all eligibility criteria are confirmed [including review of all clinical laboratory results and, if applicable, confirmation of *MECP2* pathogenic genetic mutation]). All patients entering the trial will be stratified by severity, based on their Clinical Severity Scale (CSS) score (either a CSS score within the range of 10–22, or a CSS score within the range 23–36). Patients will be randomized and will commence the 24-week treatment period, including up to 2 weeks dose escalation. The treatment period ends at Visit 9 (Day 169), after which patients will commence a 10-day taper period followed by the 4-week follow-up period. The 10-day taper period and 4-week follow-up period may not be required for patients continuing CBD-OS treatment under a separate protocol.

If a patient permanently discontinues treatment at any point during the trial, the IMP should be gradually reduced over 10 days (unless inadvisable due to an AE). Patients and caregivers will be encouraged to remain in the trial and continue to complete trial assessments and visits as per protocol.

If a patient withdraws from the trial at any point during the trial, they will be required to attend a withdrawal visit, if applicable taper the IMP and attend the end of taper visit, and then complete the 4-week follow-up period.

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

4.1.1 Primary Endpoint

- RSBQ (total score) for the 15 mg/kg/day GWP42003-P dose level compared with placebo at the end of 24 weeks.

4.1.2 Secondary Endpoints

Key Secondary Endpoint:

- CGI-I for the 15 mg/kg/day GWP42003-P dose level compared with placebo at the end of 24 weeks.

Other Secondary Efficacy Endpoints:

- To compare 5 mg/kg/day GWP42003-P with placebo using:
  - RSBQ (total score)
  - CGI-I
- To compare 15 mg/kg/day GWP42003-P and 5 mg/kg/day GWP42003-P with placebo using:
  - RSBQ subscales.
  - CGI-S.
  - MBA-9.
  - CSHQ.

Exploratory Endpoints:

- To compare 15 mg/kg/day GWP 42003-P and 5 mg/kg/day GWP42003-P with placebo for the following endpoints:
  - Caregiver QoL questionnaire (SF-36).
  - Patient QoL questionnaire (CHQ-PF50).
  - Hospital Services Use Questionnaire.
  - Caregiver assessment of Rett symptoms (symptom diary).
  - Blood levels of exploratory biomarkers.
- Additional Exploratory Endpoints:
  - Plasma concentrations of CBD and its main metabolites.

Safety:

The safety profile of GWP42003-P compared with placebo will be assessed by measuring:

- AEs.
- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- 12-lead electrocardiogram (ECG).
- Effects on menstruation cycles.
- Suicidality.
- Change in growth and development by measurement of height, weight, serum IGF-1 levels and Tanner Staging (for patients aged ≥ 7 years, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

4.2 Number of Sites

Approximately 35 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 Patients

Approximately 252 patients will be randomized to receive 1 of 2 dose levels of GWP42003-P (5 mg/kg/day or 15 mg/kg/day) or matching placebo (5 mg/kg/day dosing volumes or 15 mg/kg/day dosing volumes) on a 2:2:1:1 basis (84 patients per active dose group and 42 patients per placebo group). The placebo data for the 2 dose groups will be pooled for analysis.

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 is presented as a solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10 % v/v), 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, sweetener (sucralose) and strawberry flavoring (Table 5.2-1). The placebo formulation is identical to the active formulation without the active pharmaceutical ingredient.

Table 5.2-1 Formulation of Placebo Oral Solution

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

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

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled and/or distributed by 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 and the weight of the patient. A unique identification number will be used to identify each carton and the IMP it contains. The unique identification

number together with the 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 labeled and packaged. Label text will include the following information, as a minimum:

- Sponsor's name and address.
- Product identification (e.g., "GWP42003-P or Placebo")
- Dose and/or Potency (e.g., "100 mg/mL GWP42003-P")
- Trial code number
- Expiry date
- Storage conditions
- Instruction: "For clinical trial use only"
- Instruction: "Keep out of the 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, name, address and the telephone number of the investigator (or main contact for information about the product or the clinical trial) will be provided separately to the caregiver. Caregivers will be instructed to retain and carry this information with the patient at all times.

5.3.2 Storage

The IMP must be stored upright at room temperature (< 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 must approve storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of trial dispensing period at each 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.

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

5.3.3 Supply and Return of Investigational Medicinal Product

At trial initiation and as needed thereafter, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator's site, who will check the amount received against shipment request and the condition of the drug (i.e., integrity, physical appearance, and 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. The 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 should contain:

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

Investigational medicinal product will be dispensed at Visits 2, 5, 6, 7, 8 and 9. Caregivers will be asked to return all IMP (used and unused) at each relevant visit (Visits 5, 6, 7, 8, 9 and 10). The site will check the IMP against the usage recorded in the daily diary by the caregiver. Any discrepancies will be discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents.

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

A record of returned IMP must be completed and included in the shipment of used and unused IMP to the relevant drug distribution depot. At the end of the trial, 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 Post-trial Provision

At the end of the treatment phase of this trial, patients may be invited to continue to receive GWP42003-P in an open-label extension (OLE) study under a separate protocol.

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 United States (US) and European Union (EU) Law.

6 PATIENT ELIGIBILITY

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

6.1 Inclusion Criteria

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

6.1.1 Patient is female or male aged 2–18 years (inclusive).

6.1.2 Patients must weigh at least 10 kg.

6.1.3 Patient (if possessing adequate understanding, in the investigator's opinion) and/or the patient's parent(s)/legal representative is willing and able to give informed consent/assent for participation in the trial.

6.1.4 Patient and the patient's caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements (including the completion of all caregiver assessments by the same caregiver throughout the trial).

6.1.5 Patient must have a clinical diagnosis of RTT (typical or atypical), defined according to RettSearch Consortium criteria[9] (APPENDIX 4).

6.1.6 Patient must have a confirmed pathogenic genetic mutation of the *MECP2* gene[a].

6.1.7 Patient must be post-regression (≥ 6 months since last loss of hand use or verbal language or gross motor regression).

6.1.8 Patient must have a disease severity of between 10 and 36, defined according to the CSS.

6.1.9 All medications or interventions (including antiepileptic drugs [AEDs] and non-pharmacological interventions - dietary supplements, probiotics, physical therapy, speech therapy, etc.) for RTT-related symptoms must have been stable for 4 weeks prior to screening and the patient/caregiver must be willing to maintain a stable regimen throughout the trial.

6.1.10 Patient must have the ability to swallow the IMP provided as a liquid solution, or the ability for IMP to be delivered via gastrostomy (G) or nasogastric (NG) feeding tube (use of G- or NG-tubes is only allowed after discussion with the Medical Monitor to confirm suitability of the tubes being used).

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

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[a] For patients without a documented pathogenic *MECP2* mutation, a blood sample for pathogenic *MECP2* mutation analysis must be collected at Visit 1 or prior to Visit 1 if patient weight is < 19Kg. All patients are required to have a confirmed pathogenic mutation of the *MECP2* gene prior to randomization.

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

6.1.13

6.2 Exclusion Criteria

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

6.2.1 Patient meets exclusion criteria for RTT diagnosis (traumatic brain injury, neurometabolic disease, or severe infection that causes neurological problems; grossly abnormal psychomotor development in the first 6 months of life).

6.2.2 Patient has clinically significant abnormal laboratory values, in the investigator's opinion.

6.2.3 Patient experiences more than weekly seizures (based on history over the last 2 months prior to screening) i.e., CSS 'epilepsy/seizure' score of 4 or 5.

6.2.4 Patient is taking more than 2 concurrent AEDs.

6.2.5 Any history of suicidal behavior or any suicidal ideation in the last month or at screening.

6.2.6 Patient has clinically relevant abnormalities in the ECG measured at screening or randomization (including QT interval, corrected by Bazett's correction formula [QTcB] interval > 450 msec, average of 3 measurements).

6.2.7 Patient has any concurrent cardiovascular conditions which will, in the investigator's opinion, interfere with the ability to assess the patient's ECGs or put the patient at risk because of participation in the trial.

6.2.8 Patient's first or second degree relative has a history of significant ECG abnormalities, in the opinion of the investigator (e.g., premature cardiac arrest, sudden death).

6.2.9 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP (active or placebo), such as sesame oil.

6.2.10 Patient has moderately impaired hepatic function at screening, defined as serum ALT or AST > 3 × ULN **or** total bilirubin [TBL] > 2 × ULN.

6.2.11 Female patient is of childbearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., combined [estrogen and progestogen containing], hormonal contraception[a] associated with inhibition of ovulation [oral, intravaginal or transdermal], progestogen-only hormonal contraception[b] associated with inhibition of ovulation [oral, injectable or implantable][b], intrauterine devices/hormone-releasing systems[b], bilateral tubal occlusion[b], vasectomized partner[b,c], sexual abstinence[d]) during the trial and for 3 months thereafter.

6.2.12 Female patient is pregnant (positive pregnancy test) or lactating.

6.2.13 Male patient is fertile (i.e., after puberty unless permanently sterile by bilateral orchiectomy) 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.

6.2.14 Patient has received an IMP within the 3 months prior to the screening visit.

6.2.15 Patient has been taking felbamate for less than 1 year prior to screening.

6.2.16 Patient is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex®), or cannabidiol oral solutions (including CBD-OS [GWP42003-P]) within the 3 months prior to screening and is unwilling to abstain for the duration of the trial.

6.2.17 Patient has a positive THC test at screening.

6.2.18 Patient has any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory) or significant disease or disorder which, in the opinion of the investigator, may either put the patient, other participants, or site staff at risk because of participation in the trial, may influence the result of the trial, or the patient's ability to participate in the trial.

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

6.2.20 Patient has been previously randomized into this trial.

6.2.21 Patient has travel outside the country of residence planned during the trial.

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[a] The effect of GWP42003-P on oral contraceptives has not been investigated. GWP42003-P is not an inducer of CYP3A4 and therefore is not expected to alter the PK of hormonal contraceptives.
[b] Contraception methods that are considered to have low user dependency.
[c] Provided that partner is the sole sexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
[d] 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 patient.

7 PATIENT ENROLLMENT

Before patients may be entered into 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, informed consent/assent forms and other patient information material. Patients will be considered enrolled in the trial from the time of providing written informed consent/assent. All parent(s)/legal representatives must personally sign and date the consent forms prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2). If the patient possesses adequate understanding, assent will also be taken along with parent(s)/legal representative consent (refer to Section 9.2.1 and Section 15.2). Due to the degree of cognitive impairment in RTT patients, patients aged 18 years of age will not be required to provide consent and will only be required to provide assent, in cases where the patient possesses adequate understanding, along with parent(s)/legal representative consent.

7.1 Treatment Assignment

At the start of Visit 1 (screening), enrolled patients will be allocated a unique patient number. After completion of assessments and confirmation of eligibility at Visit 2, patients will be randomized initially to receive 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volumes of placebo in a 2:2:1:1 ratio. GW will provide all IMP in a packed and labeled state and the RTSM system will identify the pack number(s) to be dispensed to the patient at each relevant visit, according to the treatment assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP will be done by the RTSM system according to a centralized randomization schedule produced by an independent statistician. The assignment to active medication or placebo 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.

Patients will be assigned 1 of 2 dose levels of GWP42003-P or matching volumes of placebo on a 2:2:1:1 ratio (up to 84 patients per active group and 42 patients per placebo group).

The use of placebo in the current trial is deemed necessary to reduce bias when evaluating the efficacy and safety of the active treatment. All patients will be permitted to continue current therapies.

8.1.1 Dose Administration

IMP will be administered orally (swallowed) twice each day (morning and evening) using the syringe(s) provided. The IMP may be taken with other concomitant medications, as directed by the investigator. In patients with G-or NG-tubes but where oral dosing of IMP is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should IMP be administered via G-or NG-tubes. If administration via G- or NG-tubes is planned the investigator must contact the medical monitor to review suitability of the tubes used and IMP administration guidelines. IMP should be preferentially taken with food i.e., within 30 minutes after the end of a meal and in line with the patients' normal feeding schedule and dietary habits. The time of IMP administration in relation to food should be kept consistent throughout the trial.

At Visits 5, 6, 7 and 9 caregivers will be asked to record the time and date of the patients' last IMP dose.

8.1.2 Dose Escalation and Dose Adjustments

The daily volumes of IMP solution to be taken will be calculated based on the patients' weight and the dosing schedule will be provided to the caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Caregivers will be trained on dose administration at Visit 2 (Day 1). Each patient will take their first dose of IMP at the clinic at the end of Visit 2 (Day 1). The investigator

will observe IMP administration by the caregiver at Visit 2 and verify that IMP was correctly administered, and that the patient did not aspirate. If an unacceptable AE develops at any time during the dose escalation period(s), dosing should initially be suspended or amended, at the investigator's discretion and in a blinded manner, until the event has resolved or is well tolerated. Patients who have escalated above 5 mg/kg/day should return to the previous dose level tolerated in steps of 5 mg/kg/day each week, unless a faster reduction is judged to be required for safety reasons. If a patient cannot tolerate 5 mg/kg/day, doses should be reduced to 2.5 mg/kg/day. If necessary, dosing may be temporarily suspended.

Patients whose dose has been decreased can have their dose increased again, if the tolerability improves. Patients unable to tolerate the target dose may stay at a lower dose. However, if a patient cannot tolerate a dose of 2.5 mg/kg/day the patient should permanently discontinue IMP treatment, unless a lower dose level is agreed in discussion with the medical monitor and can be accurately measured (minimum single dose volume 0.1 mL). Dose adjustments should be discussed with the GW medical monitor. The final decision regarding dose adjustments should be taken by the investigator. During the maintenance period, patients should continue on a stable dosing regimen at the target dose level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period; dose adjustments should follow the guidance above. However, where possible, the patient should be encouraged to return to the target dose level.

Transaminase elevations should be medically managed by the investigator either by reducing the IMP dose as described above or, following discussion with the medical monitor, by reducing concomitant medications judged to be causing the elevation (as per Section 8.2). Dose adjustments should be discussed with the GW medical monitor. For potential cases of drug-induced liver injury see Section 12.8.

Patients will escalate IMP to the target dose level for their dose group over a period of up to 2 weeks depending on the target dose (e.g., no titration is required to 5 mg/kg/day while titration to 15 mg/kg/day takes 2 weeks [weekly increments of 5 mg/kg/day] as indicated in Table 8.1.2-1]). Following escalation patients will remain at their assigned target dose level for the duration of the maintenance period of the trial.

Table 8.1.2-1 Dose Escalation Regimen

Day	Dose GWP42003-P (mg/kg/day)*
1-7	5
8-14	10
15	15

* IMP is to be taken twice daily. Total daily doses are shown. The placebo group will take matching volumes of placebo.

After completion of dosing, patients who do not immediately enter the OLE study (under a separate protocol) at Visit 9 will have their dose of IMP tapered gradually, an average of 10% of per day, over a period of 10 days (the taper period may be shorter if the patient enters the OLE during the taper period). Patients who reach the minimum single dose volume of 0.1 mL should remain at that dose until they complete the taper period. A taper schedule will be provided for each patient.

Patients who discontinue from treatment early should also taper the IMP (unless continued dosing is inadvisable, e.g., due to an AE). The decision whether to taper IMP or not will be left to the investigator's clinical judgment.

8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant medications for RTT-related symptoms (including AEDs) must have been stable for at least 4 weeks prior to screening and should be expected to remain stable throughout the trial period. If there are side-effects suspected of being related to an elevation in the concomitant concentration, the investigator should contact the GW medical monitor to discuss best management. Decisions should be based on clinical symptoms and not plasma levels of concomitant medications. The final decision regarding dose adjustments should be taken by the investigator. CBD has the potential to induce the expression of hepatic cytochrome P450 (CYP450) enzymes (CYP1A2, 2B6 and 3A4) at clinically relevant concentrations. Careful titration of CBD in patients taking concomitant medications metabolized by CYP3A4, CYP2C19 or CYP2B6 is advised, with plasma monitoring of such medications or their metabolites to be undertaken at the investigator's discretion. Further information on drug interactions can be found in the IB[64]. Concomitant medication dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations not meeting IMP discontinuation

criteria specified in Section 10 and Section 12.8). Dose adjustments should be discussed with the GW medical monitor. Any concerns regarding potential interactions with concomitant medications can be discussed with the trial medical monitor(s).

Any non-pharmacological interventions (e.g., physical therapy, speech therapy, dietary supplements, probiotics etc.) must also be stable for 4 weeks prior to screening and the patient/caregiver must be willing to maintain a stable regimen throughout the trial.

The use of rescue medication is allowed when necessary (i.e., AED for transient exacerbation of seizures). Any medication, other than the IMP, taken during the trial must be recorded on 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. However, any patients taking these medications after screening should not be discontinued from treatment unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered during the assessment of the evaluable period (see Section 13.6.1).

- Any new medications or interventions for RTT related symptoms or changes in dosage.
- St John's Wort.
- Recreational or medicinal cannabis or cannabinoid-based medications (including Sativex or cannabidiol oral solutions [including CBD-OS]) within the 3 months prior to or during the trial.
- Any other IMP taken within the 3 months prior to or during the trial.
- Felbamate that has been taken for less than 1 year prior to screening.

Care should be taken with drugs, or their metabolites, that are CYP2C19 substrates, such as N-desmethylclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT)1A9 and UGT2B7.

8.4 Compliance in Investigational Medicinal Product Administration

The IMP is dispensed to the patient at study visits 2, 5, 6, 7, 8 and 9. IMP will be dispensed at the 'End of Treatment'/withdrawal visit (Visit 9) only if required for the

10-day taper period (i.e., patients not entering the OLE trial under a separate protocol). Further guidance on IMP dispensing will be provided in a separate Pharmacy Manual.

The caregiver will confirm if the patient has taken their IMP as per the dosing schedule for that day. If the response is 'No', caregivers will also be asked to confirm the volume of solution administered on that day. Caregivers should return all IMP (used and unused) at each of Visits 5, 6, 7, 8, 9 and 10. The medication will be checked against the expected usage and any discrepancies discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents. Caregivers will also be asked about the time of IMP administration in relation to meals.

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.

8.5 Access to Blinded Treatment Assignment

The identity of IMP assigned to patients during the treatment phase 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 is available to the relevant staff in case of an emergency and unblinding is required. A patient's treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any reason will be considered a protocol deviation.

The investigator is encouraged to contact the medical monitor to discuss the rationale for unblinding prior to doing so. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of trial medication will not be dependent upon the investigator receiving approval from 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 patient's medical notes and on the eCRF.

9 TRIAL PROCEDURES

A list of the required trial procedures is provided in the subsections that follow; refer also to the schedule of assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the eCRF.

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

9.1 Trial Procedures by Visit

Patients and their parent(s)/legal representative will be invited to take part in the trial and will be issued with the patient information and informed assent (if applicable) and the parent(s)/legal representative information and informed consent. Due to the degree of cognitive impairment in RTT patients, patients aged 18 years of age will not be required to provide consent and will only be required to provide assent, in cases where the patient possesses adequate understanding, along with parent(s)/legal representative consent. Following adequate time to discuss the trial with the investigator, nurse, relatives or caregiver, as wished, patients for which the parent(s)/legal representatives provide written informed consent, and in cases where the patient possesses adequate understanding, patients that give their assent, will be screened for entry into the trial.

Each visit should be scheduled to take place at approximately the same time of day (i.e., morning or afternoon), whenever possible. Visit 9 must be booked at a time that allows the collection of a trough PK sample, i.e., the sample must be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. Preferentially, Visits 5, 6 and 7, should also be scheduled for a time that allows collection of a trough PK sample, whenever possible. Visits 3, 4, 11 (safety visits) are to be conducted by telephone.

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

All assessments should reflect the patient's regular state, therefore it should be ensured the patient had adequate time to settle prior to each assessment.

The CGI-S and CGI-I assessments should be based on the entirety of the visit.

9.1.1 Clinic Visits

9.1.1.1 Visit 1 (Day −28, Screening)

The caregiver will complete the RSBQ (following documented training on how to complete the questionnaire).

The following assessments will be performed: demographics (including *MECP2* mutation), review of medical history and concomitant medications, vital signs, physical examination (including body weight), height, ECG and visit procedure related AEs.

The physician will complete the CSS.

Clinical laboratory samples (urine [where possible] and blood) will be taken for:

- Hematology.
- Biochemistry.
- Urinalysis (provided urine can be obtained).
- Pregnancy test (using a serum sample, as appropriate [Section 9.2.2]).
- THC screen (serum/urine)

  May be carried out at the site using a THC urine dipstick; otherwise a urine or blood sample may be sent to the central laboratory. Patients weighing < 12 kg must not provide a serum sample for THC screen at Visit 1; if there are difficulties obtaining sufficient urine for THC testing at Visit 1, then a blood or urine sample must be collected at the site on another day within ± 7 days of Visit 1.
- Determination of serum IGF-1 levels.
- Biomarker analysis (if appropriate considering the patients' weight [patient must weigh ≥ 16 kg] - Section 9.2.13).

A positive *MECP2* pathogenic mutation result is required to confirm eligibility at Visit 2. For those patients who do not have a known/documented *MECP2* mutation, a blood sample will also be taken to confirm *MECP2* genetic mutation status. In cases where patient weight (< 19 kg) prevents the collection of a blood sample at Visit 1 for *MECP2* mutation analysis (where required), in addition to other scheduled samples as listed above, a blood sample for *MECP2* mutation analysis must be collected in advance of

Visit 1 (following informed consent [and where applicable, patient assent] as per Section 9.2.1).

In all instances, the collection of blood samples for hematology, biochemistry, and pregnancy test (as appropriate) should take place at Visit 1.

The patient screening visit will be registered in the eCRF and a patient number will be issued. Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will then begin the 14 to 28-day baseline period.

The investigator will complete the suicidality assessment.

The Tanner Stage will be recorded (where appropriate).

Caregivers will be trained on how to complete the weekly symptom diary. To ensure consistency it is advised that an identified main caregiver completes all necessary diaries throughout the trial.

The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient must be screen failed.

9.1.1.2 Visit 2 (Day 1, Randomization)

This visit will occur 14 to 28 days after Visit 1. A visit window of + 6 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Information regarding AEs, changes to concomitant medications and menstruation cycle (where applicable) will be reviewed. The symptom diary will be reviewed. Vital signs assessments will be performed.

The investigator will confirm patient eligibility. Eligible patients will then be randomized to receive either 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volume of placebo in a 2:2:1:1 ratio.

Investigator and caregiver assessments must be completed prior to administration of IMP.

The investigator will complete the MBA-9 and CGI-S.

The caregiver will complete the RSBQ (following documented training on how to complete the questionnaire), CSHQ, SF-36, and CHQ-PF50.

The Hospital Services Use Questionnaire will be completed via interview.

Patients will be dispensed sufficient IMP and a dosing schedule for the following 4 weeks. Caregivers will be instructed how to use the dosing schedule, instructed how to measure and administer the medication, and how to complete the daily dosing diary.

Patients will take their first dose of IMP in the clinic at the end of Visit 2 (Day 1). As per Section 9.1.3, assessments may be performed in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.3 Visit 5 (Day 29)

This visit will occur 28 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

If possible, Visits 5 should be scheduled for a time that allows the collection of a trough PK sample, i.e., the sample should be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. If the visit takes place in the morning, caregivers should be reminded to ensure the patient does not take their morning IMP dose prior to the visit.

A blood sample will be taken for analysis of plasma levels of CBD and its main metabolites (as appropriate considering the patients' weight). The time of the patients' sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications. Clinical laboratory samples (blood) will be taken for hematology and biochemistry. Following collection of the blood sample, the IMP dose may be administered.

The caregiver will complete the RSBQ and CSHQ.

The Hospital Services Use Questionnaire will be completed via interview.

The investigator will complete the CGI-S and CGI-I, and suicidality assessment.

Information regarding AEs and changes to concomitant medications will be reviewed. The investigator must assess adherence to the dosing regimen. The symptom diary will be reviewed.

The following assessments will be performed: physical examination (including body weight), vital signs and ECG.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will receive sufficient IMP and a dosing schedule for the following 4 weeks.

9.1.1.4 Visit 6 (Day 57)

This visit will occur 56 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

If possible, Visits 6 should be scheduled for a time that allows the collection of a trough PK sample, i.e., the sample should be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. If the visit takes place in the morning, caregivers should be reminded to ensure the patient does not take their morning IMP dose prior to the visit.

A blood sample will be taken for analysis of plasma levels of CBD and its main metabolites (as appropriate considering the patients' weight). The time of the patients' sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications. Clinical laboratory samples (blood) will be taken for hematology and biochemistry. Following collection of the blood sample, the IMP dose may be administered.

Information regarding AEs and changes to concomitant medications will be reviewed. The investigator must assess adherence to the dosing regimen. The symptom diary will be reviewed.

The caregiver will complete the RSBQ and CSHQ.

The Hospital Services Use Questionnaire will be completed via interview.

The investigator will complete the CGI-S, CGI-I, and suicidality assessment.

The following assessments will be performed: vital signs and ECG.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will receive sufficient IMP and a dosing schedule for the following 4 weeks.

9.1.1.5 Visit 7 (Day 85)

This visit will occur 84 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

If possible, Visits 7 should be scheduled for a time that allows the collection of a trough PK sample, i.e., the sample should be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. If the visit takes place in the morning, caregivers should be reminded to ensure the patient does not take their morning IMP dose prior to the visit.

A blood sample will be taken for analysis of plasma levels of CBD and its main metabolites (as appropriate considering the patients' weight). The time of the patients' sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications. Clinical laboratory samples (blood) will be taken for hematology and biochemistry. Following collection of the blood sample, the IMP dose may be administered.

Information regarding AEs and changes to concomitant medications will be reviewed. The investigator must assess adherence to the dosing regimen. The symptom diary will be reviewed.

The caregiver will complete the RSBQ and CSHQ.

The Hospital Services Use Questionnaire will be completed via interview.

The investigator will complete the CGI-S and CGI-I, MBA-9, and suicidality assessment.

The following assessments will be performed: vital signs, physical examination (including body weight) and ECG.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will receive sufficient IMP and a dosing schedule for the following 6 weeks.

9.1.1.6 Visit 8 (Day 127)

This visit will occur 126 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Information regarding AEs and changes to concomitant medications will be reviewed. The investigator must assess adherence to the dosing regimen. The symptom diary will be reviewed.

The caregiver will complete the RSBQ and CSHQ.

The Hospital Services Use Questionnaire will be completed via interview.

The investigator will complete the CGI-S, CGI-I, and suicidality assessment.

The following assessments will be performed: vital signs and ECG.

For patients taking concomitant valproic acid clinical laboratory samples (blood) will be taken for hematology and biochemistry.

All IMP (used and unused) will be collected, a check of the returned IMP against usage should be made and patients will receive sufficient IMP and a dosing schedule for the following 6 weeks.

9.1.1.7 Visit 9 (Day 169, End of Treatment/Withdrawal Visit)

This visit will occur 168 days after Visit 2 or earlier if the patient withdraws from the trial. A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Information regarding AEs, changes to concomitant medications and menstruation cycle (where applicable) will be reviewed. The investigator must assess adherence to the dosing regimen. The symptom diary will be reviewed.

Visits 9 must be scheduled for a time that allows the collection of a trough PK sample, i.e., the sample must be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. If the visit takes place in the morning, caregivers must be reminded to ensure the patient does not take their morning IMP dose prior to the visit.

A blood sample will be taken for analysis of plasma levels of CBD and its main metabolites (as appropriate considering the patients' weight) as well as for analysis of blood levels of exploratory biomarkers. The time of the patients' sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications. Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology, biochemistry (includes determination of serum IGF-1 levels [see Section 9.2.10]), urinalysis (provided urine can be obtained) and a pregnancy test (using a serum sample,

as appropriate Section 9.2.2). Following collection of the trough blood sample, the IMP dose may be administered.

The caregiver will complete the, RSBQ, CSHQ, SF-36, and CHQ-PF50.

The Hospital Services Use Questionnaire will be completed via interview.

The Tanner Stage will be recorded (where appropriate).

The investigator will complete the CGI-S and CGI-I, MBA-9, and suicidality assessment.

The following assessments will be carried out: vital signs, physical examination (including body weight), height, and ECG.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Patients that discontinue treatment or complete the trial but do not immediately participate in the OLE trial (under a separate protocol) should have their dose of IMP tapered gradually over a period of 10 days. For patients who discontinue the IMP early, the taper period should start at the time the decision is made to discontinue unless tapering the dose of IMP is inadvisable (e.g., continued dosing is not possible due to an AE). For patients who discontinue the IMP early, the decision on whether or not to taper IMP will be left to the investigator's clinical judgment.

The investigator will confirm whether:

- The patient completed the trial and will transition immediately into the OLE trial.
- The patient completed the trial and will not transition immediately into the OLE trial.
- The patient withdrew from the trial.
- The patient will start the 10-day taper period.

Patients will receive sufficient IMP for the 10-day taper period, as applicable. Dosing schedule(s) will be provided accordingly.

9.1.1.8 Visit 10 (Day 179, End of Taper Visit)

This visit will occur 10 days after End of Treatment (Visit 9). A visit window of + 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Information regarding AEs and changes to concomitant medications will be reviewed. The investigator must assess adherence to the taper dosing regimen.

The investigator will complete the suicidality assessment.

The following assessments will be carried out: vital signs.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Visit 10 is only required for those patients who do not participate in the OLE trial, taper the medication prior to entering the OLE, or withdraw from the trial early and taper IMP. If a patient withdraws from the trial without taper, Visit 10 is not required.

9.1.2 Telephone Visits (Safety Follow-Ups)

9.1.2.1 Visits 3 (Day 8), 4 (Day 15), 11 (Day 207)

Visits 3 and 4 will occur 7 and 14 days after randomization (Visit 2), respectively.

Visit 11 will occur 28 days after Visit 10 (or Visit 9 if the patient did not taper) for patients who do not enter the OLE trial (under a separate protocol) or who withdraw from the trial early.

A visit window of ± 3 days from the scheduled visit date is permitted, except for Visit 11, where a window of + 3 days is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Telephone visits will be conducted and information regarding adherence to the dosing regimen (except for Visit 11), AEs, and changes to concomitant medications will be reviewed by a delegated personnel (the site investigator need only be involved if necessary, e.g., if any concerns are raised during the call). The weekly symptom diary will be reviewed (except for Visit 11).

Visit 11 constitutes the last scheduled safety follow-up. The purpose of the visit is to ascertain the status of AEs continuing after cessation of IMP or any new AEs commencing after discontinuation. All causally-related AEs that result in a patient's premature termination from the trial or are present at the end of the trial should be followed up until a satisfactory resolution occurs; that is, until the AE resolves or is considered clinically insignificant, or until an investigator is satisfied that the AE is not related to IMP and needs no further investigation.

9.1.3 Unscheduled Visits

Unscheduled visits and assessments may be performed in the event of a safety concern, as deemed necessary by the investigator. Data from any unscheduled visits should be reported on the unscheduled visits eCRF.

9.1.4 End of Trial

The end of trial is defined as last patient last visit/telephone call.

9.2 Trial Procedure Listing

9.2.1 Informed Consent/Assent

The parent(s)/legal representative of all patients in the trial must personally sign and date the IRB/IEC approved informed consent form (ICF) before any trial-specific procedures are performed or any patient-related data is recorded for the trial.

In cases where the patient possesses adequate understanding in the opinion of the investigator, assent will be taken along with parent(s)/legal representative consent, using IRB/IEC approved assent forms. If appropriate, prior to signature, the assent form will be read to the patient, and the patient will be given the opportunity to ask questions and discuss with their parent(s)/legal representative. If appropriate, the patient must personally sign and date the assent form. If the patient cannot write, they can give consent/assent by "making their mark" on the assent form (e.g., writing an "X"). If the patient possesses adequate understanding but is not physically able to sign, an impartial witness should be present during the entire assent discussion and should sign and personally date the assent form. By signing, the witness attests that the information in the assent form and any other written information were accurately explained to, and apparently understood by the patient, and that assent was freely given by the patient. Assent is defined as the minor's permission or affirmative agreement to participate in the trial. The explicit wish of a minor, who is capable of forming an opinion and assessing the information provided, to refuse participation in or to be withdrawn from the clinical trial at any time must be considered by the investigator. Given the severity of the condition we expect the majority of patients to have an insufficient level of understanding of what is proposed, where therefore solely parental/legal representative consent will be sought. All decisions made by the investigator relating to a patient's level of understanding and ability to provide assent must be documented in the patient's medical records.

The original signed informed consent/assent forms should be retained, and a copy provided to the patient and/or parent(s)/legal representative. Patients' parent(s)/legal representatives 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.

9.2.2 Contraception Requirements

Contraception requirements must be assessed by the investigator on a case by case basis. Where applicable, the patient or their partner must use highly effective contraception for the duration of the study and for three months thereafter. To be eligible for the trial, female patients 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 child bearing potential) must use highly effective birth control method 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[65]:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation[a]:
    - Oral.
    - Intravaginal.
    - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
    - Oral.
    - Injectable.
    - Implantable[b].
- Intrauterine devices[b].
- Intrauterine hormone-releasing systems[b].
- Bilateral tubal occlusion[c].

[a] The effect of GWP42003-P on oral contraceptives has not been investigated. GWP42003-P is not an inducer of CYP3A4 and therefore is not expected to alter the PK of hormonal contraceptives[64].
[b] Contraception methods that are considered to have low user dependency.
[c] Contraception methods that are considered to have low user dependency.

- Vasectomized partner[a], provided that partner is the sole sexual partner of the female patient 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 patient. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; 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[65].

Serum pregnancy tests will be performed for any female patients of childbearing potential at Visits 1 and 9; patients must test negative for pregnancy to be eligible for the trial. Additional pregnancy tests must be performed during the treatment period if considered clinically indicated by the investigator.

9.2.3 Demographics

The following information will be obtained for each patient: date of birth, sex and race (as allowed per local regulations). The CSS will be completed at Visit 1, *MECP2* mutation status (confirmation and definition) will be recorded and if not available a sample will be sent for genetic testing to confirm eligibility.

9.2.4 Medical History

Relevant, significant medical history will be obtained and is defined as any condition or disease that:

- May affect the condition under trial.
- Is ongoing on entry into the trial.
- Suspected or confirmed COVID-19 infection (or other significant communicable diseases) within year one of screening (Visit 1).

9.2.5 Menstruation

Caregivers will be asked if the patient is menstruating and details will be recorded as part of their medical history (Visit 2); any changes in menstrual cycles will be captured at the end of treatment visit.

9.2.6 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 14 days of the screening visit) will be recorded at Visit 1. All medications or interventions for RTT related symptoms used during the trial, including AEDs, should have been maintained at a stable dose over a period of 4 weeks prior to screening and patients and their caregivers 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. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in Section 8.3. The timing of concomitant medications will be collected on PK sampling visits (Section 9.2.12).

9.2.7 Physical Examination

Physical examinations will include body weight measurements. At Visit 1 and Visit 9 height will be collected, if an accurate measurement of height is not possible an estimate should be provided.

9.2.8 Vital Signs

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

9.2.9 12-Lead Electrocardiogram

Triplicate ECGs will be performed after 5 minutes rest. Triplicate ECGs should be taken as close together as possible. An ECG machine will be provided to all sites and all ECGs will be reviewed by a central reader. The central reader will provide a report within 24 hours of collection of the ECG. Additional alerts will be sent to the site in the case of clinically relevant abnormalities. The central reader will provide measurements and an overall assessment to support the investigator in their final assessment. If needed, the investigator may update clinical relevance based on patient files, medical history and any clinical symptoms. The central reader can be supportive for any discussions on patient outcomes. Any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately on the eCRF. In addition to the scheduled assessments, additional ECG measurements can be taken at any time during the trial, if clinically indicated.

Overall ECG measurements at screening must show no clinically relevant abnormalities and the average of the 3 QTcB measurements must be ≤ 450 msec, to confirm patient eligibility.

9.2.10 Clinical Laboratory Sampling

The investigator should use their judgment and knowledge of the patient to determine when best to collect the blood and urine samples in order to mitigate the risk that invasive procedures may cause the patient to become stressed, thereby affecting the results of other patient assessments. For THC screening, if a urine sample is to be provided (see Section 9.1), the urine sample must be collected during a visit (either Visit 1 or an unscheduled visit within ± 7 days of Visit 1).

Laboratory tests will include hematology, biochemistry and urinalysis (provided urine can be obtained), urine/serum THC screen, IGF-1 levels, and a serum pregnancy test (if appropriate). Analysis of all clinical blood samples, IGF-1 levels, and pregnancy tests (using a serum sample if appropriate), will be conducted at a central clinical laboratory. The THC screen may be carried out using a THC dipstick at site, otherwise a urine or blood sample can be sent to the central laboratory for analysis.

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 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.

Results from Visit 1 hematology, biochemistry, urinalysis, THC screen and pregnancy test (if appropriate) must be obtained prior to randomization to confirm patient eligibility.

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 9.2.10-1.

Table 9.2.10-1 Biochemistry, Hematology, Urinalysis and THC Screen

Biochemistry (Serum)[1]	Hematology (Whole Blood)[1]	Urinalysis (Urine)[2]	Pregnancy Test (Serum)[1]	THC Screen (Urine[1]/Serum[1])
Alanine aminotransferase	Hematocrit	Blood	Serum	THC
Albumin	Hemoglobin	Glucose		
Alkaline phosphatase	Mean cell volume	Nitrites		
Aspartate aminotransferase	Mean corpuscular hemoglobin	pH		
Calcium	Platelets	Protein		
Creatine kinase	Red blood cell count	White blood cells		
Creatinine	White blood cell count with automated differential	Bilirubin		
Creatinine clearance		Ketones		
Gamma-glutamyl transferase		Specific gravity		
Glucose		Urobilinogen		
Human chorionic gonadotropin				
HDL-cholesterol				
IGF-1*				
Potassium				
Prolactin				
Prothrombin time (plasma)				
Sodium				
Total bilirubin				
Total protein				
Triglycerides				
Urea (blood urea nitrogen)				

*Visits 1 and 9 only; IGF-1 laboratory results to remain blinded throughout the trial.
[1]Dipstick at site or analysed at a central laboratory.
[2]Analysed at the trial site by use of a dipstick (if allowed per local regulations).
HDL = high density lipoprotein

Investigators at trial sites will be notified of 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 THC screening will be reported back to the study site to permit 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 end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation. Blood sample volume requirements and processing procedures will be detailed in a separate laboratory manual; the maximum cumulative amount of blood taken in any 4-week period, including PK blood samples, will be 2.55 mL/kg of body weight and will not exceed a total of 50 mL within any 8 week period[67], taking into account possible repeat tests. The patient/caregiver must be advised that it may not be safe for the patient to undertake further blood tests within 1 month of any trial-related blood draws and to inform the investigator if they suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.11 *MECP2* Mutation Analysis

For patients with a confirmed clinical diagnosis of RTT who do not have a confirmed *MECP2* mutation, a blood sample will be collected at Visit 1 (if appropriate considering the patients' weight*) for analysis in a central laboratory. A positive *MECP2* pathogenic mutation result is required to confirm eligibility at Visit 2. In cases where the genetic report provides an uncertain result (such as possible pathogenic or unknown pathogenicity) the Investigator must contact the sponsor for adjudication on eligibility.

*In cases where the patients' weight (< 19 kg) prevents the collection of a blood sample at Visit 1 for *MECP2* mutation analysis (where required) in addition to other scheduled samples (see Section 9.2.10 and Section 9.1.1.1), a blood sample for *MECP2* mutation analysis should be collected **before** Visit 1 only after obtaining informed consent from the parent(s)/legal representative as per Section 9.2.1.

No genetic samples will be retained following this analysis.

9.2.12 Pharmacokinetic Blood Sampling

The plasma concentrations of CBD and its main metabolites will be assessed at Visits 5, 6, 7 and 9 (if possible and as appropriate considering the patients weight [patient must weigh ≥ 12 kg - Section 9.2.10]). One trough PK blood sample will be taken at Visit 9 i.e., the sample must be collected before the patient's next dose, 12 hours (−3/+6 hours) since last IMP dose. Visit 9 must be scheduled for a time that allows the collection of the trough PK sample. If the visit takes place in the morning, caregivers must be reminded to ensure the patient does not take their morning IMP dose prior to the visit. PK samples

will also be taken at Visit 5, 6 and 7, with visits preferentially scheduled for a time that allows collection of a trough PK sample, whenever possible. The IMP can then be administered during the visit, once the PK sample has been collected.

To minimize discomfort samples should be collected together with the safety laboratory sample collection. For patients who undergo PK blood sampling, the time of sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose on the day (Visits 5, 6, 7 and 9) will be recorded, as well as the time of latest concomitant medications.

Analysis of all CBD PK samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. Blood samples may be analyzed for the presence of other cannabinoids to confirm compliance with the protocol. The maximum number of PK blood draws will be determined by the criteria stated in Section 9.2.10.

The caregiver must be advised that it may not be safe for the patient to undertake further blood tests within 1 month of any trial-related blood draws and during the course of the trial and to inform the investigator if they suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.13 Biomarker Analysis

Blood samples will be collected at Visit 1 and Visit 9 (if appropriate considering the patients' weight [patient must weigh ≥ 16 kg at Visit 1] - Section 9.2.10) for the analysis of exploratory biomarkers. This may include BDNF, TNFα, interferon-gamma and interleukins, and/or other biomarkers implicated in RTT, as indicated by emerging research. IGF-1 may also be a biomarker implicated in RTT and will be measured as part of the clinical laboratory sampling panel. Samples for biomarker research will be stored for a maximum of 5 years from the date of the Last Patient's Last Visit, after which they will be destroyed; they will only be used for the purpose they were collected. Samples from patients who are screen failures will not be tested and will be destroyed and no genetic testing will be performed on any of the biomarker samples.

The results of this biomarker research may be reported either in the clinical study report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the IMP to generate hypotheses to be tested in future research.

9.2.14 Randomization and Trial Supply Management System

The RTSM system will be used to assign patients to treatment arms, manage IMP supply, and to provide treatment allocation information in the event of patient unblinding. The RTSM system information can be accessed via the eCRF.

A member of the trial team must register in the eCRF each clinic visit in order to:

- Obtain a patient's number (Visit 1).
- Randomize a patient (Visit 2).
- Obtain dispensing information (Visits 2, 5, 6, 7, 8 and 9).
- Provide completion/taper/premature termination information (Visit 9/the withdrawal visit or Visit 10, as applicable).

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

9.2.15 Dosing Diary/Compliance Review

Caregivers will be provided with a dosing schedule. Information on IMP administration will be collected daily from Visit 2 to Visit 10. Caregivers will be asked if the patient has taken their IMP as per the dosing schedule for that day; information will be collected electronically. Dosing compliance will be reviewed at each clinic visit. Any discrepancies will be discussed with the caregiver and documented accordingly within the patient's source documents. As part of the compliance review caregivers will be asked at the visits about the time of IMP administration in relation to meals.

9.2.16 Symptom Diary

The completion of an electronic symptom diary will be required from screening to Visit 9 (completed weekly). Caregivers will be asked to rate on a 0–10 numerical rating scale (NRS) the patient's condition and performance/severity of symptoms in terms of breathing, hand stereotypies, interactions, problem behaviors, constipation, seizures and sleep.

At Visit 1, caregivers will be trained on the weekly electronic diary completion.

The symptom diary will be reviewed at each clinic visit. Any discrepancies will be discussed with the caregiver and documented accordingly within the patient's source documents.

To ensure consistency it is advised that an identified main caregiver completes all necessary diaries throughout the trial.

The diary will be completed electronically.

9.2.17 Questionnaires and Assessments Completed at Scheduled Visits

Caregiver questionnaires and the symptom diary should be completed by an identified main caregiver, nominated at Visit 1. This should be a person able to assess the patient based on daily contact and most likely to be able to attend study visits. The same person should answer/complete the questionnaires/assessments in order to maintain consistency. The identified caregiver will also receive training on completion of caregiver questionnaires. Questionnaires should be completed during the scheduled visits under the supervision of a trained and delegated member of the investigator team.

To ensure consistency, investigator-completed questionnaires should be completed for each patient by the same investigator throughout the trial. Investigators must have completed the sponsor specified training for each questionnaire, before any questionnaires are completed.

9.2.17.1 Rett Syndrome Behavior Questionnaire

The RSBQ is a caregiver-completed questionnaire that measures the frequency of current disease characteristics (45 items) that may or may not apply to the patient (see Appendix 3.5). Each item is rated on a 3-point numerical scale; 0 indicating an item that is ‘not true as far as you know’, 1 indicating an item is ‘somewhat or sometimes true’, and 2 indicating an item that is ‘very true or often true’. The total maximum score is 90 and higher total scores represent greater severity. It encompasses 8 subscales: general mood, breathing problems, hand behaviors, face movements, body rocking/expressionless face, night-time behaviors, anxiety/fear, and walking/standing[54].

9.2.17.2 Clinical Global Impressions Questionnaire

The clinical global impressions (CGI) questionnaire was developed as a clinical trial measure to provide a brief, stand-alone assessment of the clinician’s view of the patient’s global functioning prior to and after initiating a study medication[55].

The CGI questionnaire is split into 2 scales; the CGI-S scale and the CGI-I scale (see Appendix 3.3 and Appendix 3.4). The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the

clinician's experience with patients who have the same diagnosis. Considering total clinical experience, a patient will be assessed on severity of illness at the time of rating. This is rated as: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill. The second section, the CGI-I, is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. 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.

To ensure consistency, investigators will be instructed to complete the CGI referring to a pre-defined set of anchors developed specifically for the use of the CGI in RTT[58].

The CGI-S and CGI-I assessments should be based on the entirety of the visit.

9.2.17.3 Rett Syndrome Motor-Behavioral Assessment Scale

The MBA-9 scale is completed by the investigator and evaluates 9 RTT symptoms. MBA-9 was derived from the full MBA scale (37 RTT symptoms) by selecting the items that are deemed to be amenable to change and that reflect areas of meaningful clinical change. It includes 5 questions from the original Behavioral/Social Assessment, 1 question from the Orofacial/Respiratory Assessment and 3 questions from the Motor Assessment/Physical Signs (see Appendix 3.2). The severity of current symptoms are rated on a 5-point numerical scale; 0 = normal or never; 1 = mild or rare; 2 = moderate or occasional; 3 = marked or frequent; 4 = very severe or constant. The total maximum score is 36 and higher total scores represent greater severity[60]. The MBA items address core symptoms of RTT.

9.2.17.4 Clinical Severity Scale

The CSS consists of a composite score based on 13 individual, ordinal categories measuring clinical features common in RTT. All scores range from 0-4 or 0-5 with 0 representing the least severe and 4 or 5 representing the most severe finding (see Appendix 3.1)[68].

The CSS will be administered at Visit 1 to evaluate disease severity. A minimum total score of 10 and a maximum total score of 36 are required for eligibility. At randomization, all patients will be stratified by severity, based on their CSS score (either a CSS score within the range of 10–22, or a CSS score within the range 23–36).

9.2.17.5 SF-36

Caregivers health-related quality of life will be assessed using the SF-36 questionnaire (see Appendix 3.6). SF-36 measures 8 domains of health-related quality of life within 8 scales: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The domains are used to calculate composite scores - physical health composite score (PCS) and mental health composite score (MCS). The scores for the SF-36 are based on a 0 to 100 scale; zero represents the lowest possible score, and 100 represents the highest possible score, with higher score indicating a better health state.

9.2.17.6 CHQ-PF50

The CHQ-PF50 is a generic QoL instrument designed and normed for children from 5 to 18 years of age. This instrument is a well-validated general QoL measure in pediatric populations with chronic illness. It measures QoL of the child and the family by parent or child report. The caregiver will be asked to complete the questionnaire on behalf of the patient. The CHQ-PF50 covers multidimensional health concepts including: Physical Functioning, Role/Social Limitations–Emotional/Behavioral, Role/Social Limitations–Physical, Behavior, Mental Health, Self-Esteem, General Health, Bodily Pain, Family Activities, Parent Impact–Time, Parent Impact–Emotional, and Family Cohesion. The CHQ-PF50 provides subscale scores as well as a Standardized Physical Summary (PhS) score and standardized Psychosocial Summary (PsS) score. Scores are based on a 0 to 100 scale and higher scores indicate better quality of life.

9.2.17.7 Hospital Services Use Questionnaire

This is a health utilization questionnaire designed to analyze the frequency of patient hospitalizations and hospital visits (see Appendix 3.8[73]). Hospitalizations will also be recorded in the patient's eCRF and through the serious adverse event (SAE) reporting process. The questionnaire will be completed via caregiver interview.

9.2.17.8 Children's Sleep Habit Questionnaire

This is a caregiver completed sleep screening instrument designed for school-aged children[9]. The CSHQ includes 33 items within eight subscales reflecting the following sleep domains: 1) Bedtime Resistance, 2) Sleep Onset Delay, 3) Sleep Duration, 4) Sleep

Anxiety, 5) Night Wakings, 6) Parasomnias, 7) Sleep-Disordered Breathing, 8) Daytime Sleepiness. Caregivers are to answer based on the last week. If the last week was unusual for a specific reason, the caregiver should choose the most recent typical week. The answers to each question are provided by a choice of 3 markers: "Usually" if it occurs 5 or more times in a week; "Sometimes" if it occurs 2 to 4 times in a week; "Rarely" if it occurs never or 1 time in a week. Some items should be reversed in scoring, so that a higher score reflects more disturbed sleep behavior (see Appendix 3.10). The caregiver is also asked to indicate for each item if the sleep item is a problem.

9.2.17.9 Suicidality Assessment

The profound cognitive impairment of RTT patients is such that the Children's Columbia-Suicide Severity Rating Scale is not considered appropriate in this trial. Instead, suicidality will be assessed by the investigator via a clinical interview with the caregiver (see Appendix 3.9).

9.2.18 Tanner Staging

The pubic hair (both sexes), genital (males only) and breast (females only) growth of all adolescent patients (i.e., ≥ 7 years of age[70] at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging (see Appendix 3.7)[,72]. The assessment can either be performed by examination during the study visit or the appropriate Tanner Stage can be indicated by the caregiver, with reference to the chart provided.

Once a patient reaches a score of V (i.e., 5) the assessment need not be performed again.

9.2.19 Investigational Medicinal Product Accountability

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

IMP will be dispensed at each of the following visits:

- Visit 2 (Day 1)
- Visit 5 (Day 29)
- Visit 6 (Day 57)
- Visit 7 (Day 85)
- Visit 8 (Day 127)

- Visit 9 (Day 169)

Caregivers will be asked to return all IMP (used and unused) to each relevant visit (Visits 5, 6, 7, 8, 9, 10). The site will check the returned IMP against the expected usage as per daily dosing diary. Any discrepancies will be discussed with the caregiver and documented accordingly within the patient's source documents.

9.2.20 Adverse Events

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

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures should be documented in the eCRF if deemed to meet the definition of an AE, in the investigator's opinion.

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

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.

9.3 Special Circumstances

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

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

- Safety follow-up may be done by a telephone call, other means of virtual contact or home visit, if appropriate.
- Patient and/or clinician-rated outcomes assessments may be done by videoconference, telephone call, 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).
- An alternative approach for IMP dispensing, secure delivery, and collection may be used.
- Biological samples may be collected and analysed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.
- If despite best efforts it is not possible to collect the biological samples or safety assessments (e.g., ECG, 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 a safety assessment cannot be performed, the investigator must review the benefit-risk for patient continuation in the study 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 IMP 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 patient has the right to withdraw from the trial at any time and for any reason, with no obligation to provide a reason, and without prejudice to his or her future medical care by the physician or at the institution.

The patient must be permanently discontinued from treatment if any of the following apply:

- Administrative decision by the investigator, GW, or a regulatory authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient assent.
- Withdrawal of parent(s)/legal representative consent.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

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

monitor. <u>The final decision regarding dose adjustments should be taken by the investigator.</u>

- Lost to follow-up.

The patient may also be permanently discontinued from treatment for any of the following:

- Patient or caregiver non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial.
- Did not meet eligibility criteria.
- Any evidence of use of drugs of abuse or drug diversion.
- Suicidal ideation or behavior during the treatment period.

Patients who discontinue IMP should have their dose of IMP gradually reduced (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue (unless inadvisable due to an AE). Patients should continue in the trial and continue to complete trial assessments and visits as per protocol. Patients who discontinue IMP and complete tapering of IMP prior to the completion visit, do not need to attend an End of Taper visit.

Should a patient request or decide to withdraw from the trial, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported on the applicable eCRF pages (refer to Section 9.2). All assessments required at the withdrawal visit should be conducted if possible. If the tapered dose is administered, patients should return for Visit 10, if possible. Wherever possible, a safety follow-up visit should take place 28 days from the date of last dose of IMP (refer to Section 9.1.2). If the withdrawing patient declines to give a reason for withdrawal of consent, the investigator must respect the patient's wishes.

11 URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator, they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to regulatory authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the regulatory authorities and IRB/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, final safety follow-up visit (Visit 11), which may or may not be considered to be related to the IMP. Any event that is the result of a trial procedure must be recorded as an AE.

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

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

12.1.2 Investigator

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

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP-related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent/assent 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., a SAE, when the event falls into 1 of the following criteria:

- Results in death.
- Is life-threatening*.

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

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

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

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 11). 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 11 which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the trial must be

treated as an SAE and reported to the GW PVD. Such post-trial SAEs do not need to be recorded on the patient's eCRF if editing rights to the eCRF have been removed due to final trial data lock. GW PVD may request safety follow-up information after the final trial visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the site files for all trial sites.

12.4 Pregnancy

Any female patient 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 patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the IMP but also other potential contributing factors. Factors for consideration of the underlying cause may include:

- Medical and disease history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- IMP discontinuation.
- 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 11), whether or not attributed to IMP and observed by the investigator or patient.

For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures should be documented in the eCRF if deemed to meet the definition of an AE, in the investigator's opinion.

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

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

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

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the eCRF. Once a diagnosis has been determined the AE section of eCRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the eCRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description.

However, the diagnosis (full or provisional) should be clearly stated, e.g., fever and malaise due to respiratory tract infection.

B) Adverse Event Start Date and Stop Date

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

C) Outcome

The outcome of the event must be recorded accurately and classified into 1 of the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

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

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

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

E) Causality

See Section 12.5 above.

F) Action Taken with Trial Medication

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

- Not applicable, patient is not taking IMP.
- Dose not changed.
- Dose reduced.
- Trial medication interrupted.
- Trial medication stopped.

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 11, after the trial.

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

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily discontinue from treatment due to what is perceived as an intolerable AE. Further details of discontinuation are presented in Section 10. If either of these occurs, the patient must permanently discontinue from treatment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If a safety concern is identified following withdrawal of a patient, GW may contact the investigator for additional follow-up information.

12.8 Potential Cases of Drug-induced Liver Injury

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

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.

- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

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

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol-defined criteria for treatment discontinuation and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24-48 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, INR, % eosinophils, alkaline phosphatase and gamma-glutamyl transferase levels, detailed history and physical examination. Patients should be followed in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state. However, if the above transaminase elevation criteria are confirmed by the first set of follow-up laboratory tests, the patient must permanently discontinue the IMP.

Elevations in ALT or AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the patient cannot return to the investigational 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 IRBs/IECs.

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. IB[64]: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the trial. The IB is updated at least 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 patients, 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 patients 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/assent, 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 statistical analysis plan (SAP), which will be produced 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 252 patients will be randomized to receive 1 of 2 dose levels of GWP42003-P (5 mg/kg/day or 15 mg/kg/day) or matching placebo (5 mg/kg/day dosing volumes or 15 mg/kg/day dosing volumes) on a 2:2:1:1 basis. The placebo data for the 2 dose groups will be pooled for analysis.

Assuming a common standard deviation of 9.38 and using a 2-sided test at a 0.05 α-level, a total sample size of 252 patients (84 patients per active dose group and 42 patients per placebo group) will provide 90% power to detect a mean difference of 5 points in change from baseline to Visit 9 in RSBQ (total score) between 15 mg/kg/day of GWP42003-P and placebo, allowing for 10% withdrawals.

The overall Type-I error of 5% will be preserved by adopting a hierarchical testing approach where the key secondary endpoint will only be tested at the 5% significance level if the primary endpoint is statistically significant. In addition, if the key secondary endpoint is statistically significant, the α of 5% will be passed down to the secondary endpoint family.

13.2 Interim Analysis

No formal interim analysis will be conducted. However, a blinded review of the aggregated variability may be performed to inform whether variability assumptions used in sample size calculations are accurate based on predicted effect sizes.

13.3 Analysis Sets

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

Full Analysis Set

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

Per Protocol Analysis Set

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

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

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

13.3.1 Protocol Deviations

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

13.4 General Considerations

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

For clinic visit based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP.

13.5 Accountability and Background Characteristics

13.5.1 Enrolment and Disposition

All patients (screened, randomized, prematurely terminated IMP, 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) and other demographic or baseline characteristics including CSS score and *MECP2* mutation

(confirmation and definition) 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 will be summarized by system organ class (SOC) by treatment arm.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the trial will be summarized separately by treatment arm, by medication class and active ingredients.

13.6 Endpoints and Statistical Methods

The primary efficacy endpoint will be analyzed as detailed in Section 13.6.2. Safety endpoints will be summarized as detailed in Section 13.6.3. Secondary endpoints will be analyzed as detailed in Section 13.6.4. Exploratory endpoints will be analyzed as detailed in Section 13.6.5. PK data will be summarized as detailed in Section 13.6.5.

13.6.1 Evaluable Period

The start of the evaluable period of the trial (Day 1) is defined as the date the patient took their first dose of IMP in the clinic at Visit 2.

The end of the evaluable period is defined as Visit 9 for the eCRF-based efficacy data.

13.6.2 Primary Efficacy Analysis

Following the treatment policy, the primary estimand is the change in RSBQ score from baseline at the end of 24 weeks of treatment for all randomized patients, regardless of treatment compliance.

The 15 mg/kg/day GWP42003-P dose level compared with placebo will be assessed using the RSBQ (total score). The change from baseline in RSBQ (total score) score will be summarized by treatment arm for each visit. Baseline will be taken as the last measurement prior to the first dose of IMP (e.g., Visit 2).

The change from baseline in RSBQ (total score) will be analyzed using mixed model repeated measures (MMRM). The model will include stratified CSS score group, baseline, visit, treatment arm, visit by treatment arm interaction and visit by baseline interaction as fixed effects, and visit repeated within each patient as a repeated effect.

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. 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 is the estimate of the treatment difference at Visit 9 (Day 169).

For patients who complete the trial, regardless of whether IMP is discontinued or not, the visit effect used in the analysis will correspond to the score at each study visit (Visits 5, 6, 7, 8 and 9). However, patients who withdraw from the trial are required to complete the procedures at Visit 9 at the time of withdrawal. For these patients, their Visit 9 data will be assigned to the nearest post-baseline visit (for which the assessment is scheduled to be performed), based on the study day of the visit. Further details will be specified in the SAP.

To preserve the overall Type-I error of 5%, a hierarchical testing approach will be adopted where the key secondary endpoint will only be tested at the 5% significance level if the primary endpoint is statistically significant. In addition, if the key secondary endpoint is statistically significant, the α of 5% will be passed down to the secondary endpoint family. Methods for adjustment for the multiple secondary endpoints will be described in the SAP.

If the data appears to not be normally distributed, alternative approaches such as transformation of the data and nonparametric analyses may be considered to express treatment effects. This will be specified in detail in the SAP.

Further details of statistical analyses will be elaborated in the SAP, including specification of the order in which the secondary endpoints will be formally tested.

13.6.2.1 Sensitivity Analyses for Primary Efficacy Analysis

The following sensitivity analyses will be conducted for the primary endpoint:

- MMRM using multiple imputation to impute missing data under the missing not at random assumption.

13.6.2.2 Supplementary Analyses for Primary Efficacy Analysis

The following supplementary analyses will be performed for the primary endpoint:

- Primary analysis repeated for the PP set.

- Analysis of covariance (ANCOVA) using the assessment performed at Visit 9 or last available visit for patients lost to follow-up.

Full details of each of the sensitivity and supplementary analyses and any further sensitivity or supplementary analyses deemed appropriate will be provided in the SAP.

13.6.3 Safety Endpoints

The safety endpoints are listed below and will be compared with placebo at each dose level as detailed in the following sections:

- AEs.
- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- ECG.
- Effects on menstruation cycles.
- Suicidality.
- Change in growth and development by measurement of height, weight, serum IGF-1 levels and Tanner Staging (for patients aged ≥ 7 years, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

13.6.3.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.3.2 Adverse Events

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 patients reporting at least 1 TEAE will be provided.

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.

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

Vital signs, ECG, physical examination, Tanner Staging, and serum IGF-1 levels will be summarized at screening, baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and serum IGF-1 levels from baseline to end of treatment will be summarized.

13.6.3.4 Clinical Laboratory Data

Clinical laboratory data at screening, during, and at the end of treatment, and the change from baseline to end of treatment will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range. Changes from baseline to end of treatment will be summarized.

13.6.3.5 Menstruation

Details of menstruation cycles (where appropriate) will be summarized and listed as appropriate.

13.6.3.5.1 Suicidality

Suicidality assessment responses will be summarized and listed as appropriate.

13.6.4 Key Secondary Endpoint and Secondary Endpoints

There are several secondary efficacy endpoints. For each endpoint, the mean change from baseline will be derived in patients taking each GWP42003-P dose and compared with

placebo. For visit based endpoints, baseline will be taken as the last measurement prior to the first dose of IMP (e.g., Visit 2 or Visit 1).

CGI-I will be analyzed in the same way as the primary endpoint, with the exception of the baseline and visit by baseline interaction fixed effects. The key secondary endpoint will be tested at a 5% significance level if the primary endpoint is statistically significant. If the key secondary endpoint is statistically significant, the α of 5% will be passed down to the secondary endpoint family. The order in which the secondary endpoints will formally be tested will be specified in the SAP.

The following other secondary endpoints will be analyzed as detailed:

- Change from baseline in RSBQ subscales.
- Change from baseline in severity of symptoms as assessed by the MBA score (change in total score, change in score of each of the MBA subscales and change index).
- Change from baseline in disease severity as measured by the CGI-S score.
- Change from baseline in the MBA-9 total score.
- Change from baseline in sleep problems as assessed by the CSHQ (total score and subscales).

The RSBQ subscale scores, CGI-S score, MBA-9 total score and the CSHQ total and subscale scores will be analyzed using the same method described for the primary endpoint.

For endpoints where normality is assumed, a graphical assessment of normality will be performed as well as conducting a test for normality such as the Shapiro-Wilk statistical test.

13.6.5 Exploratory Endpoints

Exploratory secondary endpoints for the trial are as follows and will be analyzed as detailed:

- Change from baseline in SF-36 PCS, MCS and TCS.
- Change from baseline in CHQ-PF50 standardized score.
- Hospital Services Use Questionnaire.

- Change from baseline to the last week of treatment in caregiver daily assessment of Rett symptoms (symptom diary).
- Change from baseline in caregiver daily assessment of Rett symptoms (symptom diary) by week.
- PK:
  - Plasma concentrations of CBD and its main metabolites.
- Change from baseline in blood levels of exploratory biomarkers.

The change from baseline in SF-36 scores, CHQ-PF50 standardized score, and symptom diary will be analyzed using ANCOVA. The model will include baseline and stratified CSS score group as covariates, as well as treatment arm as a fixed factor. The LS mean estimates for each treatment arm for each week, along with the standard error and 95% CIs will be presented. In addition, estimates of the treatment difference for each week will be presented along with standard errors of the difference and 95% CIs.

The Hospital Services Use Questionnaire will be summarized as appropriate and any analyses detailed in the SAP.

Plasma concentrations of CBD and its main metabolites will be summarized by visit together with any estimates of PK parameters.

The change from baseline in blood levels of exploratory biomarkers will be summarized and may be reported separately.

13.6.6 Handling of Missing Data

Analyses using MMRM account for missing data under the assumption that the missing data are missing at random. In addition, for the primary endpoint a sensitivity analysis is proposed to impute missing data under the missing not at random assumption for patients not impacted by COVID-19 and under the missing at random assumption for patients with missing data due to COVID-19.

Further details on handling of missing data will be provided in the SAP.

14 SAFETY MONITORING COMMITTEE

An independent safety monitoring committee (SMC) will be used in this trial. Details of the composition and standard operating procedures of the SMC 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/Assent

Initial master informed consent and assent forms will be prepared by GW and provided to the investigator, who will tailor these 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/assent documents should be prepared in the language(s) of the potential patient population.

Before a patient's involvement in the trial, the investigator is responsible for obtaining written informed consent from the patient's parent(s)/legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial and before any trial-specific procedures are performed or any patient-related data are recorded for the trial. In cases where the patient possesses adequate understanding, assent will be taken (if allowed per local regulations) along with parental/legal representative consent. Assent is defined as the minor's permission or affirmative agreement to participate in the trial. The patient and/or parent(s)/legal representative must have ample time to consider the information provided before giving written consent/assent. More specific definitions of 'ample time' may be in force if required by IRBs/IECs or local regulations.

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

15.3 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent/assent forms, master informed consent/assent forms, other patient 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 informed consent/assent forms before recruitment of patients 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/assent documents. 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 or designee for review before allowing any patients to consent/assent for entry into the trial:

- Signed and dated protocol signature page.
- Copy of IRB/IEC-approved informed consent/assent forms (including version number and date) and other patient information material.
- Copy of the IRB/IEC approval of the protocol, informed consent/assent forms (including version number and date) and other patient information material.
- Up to date *curricula vitae* and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/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 patient/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 Research Ltd will ensure that the site is informed of when screening of patients can commence.

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the eCRFs or other documents submitted to GW, patients should be identified by their 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 informed consent/assent forms, 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 patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the trial. The investigator is obligated to inform the patient that his/her trial-related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

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

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Trial or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The IRB/IEC and regulatory authorities must be informed of all substantial amendments and give approval. 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 early termination and send a copy of the notification to GW.

16.2 Trial Documentation and Storage

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries in and/or corrections to 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 patient'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 patient recruitment. In the rare situations of data (that would normally be recorded elsewhere) being recorded directly into the eCRF in error, then the source data from the eCRF should be transcribed into the patient's notes with appropriate signature and date to provide a full audit trail.

The investigator and study 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:

- Patient files containing completed eCRFs, informed consent/assent forms and supporting copies of source documentation.

- Trial files containing the protocol with all amendments, IB, copies of pre-trial documentation (see Section 15.4) and all correspondence to and from the IRB/IEC and GW.
- Enrolment log of all patients who consented to take part in the trial.
- Screening and recruitment log of all patients screened and whether or not they were recruited into the trial (i.e., randomized and/or dosed with IMP).
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug-related correspondence.

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

Following completion or termination of a clinical trial, GW will initiate proper archive of clinical trial-related documentation and electronic records generated by the investigator and/or GW. All clinical trial-related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by GW.

GW Research Ltd 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 the facilities and, upon request, inspecting the various records of the trial, e.g., eCRFs and other pertinent data, provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting (on-site or remotely) the eCRFs, questionnaires and available diary data at regular intervals throughout the trial

to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor must have (direct or remote) access to patient medical records and other trial-related records needed to verify the entries on the eCRFs.

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

To ensure the quality of clinical data across all patients and sites, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations, 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. Investigators and caregivers will be trained on the importance of adhering to the trial requirements and assessment completion. Where issues are identified, additional training will be provided.

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

behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW Research Ltd 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.

Any publication of the trial data will be made in accordance with the terms of the Clinical Trial Agreement.

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 Research Ltd 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 Research Ltd 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 Fehr S, Bebbington A, Nassar N, et al. Trends in the diagnosis of Rett syndrome in Australia. Pediatr Res. 2011;70(3):313-9.

2 Samaco RC, Neul JL. Complexities of Rett syndrome and MeCP2. J Neurosci. 2011;31(22):7951-9.

3 Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol. 1983;14(4):471-9.

4 Hagberg B. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev Disabil Res Rev. 2002;8(2):61-5.

5 Percy A. Rett Syndrome: Coming to Terms with Treatment. Advances in Neuroscience. 2014. 1-20.

6 Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999;23(2):185-8.

7 Luikenhuis S, Giacometti E, Beard CF, Jaenisch R. Expression of MeCP2 in postmitotic neurons rescues Rett syndrome in mice. Proc Natl Acad Sci U S A. 2004;101(16):6033-8.

8 Chahrour M, Jung SY, Shaw C, et al. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science. 2008;320(5880):1224-9.

9 Neul JL, Kaufmann WE, Glaze DG, et al. RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944-50.

10 Chahrour M, Zoghbi HY. The story of Rett syndrome: from clinic to neurobiology. Neuron. 2007;56(3):422-37.

11 Guy J, Hendrich B, Holmes M, Martin JE, Bird A. A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. Nat Genet. 2001;27(3):322-6.

12 Chen RZ, Akbarian S, Tudor M, Jaenisch R. Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. Nat Genet. 2001;27(3):327-31.

13 Guy J, Gan J, Selfridge J, Cobb S, Bird A. Reversal of neurological defects in a mouse model of Rett syndrome. Science. 2007;315(5815):1143-7.

14 Banerjee A, Castro J, Sur M. Rett syndrome: genes, synapses, circuits, and therapeutics. Front Psychiatry. 2012;3:34

15 Lioy DT, Garg SK, Monaghan CE, et al. A role for glia in the progression of Rett's syndrome. Nature. 2011;475(7357):497-500

[16] Maezawa I, Jin LW. Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate. J Neurosci. 2010;30(15):5346-56

[17] Leoncini S, De Felice C, Signorini C, et al. Cytokine Dysregulation in MECP2- and CDKL5-Related Rett Syndrome: Relationships with Aberrant Redox Homeostasis, Inflammation, and ω-3 PUFAs. Oxid Med Cell Longev. 2015;2015:421624

[18] Müller M, Can K. Aberrant redox homoeostasis and mitochondrial dysfunction in Rett syndrome. Biochem Soc Trans. 2014;42(4):959-64.

[19] Krishnan N, Krishnan K, Connors CR, et al. PTP1B inhibition suggests a therapeutic strategy for Rett syndrome. J Clin Invest. 2015;125(8):3163-77.

[20] Pozzo-Miller L, Pati S, Percy AK. Rett Syndrome: Reaching for Clinical Trials. Neurotherapeutics. 2015;12(3):631-40.

[21] http://www.nhs.uk/conditions/rett-syndrome/Pages/Introduction.aspx (page accessed 18 May 2017)

[22] Chapleau CA, Lane J, Pozzo-Miller L, Percy AK. Evaluation of current pharmacological treatment options in the management of Rett syndrome: from the present to future therapeutic alternatives. Curr Clin Pharmacol. 2013;8(4):358-69.

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

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

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

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

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

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

[29] 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.

[30] GWOR1209 Study Report. Evaluation of the role of TRP channels in the anticonvulsant effects of phytocannabinoids. Jun 2013.

[31] GWOR1141 Study Report. Evaluation of the actions of various phytocannabinoids at TRPV2, TRPV3 and TRPV4 channels. Jan 2013.

[32] GWOR1215 Study Report. Evaluation of cannabinoid metabolites at TRP channels and in the endocannabinoid system. Jun 2013

[33] GWPP17018 Study Report. Determination of the ability of pure CBD, CBDV and the synthetic metabolites 7-OH-CBD, 7-COOH-CBD, 7-OH-CBDV and 7-COOH-CBDV and a reference standard to inhibit the uptake of adenosine into rat brain synaptosomes. May 2017.

[34] Mijangos-Moreno S, Poot-Aké A, Arankowsky-Sandoval G, Murillo-Rodríguez E. Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats. Neurosci Res. 2014 Jul;84:60-3.

[35] Liou GI, Auchampach JA, Hillard CJ, et al. Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor. Invest Ophthalmol Vis Sci. 2008 Dec;49(12):5526-31.

[36] Center for Drug Evaluation and Research, Application Number 210365Orig1s000 NDA Approval Letter, June 2018. [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000Approv.pdf]

[37] GWCRI1509-B1 Study Report. The ability of cannabidiol in comparison with risperidone to improve a cognitive deficit induced by sub-chronic PCP in the novel object recognition task. May 2016.

[38] GWCRI1509-B2 Study Report. The ability of cannabidiol in comparison with risperidone to improve a deficit induced by sub-chronic PCP in the social interaction task. May 2016.

[39] GWCRI1547-C Study Report. The effects of CBD following bicuculline-induced seizure in newborn rats and piglets. Jan 2018.

[40] GWCRI09119D Study Report. Evaluation of CBD in a rat model of NHIE. Feb 2015.

[41] GWCRI1547-B Study Report. The effects of CBD and CBDV following hypoxic-ischaemic encephalopathy in newborn rats, in the presence or absence of hypothermia. Jan 2018.

[42] Pecorelli A, Cervellati C, Hayek J and Valacchi G. OxInflammation in Rett Syndrome. The International Journal of Biochemistry & Cell Biology. 2016; 81: 246-253.

[43] Sales AJ, Fogaça MV, Sartim AG, et al. Cannabidiol Induces Rapid and Sustained Antidepressant-Like Effects Through Increased BDNF Signaling and Synaptogenesis in the Prefrontal Cortex. Mol Neurobiol. 2018. doi: 10.1007/s12035-018-1143-4

[44] Devinsky O, Thiele E, Laux L, et al. Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: Update from the Expanded Access Program. American Epilepsy Society Annual Meeting 2015; Abstract No 3.397 (www.aesnet.org).

[45] Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: An open-label interventional trial. Lancet Neurol. 2015;4422(15):1–9.

[46] Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 Aug 17;377(7):699-700.

[47] Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90(14):e1204-e1211.

[48] Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018 May 17;378(20):1888-1897.

[49] GWOR1240 Study Report: An in vitro investigation of cannabinoid immunoregulation. May 2013.

[50] GWCRI1581 Study Report. Effects of cannabidiol on recovery from damage to a region of vocal-motor cortex in the zebra finch. Oct 2018.

[51] Vigli D, Cosentino L, Raggi C, Laviola G, Woolley-Roberts M, De Filippis B. Chronic treatment with the phytocannabinoid Cannabidivarin (CBDV) rescues behavioural alterations and brain atrophy in a mouse model of Rett syndrome. Neuropharmacology. 2018;140:121-129.

[52] Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia. 2017 Aug;58(8):e96-e100

[53] Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57(10):1617-24.

[54] Mount RH, Charman T, Hastings RP, Reilly S, Cass H. The Rett Syndrome Behaviour Questionnaire (RSBQ): refining the behavioural phenotype of Rett syndrome. J Child Psychol Psychiatry. 2002;43(8):1099-110.

[55] Guy, W. Clinical global impressions. In: Guy, W., editor. ECDEU assessment manual for psychopharmacology (Revised). National Institute of Mental Health; Rockville, Maryland: 1976. p. 217-221.

[56] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28-37.

[57] Busner J, Targum SD, Miller DS. The Clinical Global Impressions scale: errors in understanding and use. Compr Psychiatry. 2009;50(3):257-62.

[58] Neul JL, Glaze DG, Percy AK, et al. Improving Treatment Trial Outcomes for Rett Syndrome: The Development of Rett-specific Anchors for the Clinical Global Impression Scale. J Child Neurol. 2015;30(13):1743-8.

[59] Khwaja OS, Ho E, Barnes KV, et al. Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. Proc Natl Acad Sci U S A. 2014;111(12):4596-601

[60] FitzGerald PM, Jankovic J, Percy AK. Rett syndrome and associated movement disorders. Mov Disord. 1990;5(3):195-202.

[61] Souders MC, Mason TB, Valladares O, Bucan M, Levy SE, Mandell DS, Weaver TE, Pinto-Martin J. Sleep behaviors and sleep quality in children with autism spectrum disorders. Sleep. 2009 Dec;32(12):1566-78.

[62] Merbler AM, Byiers BJ, Garcia JJ, Feyma TJ, Symons FJ. The feasibility of using actigraphy to characterize sleep in Rett syndrome. J Neurodev Disord. 2018;10(1):8.

[63] Questions and Answers on Ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00) EMA/CHMP/507988/2013

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

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

[66] Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89(1):46–53.

[67] Directive G for. Ethical considerations for clinical trials on medicinal products with the pediatric population. EU Guidel. 2008;1–34.

[68] Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology. 2008;70(16):1313-21.

[69] Owens, J. A., Spirito, A., McGuinn, M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000, 23(8): 1043–1051.

[70] Killian JT, Lane JB, Cutter GR, et al. Pubertal development in Rett syndrome deviates from typical females. Pediatr Neurol. 2014;51(6):769-75.

[71] Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of Disease in Childhood. 1969;44(235):291-303.

[72] Marshall WA, Tanner JM. Variations in pattern of pubertal changes in boys. Archives of Disease in Childhood. 1969;45(239):13-23.

[73] Beecham, J. and Knapp, M. Costing psychiatric interventions, in G. Thornicroft (ed.) Measuring Mental Health Needs, Gaskell, 2nd edition. 2001;200-224.

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Visit Number	**1**	**2**	**3[a]**	**4[a]**	**5**	**6**	**7**	**8**	**9[b,c]**	**10[d]**	**11[a]**
Day Number (Visit window)	**−28 to −14***	**1 (+6)**	**8 (± 3)**	**15 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**127 (± 3)**	**169 (± 3)**	**179 (+3)**	**207 (+3)**
Informed consent and assent[e]	X										
Demographics	X										
Medical history	X										
CSS	X										
Eligibility check	X	X									
Genetic analysis of *MECP2* (if unknown)[f]	X										
Randomization		X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Menstruation question (where appropriate)		X							X		
Physical examination (including weight)	X				X		X		X		
Height	X								X		
ECG	X				X	X	X	X	X		
Vital signs	X	X			X	X	X	X	X	X	

Visit Number		**1**	**2**	**3[a]**	**4[a]**	**5**	**6**	**7**	**8**	**9[b,c]**	**10[d]**	**11[a]**
Day Number (Visit window)		**−28 to −14***	**1 (+6)**	**8 (± 3)**	**15 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**127 (± 3)**	**169 (± 3)**	**179 (+3)**	**207 (+3)**
Clinical laboratory blood sampling (hematology and biochemistry)[g]		X				X	X	X	X[h]	X		
Dipstick urinalysis (where possible)		X								X		
Urine/Serum THC screen[i]		X										
Serum pregnancy test (if appropriate)		X								X		
PK blood sampling (IMP)						X[j,k,l]	X[j,k,l]	X[j,k,l]		X[j,k,l]		
Biomarker blood sampling[m]		X								X		
Caregiver completed questionnaire	RSBQ	X	X			X	X	X	X	X		
	CSHQ		X			X	X	X	X	X		
	Caregiver QoL questionnaire (SF-36)		X							X		
	Patient QoL questionnaire (CHQ-PF50)		X							X		
	Symptom diary[n]	X	X	X	X	X	X	X	X	X		
Time and date of last IMP dose						X	X	X		X		
MBA-9			X					X		X		
CGI-S			X			X	X	X	X	X		
CGI-I						X	X	X	X	X		
Hospital Services Use Questionnaire			X			X	X	X	X	X		
Tanner Staging (where appropriate)		X								X		

Visit Number	**1**	**2**	**3[a]**	**4[a]**	**5**	**6**	**7**	**8**	**9[b,c]**	**10[d]**	**11[a]**
Day Number (Visit window)	**−28 to −14***	**1 (+6)**	**8 (± 3)**	**15 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**127 (± 3)**	**169 (± 3)**	**179 (+3)**	**207 (+3)**
Suicidality assessment	X				X	X	X	X	X	X	
IMP dispensing[o]		X			X	X	X	X	X		
IMP collection and compliance review					X	X	X	X	X	X	
Dosing diary[p]		X	X	X	X	X	X	X	X	X	

* Patients can be randomized as soon as they have completed at least 2 weeks of baseline and all eligibility criteria are confirmed (review of clinical laboratory results and, if applicable, genetic analysis)

[a] Visit to be conducted by telephone.

[b] To be performed for all patients completing or withdrawing from the trial. Patients who withdraw early should commence the 10-day IMP taper period, if possible.

[c] A safety follow-up visit 4 weeks after last IMP dose is required for all patients who withdraw from the trial or complete the trial but do not enroll in the OLE.

[d] Only required for those patients who do not participate in the OLE trial or for those who withdraw from the trial early and taper IMP. For patients who complete treatment but do not participate in the OLE trial, Visit 10 should be 10 (+3) days after Visit 9. For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the withdrawal visit.

[e] Informed consent must be obtained prior to any trial-related procedures. In cases where the patient possesses adequate understanding, assent will be taken along with parental/legal representative consent.

[f] For patients weighing < 19 kg and without documented pathogenic *MECP2* mutation, a blood sample for pathogenic *MECP2* genetic mutation genetic analysis must be collected in advance of Visit 1 (following informed consent [and where applicable, patient assent]).

[g] Determination of serum IGF-1 levels at Visit 1 and 9 only; IGF-1 laboratory results will remain blinded throughout the trial.

[h] For patients taking concomitant valproic acid only.

[i] THC screen using urine or serum, may be carried out at the site using a drug of abuse urine dipstick; otherwise a urine or blood sample may be sent to the central laboratory (note: patient weighing < 12 kg must not provide a serum sample for THC screen at Visit 1; if there are difficulties obtaining sufficient urine for THC testing at Visit 1 , then a blood or urine sample must be collected at the site on a another day within ± 7 days of Visit 1).

[j] To be taken together with the safety laboratory sample collection, as appropriate considering the patient's weight (patient must weigh ≥ 12 kg).

[k] Trough sample at Visit 9 (and preferentially also trough sample at Visits 5, 6 and 7, if possible) i.e., collected 9–18 hours after IMP dose. Caregivers should be advised not to administer the IMP prior to attending Visit 9 (and preferentially advised not to administer IMP prior to attending Visits 5, 6, and 7, if possible). The IMP can then be administered during the visit, once the PK sample has been collected.

[l] The time of the patients' sample collection, time of latest IMP dose, time and type of meal consumed by the patient closest to the latest IMP dose will be recorded, as well as the time of latest concomitant medications.

[m] For patients weighing < 16 kg, no blood sample will be collected for biomarker analysis.

[n] Completed weekly throughout the trial.

[o] In cases where patients are not able to attend study visits due to 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] Completed daily throughout the trial.

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	**Email: pvd@gwpharm.com** Tel: +44 (0)1223 233 410 Fax: +44 (0)1223 233 319 USA Toll-free Fax: +1-866-234-1751
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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):

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APPENDIX 3 QUESTIONNAIRES/ASSESSMENTS

Questionnaires appended exemplify the content of each specific assessment. All questionnaires will be converted to electronic versions and therefore their format will differ from what is presented here.

Appendix 3.1 Clinical Severity Scale

An example of Clinical Severity Scale (CSS) is shown below:

Clinical Severity Score			
Group A: Historical Items			
	Manifestation	**Score**	**Definition**
Onset	Age of onset of regression	0	No regression
		1	> 30 months
		2	18 months to 30 months
		3	12 months to < 18 months
		4	6 months to < 12 months
		5	< 6 months
	Onset of stereotypies	0	≥ 10 years
		1	36 months to < 10 years
		2	18 to < 36 months
		3	12 to < 18 months
		4	< 12 months
Growth	Head growth	0	None to minimal deceleration (0–1 centiles)
		1	Deceleration > 2 centiles, OFC >10th after 24 months
		2	2nd–10th centile after 24 months
		3	2nd–10th centile before 24 months
		4	< 2nd centile by 24 months
Group B: Current Exam Items			Clinical Assessment
Growth	Somatic growth at this visit	0	No growth failure (BMI 26–50% or above)
		1	Decrease in BMI (11th–25th %)
		2	Decrease in BMI (5th–10th %)
		3	Decrease in BMI (< 5th %)
		4	Decrease in BMI (<<5th %)
Motor	Independent sitting at this visit by exam	0	Sits alone acquired < 8 months
		1	Sits with delayed acquisition > 8 months
		2	Sits with delayed acquisition > 18 months
		3	Sits with delayed acquisition > 30 months
		4	Lost
		5	Never acquired
	Ambulation at this visit by exam	0	Acquired < 18 months/ Apraxic gait
		1	18 months ≤ walks alone ≤ 30 months
		2	> 30 months walks alone
		3	> 50 months walks with help
		4	Lost
		5	Never acquired

	Hand use	0	Acquired & conserved
		1	Holding of objects acquired on time (by 6-8 months) & partially conserved
		2	Holding of objects acquired late (> 10 months) and partially conserved
		3	Holding of objects acquired & lost all acquisitions (except for example scratching, rubbing nose)
		4	Never acquired
	Scoliosis	0	None
		1	1° to < 20°
		2	20° to < 40°
		3	40° to < 60°
		4	≥ 60°
		5	Surgery

Communication	Language at this visit by exam	0	Preserved, contextual
		1	Short phrases only
		2	Single words
		3	Vocalization, babbling
		4	Screaming, no utterances
	Nonverbal communication at this visit by exam	0	Preserved & propositive (points consistently with finger or eyes)
		1	Good eye contact maintained (≥ 30 seconds)
		2	Intermittent eye contact (5 seconds to < 30seconds)
		3	Infrequent eye contact (< 5 seconds)
		4	Lost and not regained
		5	None
	Respiratory dysfunction at this visit by exam	0	None
		1	Minimal hyperventilation and/or apnea (< 10% of time)
		2	Intermittent hyperventilation and/or apnea (50 % of time)
		3	Constant hyperventilation and/or apnea without cyanosis (100% of time)
		4	Constant hyperventilation or apnea with cyanosis
	Autonomic symptoms at this visit by exam	0	None
		1	Pink but cool
		2	Mottled and cold
		3	Blue-purple and cold hands or feet
		4	Blue-purple and cold hands and feet
	Epilepsy/Seizures at this visit	0	Absent
		1	< monthly
		2	< weekly to monthly seizures
		3	Weekly
		4	More than weekly
		5	Daily (intractable)

Appendix 3.2 9-items Motor-Behavioral Assessment Scale

An example of the 9-items Motor-Behavioral Assessment (MBA-9)[60] scale is shown below.

1. Regression of motor skills

- 0 None
- 1 Dyspraxia of gait and hand use including bilateral pincer grasps
- 2 Able to walk and use one or both hands
- 3 Able to walk independently or with support or to use one or both hands
- 4 No motor skill

2. Poor eye/social contact

- 0 None
- 1 25% of time
- 2 50% of time
- 3 75% of time
- 4 100% of time

3. Lack of sustained interest

- 0 None
- 1 25% of time
- 2 50% of time
- 3 75% of time
- 4 100% of time

4. Does not reach for objects or people

- 0 None
- 1 25% of time
- 2 50% of time
- 3 75% of time
- 4 100% of time

5. Chewing difficulties (by history at time of assessment)

- 0 None
- 1 Coarse chopped
- 2 Fine chopped
- 3 Pureed or mashed
- 4 Gastrostomy

6. Speech disturbance

- 0 Fluent
- 1 Phrases/sentences
- 2 Words with meaning or intention
- 3 Vocalizations, no words
- 4 No utterances

7. Hand clumsiness (by history or at time of assessment)

- 0 Purposeful hand use
- 1 Plays with toys or activates switches purposefully
- 2 Uses utensils/cup, may be adaptive
- 3 Finger feeds only
- 4 No purposeful hand use

8. Dystonia

- 0 None
- 1 Focal dystonia, one joint
- 2 Focal dystonia, more than one joint
- 3 Generalized dystonia, > 2 extremities
- 4 Fixed positional deformity

9. Hypertonia/rigidity

- 0 None
- 1 Ankle hypertonia/rigidity
- 2 Upper or lower limb hypertonia/rigidity
- 3 Generalized hypertonia without contractures
- 4 Generalized hypertonia with contractures

Appendix 3.3 Clinician Global Impressions - Severity Scale

An example of CGI-S is shown below[55]:

> *Considering your total clinical experience with this particular population, how ill is the patient at this time?*
>
> *1 = normal, not at all ill*
>
> *2 = borderline ill*
>
> *3 = mildly ill*
>
> *4 = moderately ill*
>
> *5 = markedly ill*
>
> *6 = severely ill*
>
> *7 = extremely ill*

Anchors for the Clinical Global Impression Scale-Severity produced by Neul et al, 2015, should be used by the investigator during completion of the CGI-S[58].

Appendix 3.4 Clinician Global Impressions - Improvement Scale

An example of CGI-I is shown below[55]:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his/her condition at admission to the project, how much has he/she changed?

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse

Appendix 3.5 Rett Syndrome Behaviour Questionnaire

An example of the RSBQ is shown below[54]:

RETT SYNDROME BEHAVIOUR QUESTIONNAIRE

On the following few pages there are items describing various characteristics that she may or may not currently show. In fact, many of the characteristics may not apply to her. The characteristics she shows now may be different from those she showed earlier in life. The characteristics may have changed as she has got older. We would like you to think just about the characteristics she shows **now.**

For each characteristic, you have to think whether or not it accurately describes her. If the characteristic does describe her you are asked to rate it. For these characteristics please tick box 2 if the item is **very true or often true**. Tick box 1 if the item is **somewhat or sometimes true**. If the characteristic does not describe her, please tick box 0 to indicate that the **item is not true** as far as you know. If she is unable to perform any item please also tick box 0.

0 = not true as far as you know 1 = somewhat or sometimes true 2 = very true or often true

Example If she uses gesturing very frequently to obtain desired objects you would tick box 2 to indicate that it is very true or often true.

	0	1	2	Uses gesturing to obtain desired objects.

Please tick one box for each item

1.	0	1	2	There are times when breathing is deep and fast (hyperventilation).
2.	0	1	2	Spells of screaming for no apparent reason during the day.
3.	0	1	2	Makes repetitive hand movements with hands apart.
4.	0	1	2	Makes repetitive movements involving fingers around tongue.
5.	0	1	2	There are times when breath is held.
6.	0	1	2	Air or saliva is expelled from mouth with force.
7.	0	1	2	Spells of apparent anxiety/fear in unfamiliar situations.
8.	0	1	2	Grinds teeth.
9.	0	1	2	Seems frightened when there are sudden changes in own body position.
10.	0	1	2	There are times when parts of the body are held rigid.
11.	0	1	2	Shifts gaze with a slow horizontal turn of head.
12.	0	1	2	Expressionless face.
13.	0	1	2	Spells of screaming for no apparent reason during the night.
14.	0	1	2	Abrupt changes in mood.
15.	0	1	2	There are certain days/periods where she performs much worse than usual.
16.	0	1	2	There are times when she appears miserable for no apparent reason.
17.	0	1	2	Seems to look through people into the distance.
18.	0	1	2	Does not use hands for purposeful grasping.

19.	0	1	2	Swallows air.
20.	0	1	2	Hand movements are uniform and monotonous.
21.	0	1	2	Has frequent naps during the day.
22.	0	1	2	Screams hysterically for long periods of time and cannot be consoled.
23.	0	1	2	Although can stand independently tends to lean on objects or people.
24.	0	1	2	Restricted repertoire of hand movement.
25.	0	1	2	Abdomen fills with air and sometimes feels hard.
26.	0	1	2	Spells of laughter for no apparent reason during the day.
27.	0	1	2	Has wounds on hands as a result of repetitive hand movements.
28.	0	1	2	Makes mouth grimaces.
29.	0	1	2	There are times when she is irritable for no apparent reason.
30.	0	1	2	Spells of inconsolable crying for no apparent reason during the day.
31.	0	1	2	Uses eye gaze to convey feelings, needs and wishes.
32.	0	1	2	Makes repetitive tongue movements.
33.	0	1	2	Rocks self when hands are prevented from moving.
34.	0	1	2	Makes grimacing expressions with face.
35.	0	1	2	Has difficulty in breaking/stopping hand stereotypies.
36.	0	1	2	Vocalises for no apparent reason.
37.	0	1	2	Spells of laughter for no apparent reason during the night.
38.	0	1	2	Spells of apparent panic.
39.	0	1	2	Walks with stiff legs.
40.	0	1	2	Tendency to bring hands together in front of chin or chest.
41.	0	1	2	Rocks body repeatedly.
42.	0	1	2	Spells of inconsolable crying for no apparent reason during the night.
43.	0	1	2	The amount of time spent looking at objects is longer than the time spent holding or manipulating them.
44.	0	1	2	Appears isolated.
45.	0	1	2	Vacant 'staring' spells.

---------- **THANK YOU FOR YOUR TIME** ----------

Appendix 3.6 36-item Short Form

The RAND Corporation SF-36 Survey Instrument was developed at RAND as part of the Medical Outcomes Study. An example is shown below:

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 3.7 Tanner Staging

Tanner Staging,[72] is to be completed for all patients aged 7 to less than 18 years of age[70] at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

Female Development & Pubic Hair

Please check the box next to the most appropriate stage; in the event that qualifying characteristics are not within the same stage, defer to the lesser stage as the overall Tanner Score.

Tanner Stage 1 (Prepubertal, typically 10 years and younger)

- No glandular tissue; areola follows the skin contours of the chest.
- No pubic hair at all.

Tanner Stage 2 (10–11.5 years)

- Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen.
- Small amount of long, downy hair with slight pigmentation on the labia majora.

Tanner Stage 3 (11.5–13 years)

- Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast.
- Hair becomes more coarse and curly and begins to extend laterally.

Tanner Stage 4 (13–15 years)

- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (15+ years)

- Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.
- Hair extends to medial surface of the thighs.

Male Genital Development & Pubic Hair

Please check the box next to the most appropriate stage.

Tanner Stage 1 (Prepubertal, typically 9 years and younger)

- Testicular volume less than 1.5 mL; small penis of 3 cm or less.
- No pubic hair at all.

Tanner Stage 2 (9–11 years)

- Testicular volume between 1.6 and 6 mL; skin on scrotum thins, reddens, and enlarges; penis length unchanged.
- Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum.

Tanner Stage 3 (11–12.5 years)

- Testicular volume between 6 and 12 mL; scrotum enlarges further; penis begins to lengthen to about 6 cm.
- Hair becomes more coarse and curly and begins to extend laterally.

Tanner Stage 4 (12.5–14 years)

- Testicular volume between 12 and 20 mL; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (14+ years)

- Testicular volume greater than 20 mL; adult scrotum and penis of 15 cm in length.
- Hair extends to medial surface of the thighs.

Appendix 3.8 Hospital Services Use Questionnaire

An example of the Hospital Services Use Questionnaire (based on the Health Service Use Questionnaire[73]) is shown below:

Baseline

1. Has your child used any **hospital in-patient** services in the last 12 months? (prior to starting treatment with the Study Medicine)? *[in-patient services include: Intensive Care Unit [ICU] and other hospital department wards]*
   Yes/No

2. Has your child used any **other specialist medical services** in the last 6 months?
   [other hospital services include: Emergency department, other outpatient departments (any hospital clinic e.g., neurology, cardiology, gastroenterology, etc.), Urgent care.
   Yes/No

For each in-patient hospital admission in the last 12 months, please record the following:

Reason for stay	Ward	Total Number of inpatient days
1. Health issue 2. Accident related to child's condition (due to motor disability or behaviour) 3. Accident unrelated to child's condition	1. Intensive Care Unit (ICU) 2. Other department / ward (non-ICU)	

Please complete additional in-patient hospital admission forms for each admission that occurred in the last 12 months

Please record any use of other **specialist medical services** by your child over the last 6 months.

Services used	Number of attendances due to health issues	Number of attendances due to accidents related to child's condition (due to motor disability or behaviour)	Number of attendances due to accidents unrelated to child's condition
Emergency department			
Other outpatient specialist services department			

(any hospital clinic e.g., neurology, cardiology, gastroenterology, etc.)			
Urgent Care			

Since last visit

1. Has your child used any **hospital in-patient** services since the last study visit? (prior to starting treatment with the Study Medicine)? *[in-patient services include: Intensive Care Unit [ICU] and other hospital department wards]*
   Yes/No

2. Has your child used any **other specialist medical services** since the last study visit? *[other hospital services include: Emergency department, other outpatient departments (any hospital clinic e.g., neurology, cardiology, gastroenterology, etc.), Urgent care.*
   Yes/No

For each in-patient hospital admission since the last study visit, please record the following:

Reason for stay	**Ward**	**Total Number of inpatient days**
1. Health issue 2. Accident related to child's condition (due to motor disability or behaviour) 3. Accident unrelated to child's condition	1. Intensive Care Unit (ICU) 2. Other department / ward (non-ICU)	

Please complete additional in-patient hospital admission forms for each admission that occurred since the last study visit

Please record any use of other **specialist medical services** by your child since the last study visit.

Services used	Number of attendances due to health issues	Number of attendances due to accidents related to child's condition (due to motor disability or behaviour)	Number of attendances due to accidents unrelated to child's condition
Emergency department			
Other outpatient specialist services department (any hospital clinic e.g., neurology, cardiology, gastroenterology, etc.)			
Urgent Care			

Appendix 3.9 Suicidality Assessment

An example of the suicidality assessment is shown below:

- *Has the child expressed any wish to be dead?*
- *Has the child made any suicide attempts?*
- *Has the child harmed themselves in any way or shown any non-suicidal self-injurious behavior?*

Appendix 3.10 Children's Sleep Habits Questionnaire

An example of the CSHQ is shown below[9].

Child's Sleep Habits
(Preschool and School-Aged)
(Abbreviated Version)

Coding

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if something occurs **5 or more times** in a week; answer SOMETIMES if it occurs **2-4 times** in a week; answer RARELY if something occurs **never or 1 time** during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A)".

Bedtime

Write in child's bedtime: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
1) Child goes to bed at the same time at night (R)	☐	☐	☐	Yes No N/A
2) Child falls asleep within 20 minutes after going to bed (R)	☐	☐	☐	Yes No N/A
3) Child falls asleep alone in own bed (R)	☐	☐	☐	Yes No N/A
4) Child falls asleep in parent's or sibling's bed	☐	☐	☐	Yes No N/A
5) Child needs parent in the room to fall asleep	☐	☐	☐	Yes No N/A
6) Child struggles at bedtime (cries, refuses to stay in bed, etc.)	☐	☐	☐	Yes No N/A
7) Child is afraid of sleeping in the dark	☐	☐	☐	Yes No N/A
8) Child is afraid of sleep alone	☐	☐	☐	Yes No N/A

Sleep Behavior

Child's usual amount of sleep each day: _____ hours and _____ minutes
(combining nighttime sleep and naps)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
9) Child sleeps too little	☐	☐	☐	Yes No N/A
10) Child sleeps the right amount (R)	☐	☐	☐	Yes No N/A
11) Child sleeps about the same amount each day (R)	☐	☐	☐	Yes No N/A
12) Child wets the bed at night	☐	☐	☐	Yes No N/A
13) Child talks during sleep	☐	☐	☐	Yes No N/A
14) Child is restless and moves a lot during sleep	☐	☐	☐	Yes No N/A
15) Child sleepwalks during the night	☐	☐	☐	Yes No N/A
16) Child moves to someone else's bed during the night (parent, brother, sister, etc.)	☐	☐	☐	Yes No N/A
17) Child grinds teeth during sleep (your dentist may have told you this)	☐	☐	☐	Yes No N/A
18) Child snores loudly	☐	☐	☐	Yes No N/A

CSHQ Abbreviated

Coding

Sleep Behavior (continued)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
19) Child seems to stop breathing during sleep	☐	☐	☐	Yes No N/A
20) Child snorts and/or gasps during sleep	☐	☐	☐	Yes No N/A
21) Child has trouble sleeping away from home (visiting relatives, vacation)	☐	☐	☐	Yes No N/A
22) Child awakens during night screaming, sweating, and inconsolable	☐	☐	☐	Yes No N/A
23) Child awakens alarmed by a frightening dream	☐	☐	☐	Yes No N/A

Waking During the Night

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
24) Child awakes once during the night	☐	☐	☐	Yes No N/A
25) Child awakes more than once during the night	☐	☐	☐	Yes No N/A

Write the number of minutes a night waking usually lasts: _____

Morning Waking/Daytime Sleepiness

Write in the time of day child usually wakes in the morning: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
26) Child wakes up by him/herself (R)	☐	☐	☐	Yes No N/A
27) Child wakes up in negative mood	☐	☐	☐	Yes No N/A
28) Adults or siblings wake up child	☐	☐	☐	Yes No N/A
29) Child has difficulty getting out of bed in the morning	☐	☐	☐	Yes No N/A
30) Child takes a long time to become alert in the morning	☐	☐	☐	Yes No N/A
31) Child seems tired	☐	☐	☐	Yes No N/A

Child has appeared very sleepy or fallen asleep during the following (check all that apply):

	1 Not Sleepy	2 Very Sleepy	3 Falls Asleep
32) Watching TV	☐	☐	☐
33) Riding in car	☐	☐	☐

Subscale Items
Children's Sleep Habits Questionnaire (CSHQ)

Numbers in parentheses refer to CSHQ item number

1. Bedtime Resistance (6 items)
Goes to bed at same time **(1) (R)** [A]
Falls asleep in own bed **(3) (R)**
Falls asleep in other's bed **(4)**
Needs parent in room to sleep **(5)**
Struggles at bedtime **(6)**
Afraid of sleeping alone **(8)**

2. Sleep Onset Delay (1 item)
Falls asleep in 20 minutes **(2) (R)**

3. Sleep Duration (3 items)
Sleeps too little **(9)**
Sleeps the right amount **(10) (R)**
Sleeps same amount each day **(11) (R)**

4. Sleep Anxiety (4 items)
Needs parent in room to sleep **(5)**
Afraid of sleeping in the dark **(7)**
Afraid of sleeping alone **(8)**
Trouble sleeping away **(21)**

5. Night Wakings (3 items)
Moves to other's bed in night **(16)**
Awakes once during night **(24)**
Awakes more than once **(25)**

6. Parasomnias (7 items)
Wets the bed at night **(12)**
Talks during sleep **(13)**
Restless and moves a lot **(14)**
Sleepwalks **(15)**
Grinds teeth during sleep **(17)**
Awakens screaming, sweating **(22)**
Alarmed by scary dream **(23)**

7. Sleep Disordered Breathing (3 items)
Snores loudly **(18)**
Stops breathing **(19)**
Snorts and gasps **(20)**

8. Daytime Sleepiness (8 items)
Wakes by himself **(26) (R)**
Wakes up in negative mood **(27)**
Others wake child **(28)**
Hard time getting out of bed **(29)**
Takes long time to be alert **(30)**
Seems tired **(31)**
Watching TV **(32)**
Riding in car **(33)**

Total Sleep Disturbance Score (33 items)[B]

Scoring: **Usually = 3** **Sometimes = 2** **Never/Rarely = 1**

[A] Note: Some items (*R*) should be reversed in scoring, so that a higher score reflects more disturbed sleep behavior.

[B] Note: The Total Sleep Disturbance Score: Consists of all 33 subscale items instead of 35 (although items 5 and 8 are on both the Bedtime Resistance and Sleep Anxiety scales, they should be included only once in the total score)

APPENDIX 4 RETT SEARCH CRITERIA

Revised diagnostic criteria for RTT[9].

RTT Diagnostic Criteria 2010 Consider diagnosis when postnatal deceleration of head growth observed.
Required for typical or classic RTT 1. A period of regression followed by recovery or stabilization* 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT.
Required for atypical or variant RTT 1. A period of regression followed by recovery or stabilization* 2. At least 2 of the 4 main criteria 3. 5 out of 11 supportive criteria.
Main criteria 1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language** 3. Gait abnormalities: Impaired (dyspraxia) or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms.
Exclusion criteria for typical RTT 1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease or severe infection that causes neurological problems*** 2. Grossly abnormal psychomotor development in the first 6 months of life#.

Supportive criteria for atypical RTT[##]

1. Breathing disturbance when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbance
6. Scoliosis kyphosis
7. Growth retardation
8. Small cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication - 'eye pointing'.

* Because MECP2 mutations are now identified in some individuals prior to any clear evidence of "possible" RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6-12 months for evidence of regression. If regression occurs, the diagnosis should be changed to definite RTT; however, if the child does not have any evidence of regression by 5 years, the diagnosis of RTT should be questioned.

** Loss of acquired language is based on lost acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have loss of acquired language.

*** There should be clear evidence (neurological or ophthalmological examination and MRI CT) that the preserved insult directly resulted in neurological dysfunction.

Grossly abnormal to the point that normal milestones (acquiring hand control, swallowing, developing social smile) are not med. Mild generalized hypotonic or other previously reported subtle developmental alterations during the first 6 months of life is common in RTT and do not constitute an exclusion criterion.

If an individual has ever had a clinical feature listed, it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥ 2 main criteria, but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of 'probably atypical RTT' may be given. Individuals who fall into this category should be reassessed as they age, and the diagnosis revised accordingly.

A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome

Study Code: GWND18064

EudraCT Number: 2018-003370-27

CLINICAL PROTOCOL AMENDMENT NUMBER: 3.1

to be incorporated into the Protocol, creating CLINICAL PROTOCOL MASTER VERSION 4.1, DATE 07 July 2020

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Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial Title	A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome
Indication	Rett syndrome (RTT) (typical or atypical)
Trial Design	This multisite trial consists of a double-blind, randomized, placebo-controlled design which will compare the efficacy of GWP42003-P versus placebo over a 24-week treatment period. Patients will be randomized to receive 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volumes of placebo in a 2:2:1:1 ratio. Following screening, eligible patients will complete a 2- to 4-week baseline period (patients can be randomized as soon as they have completed at least 2 weeks of baseline and all eligibility criteria are confirmed [including review of all clinical laboratory results and, if applicable, confirmation of methyl CpG binding protein 2 (MECP2) pathogenic genetic mutation]). All patients entering the trial will be stratified by severity, based on their Clinical Severity Scale (CSS) score (either a CSS score within the range of 10 to 22, or a CSS score within the range 23–36). Patients will be randomized and will commence the 24-week treatment period, including up to 2 weeks dose escalation. The treatment period ends at Visit 9 (Day 169), after which patients will commence a 10-day taper period followed by the 4-week follow-up period. The 10-day taper period and 4-week follow-up period may not be required for patients continuing Cannabidiol (CBD)-OS treatment under a separate protocol. If a patient permanently discontinues treatment at any point during the trial, the investigational medicinal product (IMP) should be gradually reduced over 10 days (unless inadvisable due to an adverse event [AE]). Patients and caregivers will be encouraged to remain in the trial and continue to complete trial assessments and visits as per protocol. If a patient withdraws from the trial at any point during the trial, they will be required to attend a withdrawal visit, if applicable taper the IMP and attend the end of taper visit, and then complete the 4-week follow-up period.
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List of Appendices

2 RATIONALE

This clinical protocol master amendment 3 (will be incorporated into the Protocol creating Clinical Protocol Master Version 4.1, Date 07 July 2020) addresses the following issues:

2.1 Inclusion of Male Subjects

Inclusion criteria changed to allow the enrolment of males, following a request from the European Medicines Agency's (EMA) Paediatric Committee (PDCO). Accordingly, contraception requirements and tanner staging has been updated for inclusion of males.

2.2 Changes in Wording Regarding Investigational Medicinal Product Mode of Administration via Gastrostomy or Nasogastric Feeding Tube

Wording regarding IMP administration via gastrostomy (G) or nasogastric (NG) feeding tube (G- or NG-tubes) updated in inclusion criteria and IMP administration sections to remove reference to specific tube materials and instead require a discussion with the medical monitor to confirm suitability of tubes being used.

2.3 Changes in Number of Sites

The number of sites expected to participate in this trial has been increased to 35 from 25.

2.4 Additional Guidance on Trial Procedures

- The requirement of patient weight to be < 13 kg has been updated to < 19 kg for collection of blood sample at Visit 1 or prior to Visit 1 for MECP2 mutation analysis due to issues with the current 1 mL volume.
- The permitted visit window for Visit 2 of + 3 days has been updated to + 6 days from the scheduled visit date so that sufficient time is available for MECP2 mutation analysis results to be available.
- Language related to meal taken at Visit 5 has been updated so that information for the meal taken with the latest IMP dose is collected rather than latest meal.
- Language related to the telephone visits (Visits 3 [Day 8], 4 [Day 15] and 11 [Day 207]) has been updated. Person responsible for conduct of telephone visits and review of information related to adherence to the dosing regimen has been updated to delegated personnel instead of site nurse for clarity.

- The requirement of a physician to be present and sign the consent form was removed from the procedure of informed consent as a result of the change in policy with the Sponsor.
- As specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied under special circumstances (e.g. COVID-19 pandemic), procedure language has been updated to detect cases of suspected or confirmed COVID-19 infection (or other significant communicable infectious diseases) within year one of screening (Visit 1). A new section for such special circumstances has been included.
- The requirement of a trained and delegated member of the investigator team to be present when questionnaires will be completed during the scheduled visits has been included as a result of the change in policy with the Sponsor.

2.5 Trial Documentation, Reporting Procedures, and Policies

The following changes have been made to trial documentation, reporting procedures, and policies:

- Reporting Procedures for All Adverse Events language has been updated in relation to action taken with trial medication.
- Trial monitoring has been updated to reflect that monitoring may occur onsite or remotely.
- Trial publication policy language has been updated to align with GW Research Ltd (GW) publication policy.

2.6 Minor Corrections, Clarifications, and Administrative Changes

- Minor formatting/spelling/punctuation/grammatical corrections have been made to ensure consistency and improve readability; however, in the interest of brevity, not all of these changes are captured in Section 4 of this amendment document.
- GW references were updated to align with GW referencing style.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Master Version 4.1, Dated 07 July 2020. It will be kept in the trial master file at GW as well as in each investigational centre file and, if applicable, pharmacy site file.

A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome.

Study Code: GWND18064

EudraCT Number: 2018-003370-27

CLINICAL PROTOCOL AMENDMENT NUMBER: 2

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL VERSION 3, DATE 18 July 2019

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Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial Title	A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P; CBD-OS) in patients with Rett syndrome.
Indication	Rett syndrome (RTT) [typical or atypical]
Trial Design	This multisite trial consists of a double-blind, randomized, placebo-controlled design which will compare the efficacy of GWP42003-P versus placebo over a 24-week treatment period. Patients will be randomized to receive 5 mg/kg/day GWP42003-P, 15 mg/kg/day GWP42003-P or matching volumes of placebo in a 2:2:1:1 ratio. Following screening, eligible patients will complete a 2 to 4-week baseline period (patients can be randomized as soon as they have completed at least 2 weeks of baseline and all eligibility criteria are confirmed [including review of all clinical laboratory results and, if applicable, confirmation of *MECP2* pathogenic genetic mutation]). All patients entering the trial will be stratified by severity, based on their Clinical Severity Scale (CSS) score (either a CSS score within the range of 10–22, or a CSS score within the range 23–36). Patients will be randomized and will commence the 24-week treatment period, including up to 2 weeks dose escalation. The treatment period ends at Visit 9 (Day 169), after which patients will commence a 10-day taper period followed by the 4-week follow-up period. The 10-day taper period and 4-week follow-up period may not be required for patients continuing CBD-OS treatment under a separate protocol. If a patient permanently discontinues treatment at any point during the trial, the investigational medicinal product (IMP) should be gradually reduced over 10 days (unless inadvisable due to an adverse event [AE]). Patients and caregivers will be encouraged to remain in the trial and continue to complete trial assessments and visits as per protocol. If a patient withdraws from the trial at any point during the trial, they will be required to attend a withdrawal visit, if applicable taper the IMP and attend the end of taper visit, and then complete the 4-week follow-up period.
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List of Appendices

2 RATIONALE

This clinical protocol amendment 2 (will be incorporated into the Protocol creating Clinical Protocol V3 18Jul19) addresses the following issues:

2.1 Change of Primary and Secondary Endpoints

Following feedback from the United States Food and Drug Administration (FDA) on 18 Dec 2018 as part of the 'Study May Proceed' notification, which highlighted the importance of demonstrating efficacy on both RSBQ and CGI-I, in order to obtain information on changes in disease signs and symptoms via the RSBQ and an assessment of clinical meaningfulness of these changes via the CGI-I, the protocol was updated to specify the RSBQ as the primary endpoint, and the CGI-I as the key secondary endpoint. This provides a clear hierarchy for testing both the RSBQ and the CGI-I. Furthermore, the primary endpoint will be tested at 5% significance level which is fully allocated to the 15 mg/kg/day dose. The 5 mg/kg/day dose is now a secondary endpoint. The 15 mg/kg/day dose was selected for the primary analysis as it is within the known efficacious range for seizure indications.

2.2 Change to Exclusion Criteria: Contraception

In response to a request made by the Medicines and Healthcare products Regulatory Agency (MHRA) on 18 January 2019 and Italian Medicines Agency (Agenzia Italiana del farmaco [AIFA]) on 13 May 2019, contraceptive measures considered highly effective were more precisely documented within the protocol, and aligned with the Clinical Trial Facilitation Group (CTFG) guideline.

2.3 Inclusion of Benefit-risk Analysis

In response to a request made by AIFA on 13 May 2019, the protocol has been updated to include a benefit-risk assessment concluding that the overall benefit-risk for the development of CBD-OS in the Rett syndrome (RTT) population is favorable.

2.4 Change in Assessments

The 'Client Service Receipt Inventory (CSRI) – Health Service Use' was replaced with a 'Hospital Services Questionnaire' in order to reduce complexity and concentrate on the services likely to have a greater cost impact.

An option to carry out the THC screen using a drugs of abuse dipstick was included to facilitate procedures at site, given the collection of sufficient urine to provide to the central lab may be problematic and the blood analysis is not suitable for patients < 12 Kg (due blood volume restrictions).

Activated partial thromboplastin time removed from biochemistry panel.

2.5 Change on *MECP2* Mutation

Clarification that *MECP2* mutation must be 'pathogenic'; removal of option to proceed with randomization without confirmation of mutation type; this is to ensure sites confirm the genetic mutation is pathogenic prior to randomization.

2.6 Clarification on IMP Discontinuation Criteria

Clarification on criteria requiring IMP discontinuation rather than study withdrawal, as patients/caregivers are encouraged to remain in the trial and continue to complete trial assessments and visits as per protocol even if IMP is discontinued.

2.7 Additional Guidance on Trial Procedures

- Inclusion of a request for investigators to contact medical monitor if planning dosing via G- NG- tube planned; this is to ensure the investigator receives appropriate guidance prior to dosing via feeding tubes and only the tube types specified in the protocol are used. Guidance document on feeding tube administration is also provided to investigators, therefore specific instructions were removed from the protocol.
- All assessment should reflect the patient's regular state, therefore it should be ensured the patient has adequate time to settle prior to each assessment.
- The CGI-S and CGI-I assessments should be based on the entirety of the visit.
- Tanner staging may be carried out by the investigator or indicated by caregiver.
- Suicidality assessment is to be carried out by the investigator.
- Information on SF-36 scoring updated.
- Define the end of trial.

2.8 Minor Corrections, Clarifications and Administrative Changes

Administrative updates have been made throughout for consistency (minor changes to grammar, punctuation or formatting are not captured in this amendment document).

Clarification that the investigator is responsible for the management of investigational medicinal product (IMP) and concomitant medication dose changes for reasons related to safety or tolerability.

A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome.

Study Code: GWND18064

EudraCT Number: 2018-003370-27

CLINICAL PROTOCOL AMENDMENT NUMBER: MASTER AMENDMENT 1

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL MASTER VERSION 2, DATE 26 FEBRUARY 2019

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1 PROTOCOL SYNOPSIS

Trial Title	A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P; CBD-OS) in patients with Rett syndrome.
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2 RATIONALE

This clinical protocol amendment master amendment 1 (will be incorporated into the Protocol creating Clinical Protocol Master Version 2, Date 26 February 2019) addresses the following issue(s):

2.1 Updates Based on US FDA Recommendations

In accordance with comments for consideration received from the United States Food and Drug Administration (FDA) on 18 Dec 2018 as part of the 'Study May Proceed' notification, the protocol has been amended as follows:

2.1.1 Change to Exclusion Criteria: Hepatic Function

Exclusion criterion has been updated to exclude patients with moderate hepatic impairment (serum alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 × upper limit of normal [ULN] or total bilirubin > 2 × ULN).

2.1.2 Clarification to Investigational Medicinal Product Dosing Instructions and Compliance Documentation

Given that the concomitant administration of CBD-OS with a high fat meal results in a predictable increase in CBD exposure (C_{max} and AUC) of 4 to 5-fold, and less total-subject variability, the instruction to take investigational medicinal product (IMP) preferentially with food has been expanded to also note that the time of IMP administration in relation to food must be kept consistent throughout the trial. The protocol has also been amended to assess as part of the IMP compliance review how patients are taking IMP with respect to meals.

2.1.3 Information collected on PK sample collection days

In order to better understand the effect of extrinsic factors in exposure for patients who undergo PK blood sampling, in addition to the time of sample collection and previous IMP dose, the time of concomitant medications and meals as well as the types of meals consumed by the patient on the day (Visits 5, 6, 7 and 9) will be collected

2.1.4 Change to List of Prohibited Therapies During the Trial

Formal CBD drug-drug interaction studies (rifampicin, itraconazole, fluconazole) have been completed but not yet reported. Initial findings suggest no important interaction of strong cytochrome P450 (CYP)3A4 or CYP2C19 inhibitors on exposure to CBD, likely reflecting that other CYPs are capable of metabolizing the drug

(CYP1A1, CYP1A2, CYP2A6, CYP3A5 and CYP2D6). In addition, the effects of grouped concomitant medications from CYP2C19 inhibitors, CYP3A4 inhibitors and CYP3A4 inducers were investigated as covariates in a population PK assessment. There were no significant effects of CYP2C19 inhibitors, CYP3A4 inducers, or CYP3A4 inhibitors observed on exposure to CBD or its major circulating metabolites. Therefore, the avoidance of grapefruit/juice is not required during the trial and neither is the avoidance in the 3 days prior to PK sampling. Accordingly, the restriction on consumption of grapefruit or grapefruit juice within 3 days of PK sampling visits has been removed.

2.1.5 Clarifications to the Statistical Analysis

2.1.5.1 Clarification of Multiplicity Adjustments for Secondary Endpoints

The protocol had been amended to note that methods for adjustment for the multiple secondary endpoints will be described in the statistical analysis plan (SAP).

2.1.5.2 Clarification of Analysis Models if Data are not Normally distributed

The protocol had been amended to state which alternative analysis models/approaches may be considered if the data appears to not be normally distributed; transformation of the data and nonparametric analyses may be considered to express treatment effects.

2.1.6 Clarifications on Trial Monitoring

The trial monitoring section has been updated to note provisions to limit missing data through the trial design: monitoring of questionnaires and the education of investigators and patients.

2.2 Updates Based on MHRA Notice of Non-acceptance

In accordance with Medicines and Healthcare products Regulatory Agency (MHRA) notice of grounds for non-acceptance and the right to amend request received on 18 January 2019, the protocol has been amended as follows:

2.2.1 Change to Exclusion Criteria: Hepatic Function

Exclusion criterion has been updated to exclude patients with moderate hepatic impairment (ALT or AST> 3 × ULN). This change was also made in response to FDA feedback, as discussed in Section 2.1.1.

2.2.2 Change to Exclusion Criteria: Cardiovascular Function

Exclusion criterion has been updated to state that patients with cardiovascular conditions will be excluded if, in the opinion of the investigator, participation in the trial may put the patient at risk.

In addition, one of the listed examples of significant ECG abnormalities has been amended from 'cardiac arrest' to 'premature cardiac arrest' (not a MHRA request).

2.2.3 Change to Exclusion Criteria: Contraception

Exclusion criterion has been added to state that patients of child bearing potential must use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for 3 months thereafter.

2.2.4 Change to Exclusion Criteria: Hypersensitivity to Cannabinoids or Excipients

Exclusion criterion has been amended to clarify that IMP is a term used to describe both investigational active product and reference therapy (placebo).

2.2.5 Safety Assessments

- The protocol has been updated to note that pregnancy tests (in addition to those performed at Visits 1 and 9) can be performed during the treatment period if considered clinically indicated by the investigator.
- Additional ECG assessments have been added at Visits 6 and 8.
- Review of ECG by central reader wording has been clarified to note that a central reader report will be provided within 24 hours of collection of the ECG.
- QT interval correction changed from Fridericia's formula to Bazett's formula; the latter is recommended for use in pediatric patients.
- Given the patient population and the time required to perform each ECG, the requirement for patients to be sitting in the same position and having ECGs performed 5 minutes apart for each measurement has been removed from the protocol.
- To cover the 12-week period between Visit 7 and Visit 9, additional clinical laboratory sampling has been added at Visit 8 only for patients taking

concomitant valproic acid, the identified risk factor for elevations of transaminases following the first 2 months of treatment.

2.2.6 Concomitant Therapy and Potential Drug Interactions

Instead of cross referencing the investigator's brochure for CBD-OS, cautions regarding potential drug interactions have been added to Section 8.2 of the protocol. This text includes discretionary guidance for investigators regarding careful titration of CBD and monitoring levels of concomitant medications or metabolites in patients taking medications metabolized by CYP3A4, CYP2C19 or CYP2B6.

2.2.7 Dose Reductions of IMP

The protocol has been amended to include guidance on dose adjustments during dose escalation and treatment as well as detail on the taper schedule.

2.3 Change to Inclusion Criteria: Age Range

The minimum age requirement for this trial has been lowered from 4 years to 2 years to better encompass the applicable pediatric age range (given that the mean age of Rett syndrome (RTT) diagnosis is 2.5 years)[1]. Homogeneity of the patient population (i.e., inclusion of patients that are post-regression and stable) will be ensured by the existing inclusion criterion 'Patient must be post-regression (≥ 6 months since last loss of hand use or verbal language or gross motor regression)'.

Safety data used to support the evaluation of CBD-OS in patients with RTT covers the age range proposed. Safety data (up to and including the 120-day Safety Update) was submitted into NDA 210365 and approved by the FDA on 25 June 2018 for the use of CBD-OS (Epidiolex®) for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

2.4 Change to the Symptom Diary

Following caregiver feedback, as part of diary content validation work, an item addressing the impact of seizures was added to the caregiver assessment of Rett symptoms (symptom diary).

2.5 Minor Corrections, Clarifications and Administrative Changes

- Blood sampling volume requirements and the specified minimum weight requirements for blood sampling (i.e., laboratory sampling [haematology and biochemistry (including coagulationVisit 2 procedures have been updated to

emphasise that investigator and caregiver assessments at Visit 2 must be completed prior to administration of IMP.

- Text has been added to Section 9.1.1.8 of the protocol to note that Visit 10 is only required for those patients who do not participate in the OLE trial, taper the medication prior to entering the OLE, or withdraw from the trial early and taper IMP.

- Medidata Safety Gateway will be implemented for this trial and will allow SAE and pregnancy reporting via eCRF rather than fax reporting. Potential cases of drug-induced liver injury will now be reported via email rather than fax reporting.

- As a change to the GW investigator's brochure (IB) format, the development core safety information is no longer a separate source from the IB. Section 12.9 of the protocol has been updated to confirm that notification of safety information to investigators, regulatory authorities and IRB/IECs will be provided through 2 sources, the IB or Council for International Organizations of Medical Sciences (CIOMS) reports. The protocol has been amended to note that the Client Service Receipt Inventory (CSRI) will be completed via interview. Administrative updates have been made throughout for consistency (NB, in the interest of brevity, minor changes to grammar, punctuation or formatting are not captured in this amendment document).