Appendix 1.1 Protocol and Protocol Amendments

GWND19002 Protocol V1 date 09-Aug-2019

GWND19002 Protocol V2 date 18-Dec-2019

GWND19002 Protocol Annex 1 V1 date 28-May-2020

GWND19002 Protocol Annex 1 V2 date 11-Nov-2020

GWND19002 Protocol Annex 1 Amendment 1 V2 date 11-Nov-2020

AN OPEN-LABEL EXTENSION TRIAL TO INVESTIGATE THE LONG-TERM SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME

Study Code: GWND19002

EudraCT Number: 2019-001605-24

CLINICAL PROTOCOL

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Investigator Agreement

I have read the attached clinical protocol entitled 'An open-label extension trial to investigate the long-term safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome', dated 09 August 2019, and agree to abide by all provisions set forth therein.

The sponsor and I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to Good Clinical Practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the trial and for 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.

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

Center No.: _____

Print name: _____ Date: _____

Principal investigator (DD-MMM-YY)

Signature: _____

GW Authorization

PI [redacted]

Date: 26-Aug-19

(DD-MMM-YY)

1 PROTOCOL SYNOPSIS

Trial Title	An Open-label Extension Trial to Investigate the Long-term 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 long-term safety of GWP42003-P in patients with RTT
Secondary Objective(s)	**Secondary objectives:** • To evaluate the effect of GWP42003-P in measures of disease severity o Rett Syndrome Behaviour Questionnaire (RSBQ) o Clinical Global Impressions - Improvement (CGI-I) o Clinical Global Impressions - Severity (CGI-S) o 9-items Motor Behavioral Assessment (MBA-9) o Children's Sleep Habits Questionnaire (CSHQ) **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 o Caregiver Assessment of Rett Symptoms
Trial Design	This is a 28-week, multicenter, open-label extension (OLE) trial for patients with RTT who have completed the randomized, double-blind, placebo-controlled trial (GWND18064). Entry to this OLE trial is recommended to be on the same day as Visit 9 of the randomized controlled trial (RCT); however, patients may enter the OLE trial up to the point of the RCT follow-up visit (Visit 11). All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg twice daily [b.i.d.]) on Day 1. Patients will be observed, and after 1 week, the dose may be escalated further, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.), in weekly

	increments of 5 mg/kg/day (2.5 mg/kg b.i.d.). Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 28 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability as deemed necessary by the investigator, until the optimal dose is found. Patients whose dose has been decreased can have their dose increased again if tolerability improves. At the end of treatment (Visit 8 [Day 197]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period. If a patient permanently discontinues treatment at any point during the trial, GWP42003-P should be gradually reduced over 10 days (unless inadvisable due to an adverse event [AE]). The patient should attend a withdrawal visit (Visit 8) as soon as possible after the decision is made to permanently discontinue GWP42003-P. Unless inadvisable due to an AE, the patient will taper GWP42003-P and attend the End of Taper visit and then complete the 4-week follow-up period.
Primary Endpoint	**Safety:** The long-term safety profile of GWP42003-P will be assessed by evaluating changes in the following, relative to the prerandomization baseline of the RCT: • 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 the onset of menarche or other signs of precocious puberty)
Secondary Endpoint(s)	**Secondary endpoints:** The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

	• RSBQ • CGI-I • CGI-S • MBA-9 • CSHQ **Exploratory endpoints:** The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT: • SF-36 • CHQ-PF50 • Hospital Services Use Questionnaire • Caregiver Assessment of Rett Symptoms
Sample Size	All patients with RTT who completed the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and meet the eligibility criteria can be included in this trial. Approximately 252 patients will be enrolled.

Summary of Patient Eligibility Criteria	**Inclusion criteria** For inclusion in the trial, patients must fulfil **all** of the following criteria: • Patient has completed all scheduled visits of the treatment phase of the RCT, GWND18064, and has transitioned to OLE by the point of RCT follow-up (Visit 11). • Patient (if possessing adequate understanding, in the investigator's opinion) and/or her parent(s)/legal representative is willing and able to give informed consent/assent for participation in the trial. • Patient and her 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 the ability to swallow the investigational medicinal product (IMP) provided as a liquid solution or the ability for the IMP to be delivered via gastrostomy (G)

	or nasogastric (NG) feeding tube (only G- or NG-tubes made from polyurethane or silicon are allowed). • 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 she has one) and consultant (if she has one) to be notified of participation in the trial if the primary care practitioner/consultant is different from the investigator. **Exclusion criteria** If the RCT 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 reassessments (as applicable) raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE trial or if the patient should be withdrawn. The patient may not enter the trial if ANY of the following apply: • Patient meets the withdrawal criteria (including clinically significant abnormal laboratory values), in the investigator's opinion. • Patient met during the RCT the criteria for permanent IMP discontinuation (unless in case of an AE, if AE was not considered related with the IMP; patients that met alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations discontinuation criteria must be excluded). • 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[a] associated with inhibition of ovulation [oral, injectable or implantable[b]] intrauterine devices/hormone-releasing systems[c], bilateral

[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] Contraception methods that are considered to have low user dependency.

	tubal occlusion[a], vasectomized partner[a,a], sexual abstinence[b] during the trial and for 3 months thereafter. • Patient has been previously enrolled and dosed in this trial. • Patient is unwilling to abstain from donation of blood during the trial.
Criteria for Withdrawal	Patient must be withdrawn from the trial if any of the following apply: • Administrative decision by the investigator, GW Research Ltd (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 × upper limit of normal (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** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5) Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant medication with known hepatotoxicity may be**

[a] Provided that partner is the sole sexual partner of the trial patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
[b] 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.

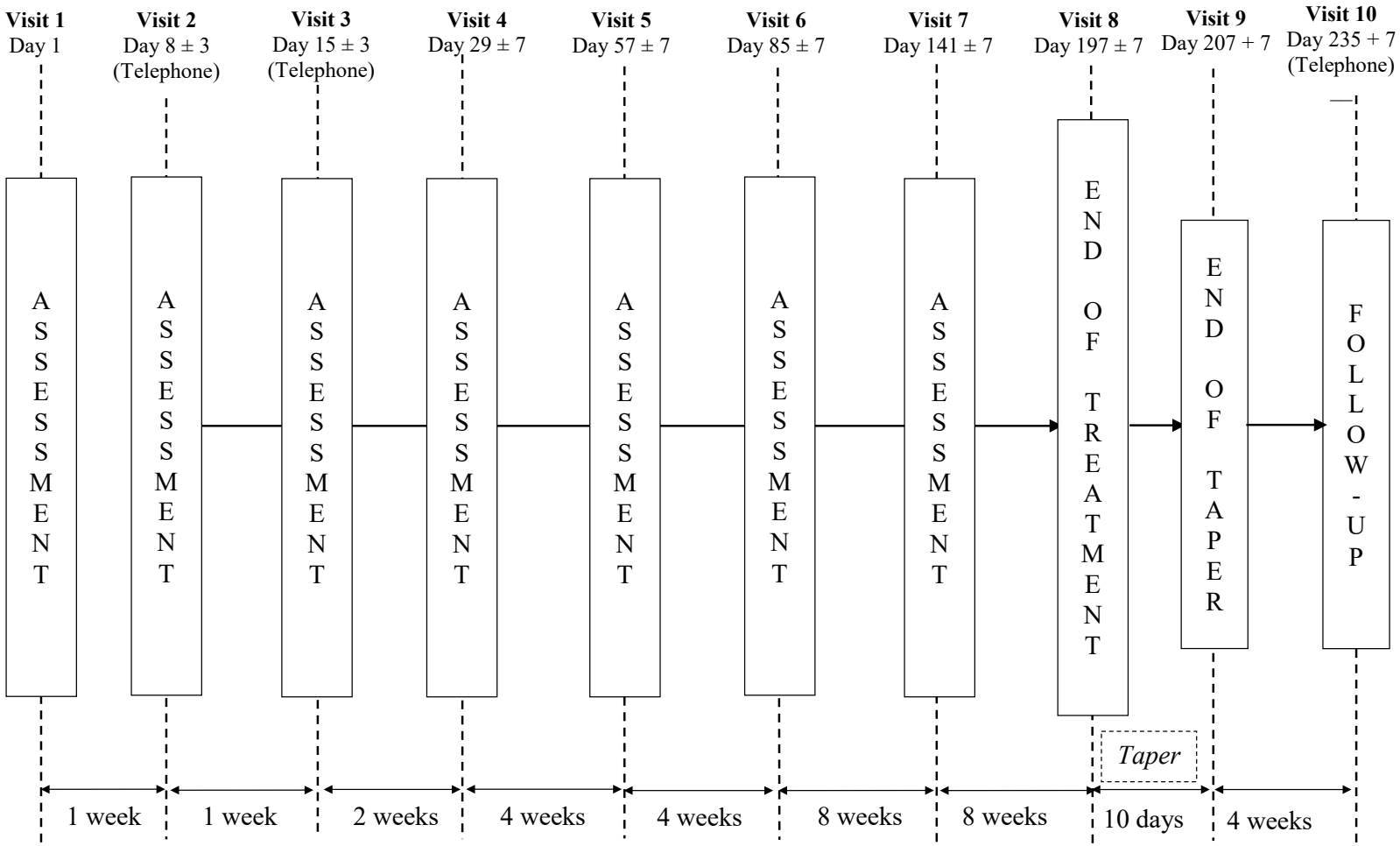
	reduced. Dose adjustments should be discussed with the GW medical monitor. The final decision regarding dose adjustments should be taken by the investigator. • Lost to follow-up. The patient may also be withdrawn from the trial for any of the following: • Patient or caregiver noncompliance • AE (including clinically significant laboratory results) that, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial • Failure to meet the 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 is formulated as follows: (100 mg/mL cannabidiol [CBD] in sesame oil with anhydrous ethanol, sweetener [sucralose], and strawberry flavoring). GWP42003-P is to be taken orally (swallowed) b.i.d. (morning and evening) using the syringe(s) provided. GWP42003-P should be taken at the same time each day consistently 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 GWP42003-P administration in relation to food should be kept consistent throughout the trial. In patients with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should GWP42003-P be administered via G- or NG-tubes made from polyurethane or silicon only The investigator should contact the medical monitor to review IMP administration guidelines if administration via G-or NG-tubes is planned. The volume of GWP42003-P will be determined by patient's weight. All patients will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) for 1 week. After 1 week's treatment, depending on clinical response and tolerability, the patients' dose can be further increased in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.) up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.). Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 28 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability, as deemed necessary by the investigator.

	Patients discontinuing GWP42003-P treatment at the end of the trial or at any other time if they discontinue treatment early should undergo a 10-day taper period (unless continued dosing is inadvisable, e.g., due to an AE).
Control Group	Not applicable.
Procedures	Before the patient undergoes any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent. The nominated caregiver will be asked to consent to complete the QoL questionnaires. In cases where the patient possesses adequate understanding, her assent will be taken, along with parent(s)/legal representative consent. Due to the degree of cognitive impairment in patients with RTT, patients 18 years of age or older 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. Visits 2, 3, and 10 (safety visits) are to be conducted by telephone. **OLE Visit 1 (Day 1):** Every effort should be made for this visit to take place on the same day as the RCT 'End of Treatment' visit. However, patients can still enter the OLE trial up to the point of the RCT follow-up visit (Visit 11). **OLE Visit 1 assessments required for all patients:** • Informed consent and assent • Eligibility check • New medical history • AE review • GWP42003-P dispensing **OLE Visit 1 assessments required if OLE Visit 1 occurs on a different date than RCT Visit 9:** • Vital signs • Suicidality assessment • Hospital Services Use Questionnaire **OLE Visit 1 assessments required if OLE Visit 1 occurs > 28 days after RCT Visit 9:** • Physical examination (including weight) • ECG • Clinical laboratory blood sampling (hematology and biochemistry) • Dipstick urinalysis (where possible)

	OLE assessments on Visit 2 to Visit 10: • Concomitant medications review (Visits 2 to 10). • AE review (Visits 1–10) • Menstruation cycle review (Visit 8) • Physical examination (including weight) (Visits 1, 4, 6, and 8) • Height (Visit 8) • ECG (Visits 1, 4, 6, and 8) • Vital signs (Visits 1, 4, 5, 6, 7, 8, and 9) • Safety laboratory assessments (hematology and biochemistry) (Visits 1, 4, 5, 6, and 8, plus Visit 7 for patients taking concomitant valproic acid as well as for patients whose dose exceeds 15 mg/kg/day) **Note**: Hepatic function monitoring should be carried out within 1 month following increases in GWP42003-P dose or introduction of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change. • Dipstick urinalysis (Visits 1 and 8) • Serum IGF-1 levels (Visits 8) • Serum pregnancy test (if appropriate) (Visit 8) • Questionnaires: o RSBQ (Visits 4, 5, 6, 7, and 8) o CSHQ (Visits 6 and 8) o SF-36 and CHQ-PF50 (Visit 8) o Hospital Services Use Questionnaire (Visits 1, 4, 5, 6, 7, and 8) o Tanner Staging (for patients aged ≥ 7 years or earlier, if clinically indicated by onset of menarche or other signs of precocious puberty) (Visit 8) o Caregiver Assessment of Rett Symptoms, to be completed by the caregiver (Visits 4, 5, 6, 7, and 8) • MBA-9 (Visits 6 and 8) • CGI-S and GCI-I (Visits 4, 5, 6, 7, and 8). • Suicidality assessment (Visits 1, 4, 5, 6, 7, 8, and 9). • GWP42003-P dispensing (Visits 1, 4, 5, 6, 7, and 8) (All caregivers will be provided with a dosing schedule.)

	• GWP42003-P collection and compliance review (Visits 4, 5, 6, 7, 8, and 9) • Caregivers are asked to confirm dosing in the dosing schedule daily throughout the trial; the dosing schedule will be reviewed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.
Statistical Considerations	All data that will be collected during this trial will be summarized across time, using appropriate descriptive statistics. Where baseline data are available from the RCT, changes from baseline will also be presented, where appropriate. There will be no formal hypothesis testing. A detailed statistical analysis plan will be written.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Trial Design and Treatment Schematic



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List of Abbreviations

Abbreviation or special term	Definition or Explanation
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAC	Blood alcohol content
BDNF	Brain-derived neurotrophic factor
BDS	Botanical drug substance
b.i.d.	Twice daily
CB	Cannabinoid
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CGI	Clinical global impressions
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CHQ-PF50	Child Health Questionnaire Parent Form 50
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organization
CSHQ	Children's Sleep Habits Questionnaire
CYP	Cytochrome P450
DS	Dissociative seizures
ECG	12-lead electrocardiogram
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
G	Gastrostomy

Abbreviation or special term	Definition or Explanation
GABA	γ-aminobutryic acid
GPR55	G-protein-coupled receptor 55
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
i.v.	Intravenous
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
NCU	Intensive Care Unit
NG	Nasogastric
NOEL	No observed effect level
OLE	Open-label extension
PCP	Phencyclidine
PCS	physical health composite score
PhS	Standardized Physical Summary
PI	Principal investigator
PRN	Packaging reference number
PsS	Standardized Psychosocial Summary

Abbreviation or special term	Definition or Explanation
PVD	Pharmacovigilance Department
QoL	Quality of life
RCT	Randomized controlled trial
RSBQ	Rett Syndrome Behaviour Questionnaire
RTSM	Randomization and Trial Supply Management
RTT	Rett syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	36-item Short Form
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States

Definition of Terms

Term	Definition
Caregiver	An assigned patient's parent or designated care provider.
Day 1	The day a patient first receives the investigational medicinal product in this trial.
End of treatment	Completion of the treatment period (Visit 8 [Day 197]) or withdrawal.
End of trial	Last patient's last visit/telephone call.
Enrolled patient	Any patient whose parent(s)/legal representative has provided written informed consent for the patient 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	The 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, and the nonitalicized abbreviation *MeCP2* denotes the protein.
Postregression	≥ 6 months since the last loss of hand use or verbal language or gross motor regression.

2 OBJECTIVES

2.1 Primary

Key objective:

- To evaluate the long-term safety of GWP42003-P in patients with Rett syndrome (RTT)

2.2 Secondary

Secondary objectives:

- To evaluate the effect of GWP42003-P in measures of disease severity
    - Rett Syndrome Behaviour Questionnaire (RSBQ)
    - Clinical Global Impressions - Improvement (CGI-I)
    - Clinical Global Impressions - Severity (CGI-S)
    - 9-items Motor Behavioral Assessment (MBA-9)
    - Children's Sleep Habits Questionnaire (CSHQ)

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

3 BACKGROUND AND RATIONALE

3.1 Disease

Rett syndrome is a rare, noninherited, X-linked neurodevelopmental disorder affecting approximately 1 in 10,000 live female births, resulting in abnormal neuronal development and function.[1,2] Rett syndrome 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 to 18 months characterized by a subtle slowing or regression of development. Infants/young children aged 1 to 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]

Rett syndrome is most commonly caused by heterozygous *de novo* mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2).[6] Methyl-CpG-binding protein 2 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% to 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 the 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 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 with 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 the morphology of mitochondria and genes associated with these structures as well as redox balance have been demonstrated in patients with RTT, 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 cannabidiol (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.

Cannabidiol 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 describing the polypharmacology of CBD and its modulation of nonendocannabinoid system targets exist. 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 transient receptor potential cation channel subfamily V member 1 (TRPV1).[30,31,32] The second is inhibition of adenosine reuptake.[33,34,35]

Based on the 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 channels, benzodiazepine, and γ-aminobutryic acid (GABA) binding sites of the $GABA_A$ receptor.

Importantly, CBD does not produce THC-like euphoric effects. Furthermore, 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 the Lennox-Gastaut syndrome or the Dravet syndrome in patients 2 years of age and older.[36]

3.2.1 Nonclinical 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 subchronic 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 and 200 mg/kg i.p. and improved bicuculline-induced memory impairments in neonatal rats at 100 mg/kg i.p.[39] Cannabidiol 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 that 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] 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] Cannabidiol 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 the tissue production of chemical mediators of inflammation, such as tumor necrosis factor alpha and interleukin-2.[49] Cannabidiol (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 premotor region of the zebra finch brain results in a temporary disruption of vocal patterns that recovers over about 7 days and is dependent on the ability of birds to hear as part of sensorimotor learning. Cannabidiol 10 and 100 mg/kg (intramuscular) improved the phonology and syntax of the zebra finch song over the first 6 to 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 Safety Pharmacology

In a rat primary observation Irwin test of central nervous system function, no behavioral, physiological, or body temperature changes were observed following administration of CBD botanical drug substance (BDS) at 10 to 100 mg/kg.[52]

In the cardiovascular system, CBD as CBD BDS inhibited human ether-à-go-go-related gene tail current in a concentration-dependent manner[52] (no-observed-effect level [NOEL], 43 ng/mL) and had no effect on Purkinje fiber action potentials or QT interval changes[52] (NOEL, 22 ng/ml). Changes in cardiovascular parameters (heart rate, blood pressure, and electrocardiogram [ECG]) in the conscious dog were not considered to be adverse.[52]

In the respiratory system, CBD as CBD BDS had no biologically significant effect on respiratory parameters in conscious rats.[52]

3.2.1.3 Mechanism of Action

Cannabidiol 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 abnormal liver function tests 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, in addition to treating seizures, CBD may have beneficial effects on cognition and behavior as well as on patient QOL.[53,54]

This open-label extension (OLE) trial will evaluate the long-term safety of GWP42003-P in patients with RTT who carry a *MECP2* gene mutation.

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.

3.3.1.1 Choice of Primary Endpoints

Safety, selected as the primary endpoint, will be assessed by evaluating changes in AEs, clinical laboratory parameters, vital signs, physical examination procedures, 12-lead ECGs, effects on menstruation cycles, and suicidality. Change in growth and development will also be measured by height, weight, serum IGF-1 levels, and Tanner Staging (for patients aged ≥ 7 years or earlier, if clinically indicated by the onset of menarche or other signs of precocious puberty).

3.3.1.2 Choice of Secondary Endpoints

Secondary endpoints, scales, and assessments were selected to evaluate a wide range of symptoms observed in patients with RTT:

- RSBQ. This caregiver-completed assessment has been specifically developed for use in patients with RTT.[55] The RSBQ total score is used as a global measure to assess the patient's overall condition, whereas subscales of the RSBQ allow evaluation of more-specific domains (behavior and emotion, motor function, and breathing abnormalities).
- CGI-I and CGI-S. CGI-I was selected as a clinician-rated assessment that has been used extensively in neuropsychiatric disorders in both clinical practice and clinical trial settings[56,57,58] and reported to have successfully been implemented in the RTT patient population.[59] CGI-I is a global measure used to assess the

patient's overall condition. CGI-I assesses change in symptoms relative to the baseline CGI-S.

- MBA-9. This scale was selected as it provides a clinician assessment of a set of motor and behavior items of the original MBA[60,61] that are deemed amenable to change.
- CSHQ. This questionnaire was selected as sleep problems are reported for the majority of patients with RTT. CSHQ has been used to characterize sleep in other developmental disability populations (e.g., autism spectrum disorder[62]) and in a sample of patients with RTT.[63]

3.3.1.3 Choice of Exploratory Endpoints

The required constant care and supervision of patients with RTT places a significant burden on the 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 be assessed using CHQ-PF50. Information on health utilization will be assessed using the Hospital Services Use Questionnaire, which aims to analyze the frequency of patient hospitalizations and hospital visits.

The Caregiver Assessment of Rett Symptoms has been specifically developed for the proposed clinical trial with the intent of obtaining 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.

3.3.2 Choice of Dosing Regimen

Given that the objective of the trial is to monitor long-term safety, a flexible dose escalation based on efficacy and tolerability, as judged by the investigator, will be used. The maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) is set in accordance with the maximum dose per the United States (US) prescribing information for CBD.[64]

The GWP42003-P solution contains 7.9% w/v anhydrous ethanol, which is required as sucralose is not soluble in sesame oil. A dose of 15 mg/kg/day (administered as 7.5 mg/kg twice daily [b.i.d.]) in a 10 kg child will result in a blood alcohol content (BAC) of 0.0098 g/L, which equates to an ethanol ingestion of 5.93 mg/kg. Both these amounts are well under the threshold for a BAC of 0.125 g/L and an ethanol ingestion of 75 mg/kg for patients 6 years and older and also under the maximum BAC level of

0.01 g/L and ethanol ingestion of 6 mg/kg for children less than <6 years old.[65] At the highest recommended therapeutic dose of 20 mg/kg/day (administered as 10 mg/kg b.i.d.), a single dose of 10 mg/kg cannabidiol oral solution (CBD-OS) in a 10 kg child theoretically results in a BAC of 0.013 g/L and an ethanol ingestion of 7.9 mg/kg, slightly above the recommended threshold for BAC of 0.01 g/L for children less than 6 years old. In light of the wide safety margins observed in toxicology studies and taking the severity of the condition into account, this theoretical risk is judged to be acceptable.

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 Lennox-Gestaut Syndrome (LGS) and dissosicated seziures (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 level (maximum dose of 20 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

There will be no formal hypothesis testing in this trial.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This is a 28-week, multicenter, OLE trial for patients with RTT who have completed the randomized, double blind, placebo-controlled trial (GWND18064).

Entry to this OLE trial is recommended to be on the same day as Visit 9 of the randomized controlled trial (RCT); however, patients may enter the OLE up to the RCT follow-up visit (Visit 11).

All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1. Patients will be observed, and after 1 week, the dose may further be escalated, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.) in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.).

Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 28 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability, as deemed necessary by the investigator, until the optimal dose is found. Patients whose dose has been decreased can have their dose increased again if tolerability improves.

At the end of treatment (Visit 8 [Day 197]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period.

If a patient permanently discontinues treatment at any point during the trial, GWP42003-P should be gradually reduced over 10 days (unless inadvisable due to an AE). The patient should attend a withdrawal visit (Visit 8) as soon as possible after the decision is made to permanently discontinue GWP42003-P. If applicable, the patient will taper GWP42003-P, 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

Safety:

The long-term safety profile of GWP42003-P will be assessed by evaluating changes in the following, relative to the prerandomization baseline of the RCT:

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

4.1.2 Secondary Endpoints

4.1.2.1 Secondary endpoints:

The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

- RSBQ
- CGI-I
- CGI-S
- MBA-9
- CSHQ

4.1.2.2 Exploratory endpoints:

The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

- SF-36
- CHQ-PF50

- Hospital Services Use Questionnaire
- Caregiver Assessment of Rett Symptoms

4.2 Number of Trial Centers

Approximately 25 trial centers are expected to participate in this trial. The number of centers may be reduced or increased depending on recruitment performance.

4.3 Number of Patients

All patients with RTT who complete the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and meet the eligibility criteria will transition to 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1 of the OLE. Approximately 252 patients will be enrolled.

5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate pharmacy manual for more detailed information on GWP42003-P.

5.1 GWP42003-P Oral Solution

The 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	Makes up to 1 mL

5.2 Packaging, Storage, and Drug Accountability

5.2.1 Packaging and Labeling

GWP42003-P will be manufactured, packaged, labeled, and/or distributed by GW or delegated contractors. GWP42003-P will be presented in 100 mL amber glass bottles with child-resistant screw caps and packed in cartons. GWP42003-P will be dispensed at each relevant visit. A unique identification number will be used to identify each carton and the GWP42003-P 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 GWP42003-P 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")
- 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 for use and the name, address, and telephone number of the investigator (or the 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.

5.2.2 Storage

GWP42003-P 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.

GWP42003-P must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve the storage location and facilities. Temperature records of the clinical center storage location must be maintained (recording a minimum of Monday to Friday, excluding public holidays) from the date of receipt of the first shipment until the end-of-trial dispensing period at each center. These records must contain at least the minimum and maximum daily temperatures and must be made available to the appropriate GW personnel for review throughout the trial. Temperature during the transit of GWP42003-P to the center must be checked on receipt and compliance/noncompliance to the minimum and maximum recorded.

Should storage conditions deviate from these specified requirements, the GW trial monitor must be contacted immediately to confirm if GWP42003-P remains suitable for use. GWP42003-P must be placed under quarantine until written confirmation is received that GWP42003-P is suitable for use.

Caregivers will be provided with instructions regarding home storage requirements for GWP42003-P.

5.2.3 Supply and Return of Investigational Medicinal Product

At trial initiation and as needed thereafter, GWP42003-P will be shipped to the identified responsible person, such as the pharmacist, at the investigator’s center, who will check

the amount received against the shipment request and the condition of the drug (i.e., integrity, physical appearance, and temperature during transit). Details of GWP42003-P received will be recorded in the GWP42003-P accountability record (see Section 5.2.4). The center will acknowledge the GWP42003-P receipt and will complete any receipt forms required. GWP42003-P 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 the GW/depot or destroyed at a GW-approved center if agreed in writing by the trial monitor.

5.2.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused GWP42003-P. A drug accountability record for GWP42003-P must be kept current and should contain the following:

- Trial code
- PRN, treatment number, date of receipt, and quantity of GWP42003-P received
- Patient's trial identification and/or treatment number
- Date and quantity of GWP42003-P dispensed
- The initials of the dispensing/dosing party
- Date and quantity of GWP42003-P returned to the investigator
- GWP42003-P expiry dates

GWP42003-P will be dispensed at Visits 1, 4, 5, 6, 7, and 8 (at Visit 8 for patients entering the 10-day taper period). Caregivers will be asked to return all GWP42003-P (used and unused) at each relevant visit (Visits 4, 5, 6, 7, 8, and 9). The center will check the returned GWP42003-P against the expected usage. 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 GWP42003-P.

A record of returned GWP42003-P must be completed and included in the shipment of used and unused GWP42003-P 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 GWP42003-P.

5.2.5 Post-trial Provision

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 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, and 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 has completed all scheduled visits of the treatment phase of the RCT, GWND18064, and has transitioned to OLE by the point of RCT follow-up (Visit 11).

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

6.1.3 Patient and her 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).

6.1.4 Patient must have the ability to swallow the IMP provided as a liquid solution or the ability for the IMP to be delivered via gastrostomy (G) or nasogastric (NG) feeding tube (only G- or NG-tubes made from polyurethane or silicon are allowed).

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

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

6.2 Exclusion Criteria

If the RCT 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 reassessments (as applicable) raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE trial or if the patient should be withdrawn. The patient may not enter the trial if ANY of the following apply:

6.2.1 Patient meets the withdrawal criteria (including clinically significant abnormal laboratory values) in the investigator's opinion (refer to Section 10).

6.2.2 Patient met during the RCT the criteria for permanent IMP discontinuation (unless in case of an AE, if AE was not considered related with the IMP; patients that met ALT/AST elevations discontinuation criteria must be excluded).

6.2.3 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[a] 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.

6.2.4 Patient has been previously enrolled and dosed in this trial.

6.2.5 Patient is unwilling to abstain from donation of blood 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 trial 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 center'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). The nominated caregiver will be asked to consent to complete the QoL questionnaires. 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 patients with RTT, patients 18 years of age or older 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

As this is a single-group OLE trial, all patients will receive GWP42003-P. Patients will not be informed of their allocated treatment group in the RCT. Patients will retain the patient number allocated to them during the RCT.

7.2 Randomization

This is an OLE of the GWND18064 trial. Randomization will not occur. At the start of the GWND18064 trial, enrolled patients were allocated a unique patient number. Patients will retain this number during the OLE trial.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration, and Schedule

GWP42003-P will be presented as an oral solution containing 100 mg/mL CBD. For details regarding IMP formulations, see Section 5.

Before the patient undergoes any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent or assent (see Section 9.2.1 and Section 15.2). The nominated caregiver will be asked to consent to complete the QoL questionnaires.

8.1.1 Dose Administration

GWP42003-P will be administered orally (swallowed) b.i.d. (morning and evening) using the syringe(s) provided. GWP42003-P may be taken with other concomitant medications, as directed by the investigator. In patients with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should GWP42003-P be administered via G- or NG-tubes made from polyurethane or silicon only. GWP42003-P 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 GWP42003-P administration in relation to food should be kept consistent throughout the trial The investigator should contact the medical monitor to review IMP administration guidelines if administration via G-or NG-tubes is planned.

8.1.2 Dose Escalation and Dose Adjustments

The daily volumes of the GWP42003-P 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 during the GWND18064 trial.

All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1. Patients will be observed, and after 1 week the dose may escalate further, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.) in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.).

Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 28 weeks), with the option for doses to be

decreased or increased if deemed necessary by the investigator, to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.).

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, until the event has resolved. 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 quicker 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 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 be withdrawn from treatment, unless a lower dose level is agreed in discussion with the medical monitor and can be accurately measured (minimum single-dose volume of 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.

Hepatic function monitoring should be carried out within 1 month following increases in GWP42003-P dose or introduction or dose increases of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change.

Transaminase elevations should be medically managed by the investigator either by reducing the GWP42003-P dose as described above or by reducing concomitant medications judged to be causing the elevation (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.

At the end of treatment (Visit 8 [Day 197]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period.

Patients discontinuing GWP42003-P treatment at any other time should undergo a 10-day taper period (unless continued dosing is inadvisable, e.g., due to an AE). The decision on whether to taper GWP42003-P 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 antiepileptic drugs [AEDs]) administered concurrently, and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. 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. Cannabidiol has the potential to induce the expression of hepatic CYP 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 [52]. Any concerns regarding potential interactions with concomitant medications can be discussed with the trial medical monitor(s).

Changes in concomitant medications are allowed, but increases in dose of medications that affect liver function should be discussed with the medical monitor. Introduction of new medications is allowed, but introduction of new psychotropic and/or central acting agents intended as long-term treatment requires prior discussion with the medical monitor.

The use of rescue medication is allowed, when necessary (i.e., AED for transient exacerbation of seizures). Any medication, other than GWP42003-P, taken during the trial must be recorded on the electronic case report form (eCRF).

8.3 Prohibited Therapy During the Trial Period

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

- St John's wort
- Recreational or medicinal cannabis or cannabinoid-based medications (including Sativex or CBD oral solutions)
- Any other IMP

- Felbamate that has been taken for less than 1 year

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

GWP42003-P is dispensed to the patient at Visits 1, 4, 5, 6, 7, and 8 (at Visit 8 for patients entering the 10-day taper period). Further guidance on GWP42003-P dispensing will be provided in a separate pharmacy manual.

Caregivers will be asked to confirm dosing in the dosing schedule daily. Caregivers should return all GWP42003-P (used and unused) at each of Visits 4, 5, 6, 7, 8, and 9. The returned medication will be checked against the expected usage, and any discrepancies will be 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 GWP42003-P administration in relation to meals.

The investigator must inform GW promptly of all missing or unaccountable GWP42003-P.

Records of GWP42003-P accountability will be maintained according to Section 5.2.4.

8.5 Access to Blinded Treatment Assignment

This is not applicable.

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 center, 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 patients with RTT, patients 18 years of age or older 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 ample time to discuss the trial with the investigator, nurse, relatives, or caregiver, as wished, patients for whom the parent(s)/legal representatives provide written informed consent, and in cases where the patient possesses adequate understanding, patients who give their assent will be screened for entry into the trial. The nominated caregiver will be asked to consent to complete the QoL questionnaires.

Each visit should be scheduled to take place at approximately the same time of day (i.e., morning or afternoon), whenever possible. Visits 2, 3, and 10 are to be conducted by telephone.

The investigator should use his/her judgment and knowledge of the patient to determine when to best 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 1)

Every effort should be made for this visit to take place on the same day as the RCT 'End of Treatment' visit. However, patients can still enter the OLE trial up to the point of the RCT follow-up (Visit 11).

OLE Visit 1 Assessments required for all patients:

- Informed consent and assent
- Eligibility check
- New medical history
- AE review
- GWP42003-P dispensing

OLE Visit 1 assessments required if OLE Visit 1 occurs on a different date than RCT Visit 9:

- Vital signs
- Hospital Services Use Questionnaire
- Suicidality assessment

OLE Visit 1 assessments required if OLE Visit 1 occurs > 28 days after RCT Visit 9:

- Physical examination (including weight)
- ECG
- Clinical laboratory blood sampling (hematology and biochemistry)
- Dipstick urinalysis (where possible)

Patients who satisfy all of the inclusion criteria and none of the exclusion criteria specified in Section 6 will begin the treatment period.

Patients will be dispensed sufficient GWP42003-P and a dosing schedule for the following 3 weeks. Caregivers will be instructed on how to use the dosing schedule and how to measure and administer the medication. At the next visit, all GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made.

Based on Section 9.1.3, assessments may be performed at unscheduled visits in the event of a safety concern, as deemed necessary by the investigator.

The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient will fail screening.

9.1.1.2 Visit 4 (Day 29 [± 7])

This visit will occur 28 days after Visit 1. A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Physical examination (including body weight) and ECG assessments will be performed. Vital sign assessments will be performed.

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

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 4 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.3 Visit 5 (Day 57 [± 7])

This visit will occur 28 days after Visit 4. A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

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

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be conducted via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 4 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.4 Visit 6 (Day 85 [± 7])

This visit will occur 28 days after Visit 5. A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Physical examination (including body weight) and ECG assessments will be performed. Vital sign assessments will be performed.

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

The caregiver will complete the RSBQ, CSHQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 8 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.5 Visit 7 (Day 141 [± 7])

This visit will occur 56 days after Visit 6. A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology and biochemistry for patients taking concomitant valproic acid, as well as for patients whose dose exceeds 15 mg/kg/day.

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 8 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.6 Visit 8 (Day 197 [± 7], End of Treatment/Withdrawal Visit)

This visit will occur 56 days after Visit 7 or earlier, if the patient withdraws from the trial. A visit window of ± 7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible.

The patient should attend a withdrawal visit (Visit 8) as soon as possible after the decision is made to permanently discontinue GWP42003-P.

Information regarding changes to concomitant medications, AEs, and menstruation cycle (where applicable) will be reviewed. Physical examination (including body weight), height, and ECG assessments will be performed. Vital sign assessments will be performed.

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

- Hematology

- Biochemistry
- Dipstick urinalysis (provided urine can be obtained)
- Pregnancy test using a serum sample (as appropriate [Section 9.2.2])
- Determination of serum IGF-1 levels (Section 9.2.9)

The caregiver will complete the RSBQ, CSHQ, SF-36, CHQ-PF50, and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

The Tanner Stage will be recorded (where appropriate).

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

The investigator must assess adherence to the dosing schedule.

Patients will receive sufficient GWP42003-P for the 10-day taper period, as applicable. Dosing schedules will be provided accordingly. For patients who discontinue GWP42003-P early, the taper period should start at the time the decision is made to discontinue, unless tapering the dose of GWP42003-P is inadvisable (e.g., continued dosing is not possible due to an AE). For patients who discontinue GWP42003-P early, the decision on whether or not to taper GWP42003-P will be left to the investigator's clinical judgment.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.7 Visit 9 (Day 207 [+ 7], End of Taper)

This visit will occur 10 days after the end of treatment (Visit 8). A visit window of + 7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible. This visit marks the end of the taper period.

Information regarding changes to concomitant medications and AEs will be reviewed. Vital sign assessments will be performed. The investigator must assess adherence to the dosing schedule.

The investigator will complete the suicidality assessment.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made.

9.1.2 Telephone Visits

9.1.2.1 Visits 2 (Day 8 [± 3]) and 3 (Day 15 [± 3])

Visits 2 and 3 will occur 7 and 14 days after randomization (Visit 1), respectively.

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.

Telephone visits will be conducted by a center nurse (the center investigator only needs to be involved if necessary, e.g., if any concerns are raised during the call). Information regarding changes to concomitant medications and AEs will be reviewed. The center (the nurse and, if necessary, the investigator) must assess adherence to the dosing schedule.

9.1.2.2 Visit 10 (Day 235+7, End of Trial)

This visit will occur 28 days after Visit 9 (or Visit 8 if the patient did not taper). A visit window of + 7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible. This visit marks the end of the trial.

Visit 10 constitutes the last scheduled safety follow-up. The purpose of the visit is to ascertain the status of AEs continuing after the cessation of GWP42003-P or any new AEs commencing after discontinuation. All causally related AEs that result in a patient's early termination from the trial or are present at the end of the trial should be followed up until a satisfactory resolution occurs, i.e., until the AE resolves or is considered clinically insignificant, or until the investigator is satisfied that the AE is not related to GWP42003-P and needs no further investigation. Information regarding changes to concomitant medications will be reviewed.

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 are recorded for the trial. The nominated caregiver will be asked to consent to complete the QoL questionnaires.

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 signing, 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. Patients who cannot write 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. If a minor who is capable of forming an opinion and assessing the information provided makes an explicit wish to refuse participation in or to be withdrawn from the clinical trial at any time, this wish must be considered by the investigator. Given the severity of the condition, it is expected that the majority of patients will have an insufficient level of understanding of what is proposed, in which case solely parent(s)/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.

GW Research Ltd requires a physician to be present for consent and assent and to also sign the consent and assent forms. The original signed informed consent/assent forms should be retained, and a copy should be 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. Contraception requirements must be assessed by the investigator on a case-by-case basis. Where applicable, 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 per the definition of woman of childbearing 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.[66] Such methods include:

- 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[b].

[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.

- Vasectomized partner[a],[b] provided that partner is the sole sexual partner of the patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Abstinence, as referenced above, is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.[67]

Serum pregnancy tests will be performed for any patients of childbearing potential at RCT Visit 9 and OLE Visit 8; 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 Concomitant Medication

Details of all current medications will be recorded during the RCT. Any changes in concomitant medication during the trial must be recorded on the eCRF at trial visits. Changes in concomitant medications are allowed, but increases in the dose of medications that affect liver function should be discussed with the medical monitor. Introduction of new medications is allowed, but introduction of new psychotropic and/or central acting agents intended as long-term treatment requires prior discussion with the medical monitor.

9.2.4 New Medical History

Any changes to medical history since the RCT will be recorded.

9.2.5 Menstruation

Any changes in menstrual cycles since the RCT will be captured at the end-of-treatment visit.

[a] Contraception methods that are considered to have low user dependency.
[b] Provided that partner is the sole sexual partner of the trial patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.

9.2.6 Physical Examination

Physical examinations will include body weight measurements. At Visit 8, height will be collected. If an accurate measurement of height is not possible, an estimate should be provided.

9.2.7 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 centers, 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 center in the case of clinically relevant abnormalities. The central reader will provide measurements and an overall assessment to support the investigator in his/her 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.

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 Clinical Laboratory Sampling

The investigator should use his/her judgment and knowledge of the patient to determine when to best 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.

Laboratory tests will include hematology, biochemistry, and urinalysis (provided urine can be obtained), IGF-1 levels, and a serum pregnancy test (if appropriate). Analysis of all clinical blood samples and pregnancy tests will be conducted at a central clinical laboratory.

Urine samples for biochemistry will be analyzed at the trial center by use of a dipstick, with any relevant findings being sent for further urinalysis at the central laboratory

(urinalysis, microscopy, culture, and sensitivity, as applicable). In cases where urine samples cannot be analyzed at the center due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis. Urine sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

The investigator and trial monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the trial and a statement of accreditation (or similar) for the laboratory.

The investigator should be aware of blood sampling volume restrictions, particularly for patients with low weight, and if additional monitoring is required (maximum total daily volume of 0.85mL/kg of body weight[68,69] maximum 4-week period volume of 2.55 mL/kg of body weight, and maximum 8-week period volume of 50 mL).

Clinical laboratory sample parameters are detailed in Table 9.2.9-1.

Table 9.2.9-1 Biochemistry, Hematology, and Urinalysis

Biochemistry (Serum)[1]	Hematology (Whole Blood)[1]	Urinalysis (Urine)[2]	Pregnancy Test (Serum)[1]
Alanine aminotransferase[3]	Hematocrit	Blood	Serum
Albumin[3]	Hemoglobin	Glucose	
Alkaline phosphatase[3]	Mean cell volume	Nitrites	
Aspartate aminotransferase[3]	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[3]		Specific gravity	
Glucose		Urobilinogen	
Human chorionic gonadotropin			
HDL-cholesterol			
IGF-1[4]			
Potassium			
Prolactin			
Prothrombin time and INR (plasma)[5]			
Sodium			
Total bilirubin[3]			
Total protein[3]			
Triglycerides			

Table 9.2.9-1	**Biochemistry, Hematology, and Urinalysis**		
Biochemistry (Serum)[1]	**Hematology (Whole Blood)[1]**	**Urinalysis (Urine)[2]**	**Pregnancy Test (Serum)[1]**
Urea (blood urea nitrogen)			

[1] Analyzed at a central laboratory.
[2] Analyzed at the trial center by use of a dipstick (if allowed per local regulations).
[3] Hepatic function monitoring panel.
[4] Visits 1 and 8 only; IGF-1 laboratory results to remain blinded throughout the trial.
[5] To be requested if ALT or AST > 3 × ULN after Visit 1 (to evaluate IMP discontinuation criteria)

HDL = high-density lipoprotein; INR = international normalized ratio.

Investigators at trial centers will be notified of laboratory test results. All laboratory results will be reviewed, and the reports will be signed and dated by the investigator. Any results considered to be of clinical significance must be addressed and followed up, as clinically appropriate. In cases where after Visit 1, ALT or AST are > 3 × ULN, international normalized ratio (INR) testing must be requested. If only the hepatic function monitoring panel was requested and ALT or AST > 3 × ULN, both INR and hematology panel (eosinophils) must be requested. 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 the investigator is satisfied that the abnormality is not related to GWP42003-P and needs no further investigation.

Additional samples may be collected, as needed, e.g., for monitoring of hepatic function (hepatic function monitoring panel) (see Section 8.1.2 and Table 9.2.9-1).

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 will be 2.55 mL/kg of body weight and will not exceed a total of 50 mL within any 8 week period[68,69] 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 the patient suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.10 Randomization and Trial Supply Management System

The RTSM system will be used to manage the IMP supply. 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 dispensing information (Visits 1, 4, 5, 6, 7, and 8).
- Provide completion/taper/early termination information (Visit 8/the withdrawal visit, or Visit 9, as applicable).

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

9.2.11 Dosing Schedule/Compliance Review

Caregivers will be provided with a dosing schedule. Caregivers will be asked to confirm dosing in the dosing schedule daily from Visit 1 through Visit 9. 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 GWP42003-P administration in relation to meals.

9.2.12 Questionnaires and Assessments Completed at Scheduled Visits

Caregiver questionnaires should be completed by the identified caregiver, nominated at Visit 1 of the RCT. The same person should answer/complete the questionnaires/assessments in order to maintain consistency. Questionnaires should be completed during the scheduled visits. The nominated caregiver must have given consent to complete the QoL questionnaires prior to the completion of the questionnaires.

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.

9.2.12.1 Rett Syndrome Behaviour 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 3.4). Each item is rated on a 3-point numerical scale; 0 indicates an item that is 'not true as far as you know,' 1 indicates an item is 'somewhat or sometimes true,' and 2 indicates 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.[55]

9.2.12.2 Children's Sleep Habit Questionnaire

This is a caregiver-completed sleep screening instrument designed for school-aged children.[70] CSHQ includes 33 items within 8 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; and 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; and "Rarely" if it occurs never or 1 time in a week. Some items should be reversed in scoring, so a higher score reflects more-disturbed sleep behavior (see Appendix 3.9). The caregiver is also asked to indicate for each item if the sleep item is a problem.

9.2.12.3 36-Item Short Form

Caregivers' health-related QoL will be assessed using the SF-36 questionnaire (see Appendix 3.5). SF-36 measures 8 domains of health-related QoL 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 SF-36 are based on a 0-to-100 scale; 0 represents the lowest possible score, and 100 represents the highest possible score, with a higher score indicating a better health state.

9.2.12.4 Child Health Questionnaire Parent Form 50

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 the 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 mutlidimensional 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; a higher score indicates better QoL.

9.2.12.5 Hospital Services Use Questionnaire

This is a health utilization questionnaire designed to analyze the frequency of patient hospitalizations and hospital visits (see Appendix 3.7). Hospitalizations will also be recorded in the patient's CRF and through the serious adverse event (SAE) reporting process. The questionnaire will be completed via caregiver interview.

9.2.12.6 Caregiver Assessment of Rett Symptoms

Caregivers will be asked to rate, on a 0-to-10 numerical rating scale, the patient's condition and performance/severity of symptoms in terms of breathing, hand stereotypies, interactions, problem behaviors, constipation, seizures, and sleep (see Appendix 3.10). This assessment corresponds to the symptom diary completed weekly in the RCT but will be completed at trial visits only in the OLE.

9.2.12.7 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 3.1). The severity of the 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; or 4 = very severe or constant. The total maximum score is 36, and higher total scores represent greater severity.[61] The MBA-9 items address the core symptoms of RTT.

9.2.12.8 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.[56]

The CGI questionnaire is split into 2 scales: the CGI-S scale and the CGI-I scale (see Appendix 3.2 and Appendix 3.3, respectively). 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 the total clinical experience, a patient will be assessed on the severity of illness at the time of rating. This is rated as follows: 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 scale, 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 (RCT Visit 2). This is rated as follows: 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 predefined set of anchors developed specifically for the use of CGI in RTT.[59]

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

9.2.12.9 Suicidality Assessment

The profound cognitive impairment of patients with RTT 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 3.8).

9.2.13 Tanner Staging

The pubic hair growth and breast development of all adolescent patients (i.e., ≥ 7 years of age[71] at the time of signing the ICF or earlier, if clinically indicated by the onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging (see Appendix 3.6).[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.

9.2.14 Investigational Medicinal Product Accountability

Records of GWP42003-P accountability will be maintained according to Section 5.2.4.

GWP42003-P will be dispensed at each of the following visits:

- Visit 1 (Day 1)
- Visit 4 (Day 29)
- Visit 5 (Day 57)
- Visit 6 (Day 85)
- Visit 7 (Day 141)
- Visit 8 (Day 197)

Caregivers will be asked to return all GWP42003-P (used and unused) at each relevant visit (Visits 4, 5, 6, 7, 8, and 9). The center will check the returned GWP42003-P against the expected usage. Any discrepancies will be discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents.

9.2.15 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 10), whether or not attributed to GWP42003-P 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 a 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 that meets SAE criteria should still be reported as a SAE.

Serious adverse events 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.

10 IMP WITHDRAWAL

In accordance with the Declaration of Helsinki[73] the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2)[74] the FDA regulations relating to GCP and clinical trials[75,76,77] the EU Clinical Trials Directive[78] the EU GCP Directive[79] 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 her future medical care by the physician or at the institution.

The patient must be withdrawn permanently discontinued from the trial 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** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5)

  Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where the transaminase elevation withdrawal 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 withdrawn permanently from the trial for any of the following:

- Patient or caregiver noncompliance
- AE (including clinically significant laboratory result) that, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial
- Failure to meet the eligibility criteria
- Any evidence of the use of drugs of abuse or drug diversion
- Suicidal ideation or behavior during the treatment period

The patient should attend a withdrawal visit (Visit 8) as soon as possible after the decision is made to permanently discontinue GWP42003-P. Patients who discontinue the 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 per protocol. Patients who discontinue the IMP and complete tapering of the 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. All assessments required at the withdrawal visit should be conducted, if possible. If the tapered dose is administered, patients should return for Visit 9, if possible. Wherever possible, a safety follow-up visit should take place 28 days from the date of last dose of IMP. 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 follows:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant) or diagnosis or worsening of a pre-existing condition that occurs at any point up to the post-treatment, final safety follow-up visit (Visit 10), which may or may not be considered to be related to GWP42003-P. 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 pretrial existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization that prolongs the scheduled hospital stay, in which case it would be considered an SAE (refer to Section 12.2).

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

12.1.2 Investigator

The term "investigator" refers to the trial principal investigator (PI) or a formally delegated trial physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur, which if suspected to be GWP42003-P-related, might be significant enough to lead to important changes in the way GWP42003-P 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., an SAE, when the event falls into one of the following criteria:

- Results in death
- Is life threatening*

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

* The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that, 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 Research Ltd 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 that occur up to the last formal follow-up observational period (Visit 10). If the investigator subsequently becomes aware of any deaths or a new GWP42003-P-related SAE after the last formal follow-up period of the trial, these should still be reported to GW PVD.

Any other problem discovered after Visit 10 that 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 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 the final trial data lock. GW Research Ltd PVD may request safety follow-up information after the final trial visit in order to investigate a potential safety issue.

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

12.4 Pregnancy

Any patient who has become pregnant while receiving GWP42003-P or within 90 days of the last dose of GWP42003-P must be reported to 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 awareness. 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 GWP42003-P. However, if the investigator becomes aware of a new pregnancy outside this time limit, then he/she should report it as above. 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 GWP42003-P 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 GWP42003-P:

"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 the IMP (pretreatment) should be considered as not causally related. Where a pretreatment event worsens in severity following the first dose of the 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, especially SAEs, it is important that the investigator assess not only the possible role of GWP42003-P but also other potential contributing factors. Factors for consideration of the underlying cause may include the following:

- 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 10), whether or not attributed to GWP42003-P 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 a change in the pattern or severity of seizures, should be documented in the CRF if deemed to meet the definition of an AE, in the investigator's opinion.

Any AE that meets the SAE criteria should still be reported as an 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 the 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., the month and year or, in exceptional circumstances, just the year). When the actual start date becomes known, the eCRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one 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 the AE start and stop dates relating to the overall event duration, regardless of severity.

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

E) Causality

See Section 12.5.

F) Action Taken with IMP

This question refers to the action taken with GWP42003-P due to an AE. The action with GWP42003-P must be classified as follows:

- None
- Dose reduced temporarily
- Dose reduced
- IMP interrupted
- IMP stopped

12.7 Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur post Visit 10, after the trial.

Adverse events considered related to GWP42003-P 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 she perceives 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 centers are required to submit to GW PVD the laboratory results for any patient after randomization who 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 GW PVD via e-mail (see Appendix 2.2) within 24 hours of becoming aware of the results. In addition, a copy of the patient's baseline laboratory results with all reports should be sent to 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 center as soon as possible (within 24 to 48 hours of notice of abnormal results) for a repeat assessment of ALT, AST, TBL, alkaline phosphatase, gamma-glutamyl transferase levels, eosinophils as well as for testing INR (prothrombin time), detailed history; and physical examination. Patients should be followed 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 be withdrawn from the trial.

Elevations in ALT or AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury but will be followed as detailed above, within 72 hours' notice of abnormal results. In cases where after Visit 1, ALT or AST are > 3 × ULN, INR testing must be requested. If only the hepatic function monitoring panel was requested and ALT or AST > 3 × ULN, both INR and hematology panel (eosinophils) must be requested. If the patient cannot return to the investigational center, repeat assessments may be done at a local laboratory, and the results should be 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[78] relevant parts of the FDA Code of Federal Regulations[80] and any national regulations, GW will inform the 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[52]: A compilation of the clinical and nonclinical safety data available on the IMP that are 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 ethics committees that have approved the trial, and the investigators. As required, the investigators should notify their regional IRBs/IECs of SAEs or SUSARs occurring at their center and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the 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[75] 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, were 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[80] states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multicenter trial may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW Research Ltd will inform the 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 the 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, as well as relevant updates between the period from ethical approval and the final database lock.

13 STATISTICAL CONSIDERATIONS

Further details of the proposed statistical analysis will be documented in a statistical analysis plan (SAP). Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power, and Significance Levels

There is no formal sample size calculation for this trial. All patients with RTT who completed the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and who meet eligibility criteria can be included in this trial.

Approximately 252 patients will be enrolled.

13.2 Interim Analysis

No formal interim analysis will be conducted.

13.3 Analysis Sets

For this trial there will be 1 analysis set:

Safety Analysis Set

- All patients who receive at least 1 dose of GWP42003-P in the trial will be included. Only patients for whom it has been confirmed that they did not take any GWP42003-P will be excluded from this safety analysis set. This analysis set will be used to report the safety data.

13.3.1 Protocol Deviations

Protocol deviations will be listed and reasons for exclusion from the analysis population will be summarized.

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of nonmissing values (n), mean, standard deviation, 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 in the RCT.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, randomized, prematurely terminated IMP, etc.) will be accounted for in the enrollment 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 Clinical Severity Scale score and *MECP2* mutation (confirmation and definition) will be summarized.

13.5.3 Concomitant Medication

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

13.6 Endpoints and Statistical Methods

The primary safety endpoint will be analyzed as detailed in Section 13.6.2. Secondary endpoints will be analyzed as detailed in Section 13.6.3. Exploratory endpoints will be analyzed as detailed in Section 13.6.4.

13.6.1 Evaluable Period

The start of the evaluable period of the OLE trial (Day 1) is defined as the date the patient took his/her first dose of IMP in the clinic at Visit 1. All data that will be collected during this trial will be summarized over time using appropriate descriptive statistics. Changes from baseline of the RCT will also be presented where appropriate.

13.6.2 Primary Safety Endpoints

The safety endpoints are listed below and will be evaluated as detailed in the following sections:

- AEs.
- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- 12-lead 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).

13.6.2.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.2.2 Adverse Events

AEs 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 system organ class 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.

13.6.2.3 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 each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and serum IGF-1 levels from baseline of the RCT to end of treatment will be summarized.

13.6.2.4 Clinical Laboratory Data

Clinical laboratory data at the end of treatment in the OLE and the change from baseline of the RCT 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.

13.6.2.5 Menstruation

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

13.6.2.5.1 Suicidality

Suicidality assessment responses will be summarized and listed as appropriate.

13.6.3 Secondary Endpoint(s)

There are several secondary endpoints. For each endpoint, the change from baseline of the RCT will be derived in patients taking each GWP42003-P dose. For visit-based endpoints, baseline will be taken as the last measurement prior to the first dose of IMP (e.g. Visit 1 of the RCT).

The following secondary endpoints will be assessed by evaluating changes relative to the prerandomization baseline of the RCT and will be summarized using appropriate descriptive statistics:

- RSBQ.
- CGI-I.
- CGI-S.
- MBA-9.
- CSHQ.

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 trial visit (see Appendix 1). However, patients who withdraw from the trial are required to complete the procedures at Visit 8 at the time of withdrawal. For these patients, their Visit 8 data will be assigned to the nearest visit (for which the assessment is scheduled to be performed), based on the day of the visit. Further details will be specified in the SAP.

13.6.4 Exploratory Endpoint(s)

The following exploratory endpoints for the trial will be assessed by evaluating changes relative to the prerandomization baseline of the RCT and will be summarized by time point:

- SF-36.
- CHQ-PF50.
- Hospital Services Use Questionnaire
- Caregiver Assessment of Rett Symptoms.

13.6.5 Handling of Missing Data

There will be no imputation of missing data, and all observed data will be summarized.

14 SAFETY MONITORING COMMITTEE

No safety monitoring committee will be used in this trial.

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[73] the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] the EU Clinical Trials Directive[78] the EU GCP Directive[79] and the clinical trial regulations adopting European Commission Directives into national legislation.[81,82,83,84,85]

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 center by adding the center'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. The nominated caregiver will be asked to consent to complete the QoL questionnaires. In cases where the patient possesses adequate understanding, assent will be taken (if allowed per local regulations) along with parent(s)/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 enforced 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/nominated caregiver (as applicable) and by the person who conducted the informed consent/assent discussion. GW Research Ltd also requires a physician to be present for consent/assent and to sign the consent/assent forms. The original signed informed consent/assent forms should be retained and a copy

provided to the patients' parent(s)/legal representative/nominated caregiver (see Section 9.2.1).

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 center, 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 Pretrial 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[75,76,77,86] the EU Clinical Trials Directive[78] the EU GCP Directive[79] or the ICH Harmonised

Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] 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 will ensure that the center is informed of when screening of patients can commence.

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the eCRFs or other documents submitted to GW, patients should be identified by their 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[75,76,77,86] and the EU Clinical Trials Directive[78]and the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] 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 center, will be agreed with each center 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 trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related, essential documentation (as outlined in ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6[R2], Section 8.2[74]), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include the following:

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

In addition, all original source documents supporting entries in the eCRFs 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 on the 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[79] or if needed by GW.

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

16.3 Trial Monitoring and Data Collection

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

The GW trial monitor, or designee, is responsible for inspecting the eCRFs, questionnaires, and dosing schedule at regular intervals throughout the trial to verify

adherence to the protocol, completeness, accuracy and consistency of the data, and adherence to local regulations on the conduct of clinical research. The trial monitor must have 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 trial monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a 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[75,76,77,86] ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable. 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[75,76,77,86] the EU Clinical Trials Directive[78], the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2),[74] and the sponsor's audit plans, representatives from GW's Clinical Quality Assurance Department may select this trial for audit. Inspection of center facilities, e.g. pharmacy, drug storage areas, and laboratories and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, the EU Clinical Trials Directive,[78] the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2),[74] and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the trial center in the event of any claim in respect of personal injury arising due to a patient's involvement in the trial, provided 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, provided that there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

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

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

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

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

16.7 Intellectual Property Rights

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

16.8 Confidential Information

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

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Appendix 1 Schedule of Assessments

Visit Number	**1**	**2[a]**	**3[a]**	**4**	**5**	**6**	**7**	**8[b,c]**	**9**	**10[a]**
Day Number (Visit Window)	**1**	**8 (±3)**	**15 (± 3)**	**29 (± 7)**	**57 (± 7)**	**85 (± 7)**	**141 (± 7)**	**197 (± 7)**	**207 (+ 7)**	**235 (+ 7)**
Informed consent and assent[d]	X[e]									
Eligibility check	X[e]									
Concomitant medications		X	X	X	X	X	X	X	X	X
New medical history	X[e]									
Adverse events	X[e]	X	X	X	X	X	X	X	X	X
Menstruation question (where appropriate)								X		
Physical examination (including weight)	X[f]			X		X		X		
Height								X		
ECG	X[f]			X		X		X		
Vital signs	X[g]			X	X	X	X	X	X	
Clinical laboratory blood sampling (hematology and biochemistry)[h]	X[f]			X	X	X		X		
Hepatic function monitoring panel[i]							X[i]			
Dipstick urinalysis (where possible)	X[f]							X		
Serum pregnancy test (if appropriate)								X		

Visit Number		**1**	**2**[a]	**3**[a]	**4**	**5**	**6**	**7**	**8**[b,c]	**9**	**10**[a]
Day Number (Visit Window)		**1**	**8 (±3)**	**15 (± 3)**	**29 (± 7)**	**57 (± 7)**	**85 (± 7)**	**141 (± 7)**	**197 (± 7)**	**207 (+ 7)**	**235 (+ 7)**
Caregiver completed questionnaire/assessment	RSBQ				X	X	X	X	X		
	CSHQ						X		X		
	Caregiver QoL questionnaire (SF-36)								X		
	Patient QoL questionnaire (CHQ-PF50)								X		
	Hospital Services Use Questionnaire	X[g]			X	X	X	X	X		
	Tanner Staging (where appropriate)								X		
	Caregiver Assessment of Rett Symptoms				X	X	X	X	X		
MBA-9							X		X		
CGI-S					X	X	X	X	X		
CGI-I					X	X	X	X	X		
Suicidality assessment		X[g]			X	X	X	X	X	X	
GWP42003-P dispensing		X[e]			X	X	X	X	X		
GWP42003-P collection and compliance review					X	X	X	X	X	X	
Dosing schedule[j]			X	X	X	X	X	X	X	X	

a Visit to be conducted by telephone.

b To be performed to all patients completing or withdrawing from the trial. Patients who withdraw early should commence the 10-day GWP42003-P taper period, if possible.
c A safety follow-up Visit 4 weeks after last GWP42003-P dose is required for all patients who withdraw from the trial or complete the trial.
d 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 parent(s)/legal representative consent. The nominated caregiver will be asked to complete the quality of life questionnaires.
e Always required.
f Required only if OLE Visit 1 is > 28 days after RCT Visit 9.
g Required if OLE Visit 1 does not occur on the same day as RCT Visit 9.
h Determination of serum IGF-1 levels at Visit 1 and 8 only; IGF-1 laboratory results will remain blinded throughout the trial.
i Hepatic function monitoring is required following increases in GWP42003-P dose or introduction of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change. Hepatic monitoring at Visit 7 is required for patients taking concomitant valproic acid or whose dose exceeds 15 mg/kg/day.
j The dosing schedule is to be completed by the caregiver daily throughout the trial and reviewed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

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 Research Ltd (GW) master files (electronically and added to the trial master file at the end of the trial).

Appendix 2.2 Sponsor Contact Details

PI	**Email:** PI Tel: PI Fax: PI USA Toll-free Fax: PI
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1223 266 800 Fax: +44 (0) 1223 235 667

At the time of protocol production, the contract research organizations (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):

Trial Conduct	Premier Research Europe 1st Floor, Rubra 2 Mulberry Business Park Fishponds Road Wokingham, RG41 2GY United Kingdom Tel: PI

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 9-Item Motor-Behavioral Assessment Scale

An example of the MBA-9[61] 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 Coarsely chopped
- 2 Finely 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 1 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 3.2 Clinician Global Impressions - Severity Scale

An example of CGI-S is shown below[56]:

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 CGI-S produced by Neul *et al*. (2015), should be used by the investigator during completion of the CGI-S[59].

Appendix 3.3 Clinician Global Impressions - Improvement Scale

An example of CGI-I is shown below[56]:

Rate total improvement whether, in your judgement, it is due entirely to drug treatment.

Compared with the patient's condition at admission to the project, how much has the patient 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 3.4 Rett Syndrome Behaviour Questionnaire

An example of the RSBQ is shown below[55]:

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 3.5 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 3.6 Tanner Staging

Tanner Staging[72] is to be completed by all female adolescent patients (i.e. ≥ 7 years or 7 to less than 18 years of age[71] 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 and 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 to 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 to 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 to 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.

Appendix 3.7 Hospital Services Use Questionnaire

An example of the Hospital Services Use questionnaire (based on the Health Service Use Questionnaire) is shown below[87]:

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			

Appendix 3.8 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 herself/himself in any way or shown any nonsuicidal self-injurious behavior?*

Appendix 3.9 Children's Sleep Habits Questionnaire

An example of the CSHQ is shown below.[70]

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 3.10 Caregiver Assessment of Rett Symptoms

An example of the Caregiver Assessment of Rett Symptoms is shown below:

For each question, please choose the number on the scale that best describes your child.
Please choose your answers based on what you observed over the past 7 days (since the last time you completed the diary).

1. Based on what you observed over the past 7 days, how was your child's condition overall?

0	1	2	3	4	5	6	7	8	9	10
Poor										Excellent

2. Based on what you observed over the past 7 days, how much of the time was your child's **breathing pattern irregular** overall?
   Please consider any episodes of irregular breathing, such as your child's hyperventilation and breath holding.

0	1	2	3	4	5	6	7	8	9	10
None of the Time										All of the time

3. Based on what you observed over the past 7 days, how **constipated** was your child overall?
   Please consider how often your child has had bowel movements, how hard it was to push, and the size and consistency.

0	1	2	3	4	5	6	7	8	9	10
Not at all constipated										Extremely constipated

4. Based on what you observed over the past 7 days, how much of the time did your child have **repetitive hand movements**?
   Please consider hand movements such as wringing, tapping, rubbing, washing movements, and hand mouthing

0	1	2	3	4	5	6	7	8	9	10
None of the time										All of the time

5. Based on what you observed over the past 7 days, overall, how much of the time did your child engage in **behavior that led to harm or potential harm to herself or others**?
Please consider any self-injurious behavior and behavior that led to physical harm or potential harm to the child herself or others.

0	1	2	3	4	5	6	7	8	9	10
None of the time										All of the time

6. Based on what you observed over the past 7 days, overall, how **anxious or sad** was your child?
Please consider whether your child showed signs such as fidgeting, crying or screaming. Also consider whether she appeared sad, withdrawn, or irritable.

0	1	2	3	4	5	6	7	8	9	10
Not at all anxious/sad										Extremely anxious/sad

7. Based on what you observed over the past 7 days, how difficult was it for your child to **communicate her needs**?
Please consider all forms of communication your child may use (including both verbal and nonverbal communication, such as gestures, eye pointing, and communication devices).

0	1	2	3	4	5	6	7	8	9	10
Not difficult at all										Did not communicate her needs at all

8. Based on what you observed over the past 7 days, how difficult was it for your child to make **appropriate eye contact**?
Please consider your child's eye contact when you speak to her and when she communicates with you.

0	1	2	3	4	5	6	7	8	9	10
Not difficult at all										Extremely difficult

9. Based on what you observed over the past 7 days, how much of the time was your child **attentive to her environment and activities**?
Please consider signs of being aware of her surroundings, such as eye movement, turning her head, moving her body, and making sounds.

0	1	2	3	4	5	6	7	8	9	10
None of the time										All of the time

10. Based on what you observed over the past 7 days, how difficult was it for your child to **sleep**? *Please consider your child's night time sleep, if she woke up during the night, how long it took her to go back to sleep, and how long she slept overall.*

0	1	2	3	4	5	6	7	8	9	10
Not difficult at all										Extremely difficult

11. Based on what you observed over the past 7 days, did your child **eat by mouth**?

☐ Yes
☐ No

11a. Based on what you observed over the past 7 days, how difficult was it for your child to **eat (by mouth)**? *Please consider your child's ability to chew and swallow including any choking episodes. Also consider, what she ate, how she ate, and how much time it took to complete meals and snacks.*

0	1	2	3	4	5	6	7	8	9	10
Not difficult at all										Extremely difficult

12. Based on what you observed over the past 7 days, did your child **have seizures**?

☐ Yes
☐ No

12a. Based on what you observed over the past 7 days, how much was your child's condition **affected by seizures**?

0	1	2	3	4	5	6	7	8	9	10
Not affected at all										Extremely affected

Thank you. You have finished completing the Diary.

AN OPEN-LABEL EXTENSION TRIAL TO INVESTIGATE THE LONG-TERM SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME

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Confidentiality Statement

Study Code: GWND19002
EudraCT Number: 2019-001605-24
Clinical Protocol V2 18Dec19

Investigator Agreement

I have read the attached clinical protocol entitled 'An open-label extension trial to investigate the long-term safety of cannabidiol oral solution (GWP42003-P, CBD-OS) in patients with Rett syndrome', dated 18 December 2019, and agree to abide by all provisions set forth therein.

The sponsor and I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to Good Clinical Practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the trial and for 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.

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

Center No.: _____

Print name: _____ Date: _____

Principal investigator (DD-MMM-YY)

Signature: _____

GW Authorization

PI [redacted] Date: 18 DEC 2019

(DD-MMM-YY)

1 PROTOCOL SYNOPSIS

Trial Title	An Open-label Extension Trial to Investigate the Long-term 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 long-term safety of GWP42003-P in patients with RTT
Secondary Objective(s)	**Secondary objectives:** • To evaluate the effect of GWP42003-P in measures of disease severity o Rett Syndrome Behaviour Questionnaire (RSBQ) o Clinical Global Impressions - Improvement (CGI-I) o Clinical Global Impressions - Severity (CGI-S) o 9-items Motor Behavioral Assessment (MBA-9) o Children's Sleep Habits Questionnaire (CSHQ) **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 o Caregiver Assessment of Rett Symptoms
Trial Design	This is a multicenter, open-label extension (OLE) trial for patients with RTT who have completed the randomized, double-blind, placebo-controlled trial (GWND18064). Entry to this OLE trial is recommended to be on the same day as Visit 9 of the randomized controlled trial (RCT), GWND18064; however, patients may enter the OLE trial up to the point of the RCT follow-up visit (Visit 11). All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg twice daily [b.i.d.]) on Day 1. Patients will be observed, and after 1 week, the dose may be escalated further, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.), in weekly

	increments of 5 mg/kg/day (2.5 mg/kg b.i.d.). Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability as deemed necessary by the investigator, until the optimal dose is found. Patients whose dose has been decreased can have their dose increased again if tolerability improves. At the end of treatment (Visit 14 [Day 729]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period. If a patient permanently discontinues treatment at any point during the trial, GWP42003-P should be gradually reduced over 10 days (unless inadvisable due to an adverse event [AE]). The patient should attend a withdrawal visit (Visit 14) as soon as possible after the decision is made to permanently discontinue GWP42003-P. Unless inadvisable due to an AE, the patient will taper GWP42003-P and attend the End of Taper visit (Visit 15) and then complete the 4-week follow-up period.
Primary Endpoint	**Safety:** The long-term safety profile of GWP42003-P will be assessed by evaluating changes in the following, relative to the prerandomization baseline of the RCT: • 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 the onset of menarche or other signs of precocious puberty)
Secondary Endpoint(s)	**Secondary endpoints:** The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

	• RSBQ • CGI-I • CGI-S • MBA-9 • CSHQ **Exploratory endpoints:** The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT: • SF-36 • CHQ-PF50 • Hospital Services Use Questionnaire • Caregiver Assessment of Rett Symptoms
Sample Size	All patients with RTT who completed the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and meet the eligibility criteria can be included in this trial. Approximately 252 patients will be enrolled.
Summary of Patient Eligibility Criteria	**Inclusion criteria** For inclusion in the trial, patients must fulfil **all** of the following criteria: • Patient has completed all scheduled visits of the treatment phase of the RCT, GWND18064, and has transitioned to OLE by the point of RCT follow-up (Visit 11). • 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 the ability to swallow the investigational medicinal product (IMP) provided as a liquid solution or the ability for the IMP to be delivered via gastrostomy (G) or nasogastric (NG) feeding tube (only G- or NG-tubes made from polyurethane or silicon are allowed). • 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 from the investigator. **Exclusion criteria** If the RCT 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 reassessments (as applicable) raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE trial or if the patient should be withdrawn. The patient may not enter the trial if ANY of the following apply: • Patient meets the withdrawal criteria (including clinically significant abnormal laboratory values), in the investigator's opinion. • Patient met during the RCT the criteria for permanent IMP discontinuation (unless in case of an AE, if AE was not considered related with the IMP; patients that met alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations discontinuation criteria must be excluded). • Females 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[a] associated with inhibition of ovulation [oral, injectable or implantable[b]] intrauterine devices/hormone-releasing systems[c], bilateral tubal occlusion[a], vasectomized partner[a,d], sexual abstinence[e] during the trial and for 3 months after the last

[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] Contraception methods that are considered to have low user dependency.
[d] Provided that partner is the sole sexual partner of the trial 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.

	dose. • Patient has been previously enrolled and dosed in this trial. • Patient is unwilling to abstain from donation of blood during the trial. • Male participants who are fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) and with a partner of childbearing potential unless agree to ensure that they use male contraception (e.g., condom) or remain sexually abstinent during the trial and for 3 months after the last dose.
Criteria for Withdrawal	Patient must be withdrawn from the trial if any of the following apply: • Administrative decision by the investigator, GW Research Ltd (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 × upper limit of normal (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** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5) Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where the transaminase elevation withdrawal 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**

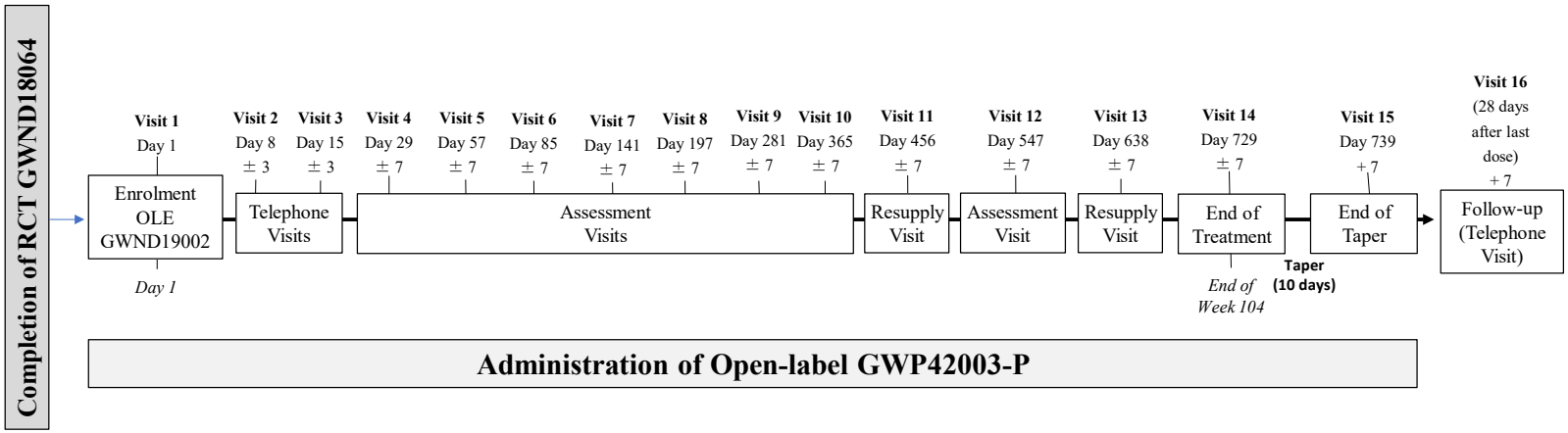
	adjustments should be taken by the investigator. • Lost to follow-up. The patient may also be withdrawn from the trial for any of the following: • Patient or caregiver noncompliance • AE (including clinically significant laboratory results) that, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial • Failure to meet the 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 is formulated as follows: (100 mg/mL cannabidiol [CBD] in sesame oil with anhydrous ethanol, sweetener [sucralose], and strawberry flavoring). GWP42003-P is to be taken orally (swallowed) b.i.d. (morning and evening) using the syringe(s) provided. GWP42003-P should be taken at the same time each day consistently 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 GWP42003-P administration in relation to food should be kept consistent throughout the trial. In patients with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should GWP42003-P be administered via G- or NG-tubes made from polyurethane or silicon only The investigator should contact the medical monitor to review IMP administration guidelines if administration via G-or NG-tubes is planned. The volume of GWP42003-P will be determined by patient's weight. All patients will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) for 1 week. After 1 week's treatment, depending on clinical response and tolerability, the patients' dose can be further increased in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.) up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.). Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability, as deemed necessary by the investigator. Patients discontinuing GWP42003-P treatment at the end of the trial or at any other time if they discontinue treatment early should

	undergo a 10-day taper period (unless continued dosing is inadvisable, e.g., due to an AE).
Control Group	Not applicable.
Procedures	Before the patient undergoes any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent. The nominated caregiver will be asked to consent to complete the QoL questionnaires. In cases where the patient possesses adequate understanding, the patient's assent will be taken, along with parent(s)/legal representative consent. Due to the degree of cognitive impairment in patients with RTT, patients 18 years of age or older 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. Visits 2, 3, and 16 (safety visits) are to be conducted by telephone. **OLE Visit 1 (Day 1):** Every effort should be made for this visit to take place on the same day as the RCT 'End of Treatment' visit. However, patients can still enter the OLE trial up to the point of the RCT follow-up visit (Visit 11). **OLE Visit 1 assessments required for all patients:** • Informed consent and assent • Eligibility check • New medical history • AE review • GWP42003-P dispensing **OLE Visit 1 assessments required if OLE Visit 1 occurs on a different date than RCT Visit 9:** • Vital signs • Suicidality assessment • Hospital Services Use Questionnaire **OLE Visit 1 assessments required if OLE Visit 1 occurs > 28 days after RCT Visit 9:** • Physical examination (including weight) • ECG • Clinical laboratory blood sampling (hematology and biochemistry) • Dipstick urinalysis (where possible) **OLE assessments on Visits 2 to Visit 16** (Follow-up) (see Appendix 1 for time points of each assessment)**:**

	• Concomitant medications review • AE review • Menstruation cycle review • Physical examination (including weight) • Height • ECG • Vital signs • Safety laboratory assessments (hematology and biochemistry) (Visit 7 only for patients taking concomitant valproic acid as well as for patients whose dose exceeds 15 mg/kg/day) **Note**: Hepatic function monitoring should be carried out within 1 month following increases in GWP42003-P dose or introduction of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change. • Dipstick urinalysis • Serum IGF-1 levels • Serum pregnancy test (if appropriate) • Questionnaires: o RSBQ o CSHQ o SF-36 and CHQ-PF50 o Hospital Services Use Questionnaire o Tanner Staging (for patients aged ≥ 7 years or earlier, if clinically indicated by onset of menarche or other signs of precocious puberty) o Caregiver Assessment of Rett Symptoms o MBA-9 o CGI-S and GCI-I o Suicidality assessment • GWP42003-P dispensing (All caregivers will be provided with a dosing schedule.) • GWP42003-P collection and compliance review Caregivers are asked to confirm dosing in the dosing schedule daily throughout the trial; the dosing schedule will be reviewed
Statistical	All data that will be collected during this trial will be summarized

Considerations	across time, using appropriate descriptive statistics. Where baseline data are available from the RCT, changes from baseline will also be presented, where appropriate. There will be no formal hypothesis testing. A detailed statistical analysis plan will be written.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Trial Design and Treatment Schematic



OLE = open-label extension; RCT = randomized controlled trial

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List of Abbreviations

Abbreviation or special term	Definition or Explanation
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAC	Blood alcohol content
BDNF	Brain-derived neurotrophic factor
BDS	Botanical drug substance
b.i.d.	Twice daily
CB	Cannabinoid
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CGI	Clinical global impressions
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CHQ-PF50	Child Health Questionnaire Parent Form 50
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organization
CSHQ	Children's Sleep Habits Questionnaire
CYP	Cytochrome P450
DS	Dravet Syndrome
ECG	12-lead electrocardiogram
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
G	Gastrostomy

Abbreviation or special term	Definition or Explanation
GABA	γ-aminobutryic acid
GPR55	G-protein-coupled receptor 55
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
i.v.	Intravenous
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
NCU	Intensive Care Unit
NG	Nasogastric
NOEL	No observed effect level
OLE	Open-label extension
PCP	Phencyclidine
PCS	physical health composite score
PhS	Standardized Physical Summary
PI	Principal investigator
PRN	Packaging reference number
PsS	Standardized Psychosocial Summary

Abbreviation or special term	Definition or Explanation
PVD	Pharmacovigilance Department
QoL	Quality of life
RCT	Randomized controlled trial
RSBQ	Rett Syndrome Behaviour Questionnaire
RTSM	Randomization and Trial Supply Management
RTT	Rett syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	36-item Short Form
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States

Definition of Terms

Term	Definition
Caregiver	An assigned patient's parent or designated care provider.
Day 1	The day a patient first receives the investigational medicinal product in this trial.
End of treatment	Completion of the treatment period (Visit 14 [Day 729]), or withdrawal.
End of trial	Last patient's last visit/telephone call.
Enrolled patient	Any patient whose parent(s)/legal representative has provided written informed consent for the patient 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	The 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, and the nonitalicized abbreviation *MeCP2* denotes the protein.
Postregression	≥ 6 months since the last loss of hand use or verbal language or gross motor regression.

2 OBJECTIVES

2.1 Primary

Key objective:

- To evaluate the long-term safety of GWP42003-P in patients with Rett syndrome (RTT)

2.2 Secondary

Secondary objectives:

- To evaluate the effect of GWP42003-P in measures of disease severity
    - Rett Syndrome Behaviour Questionnaire (RSBQ)
    - Clinical Global Impressions - Improvement (CGI-I)
    - Clinical Global Impressions - Severity (CGI-S)
    - 9-items Motor Behavioral Assessment (MBA-9)
    - Children's Sleep Habits Questionnaire (CSHQ)

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

3 BACKGROUND AND RATIONALE

3.1 Disease

Rett syndrome is a rare, noninherited, X-linked neurodevelopmental disorder affecting approximately 1 in 10,000 live female births, resulting in abnormal neuronal development and function.[1,2] Rett syndrome 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 to 18 months characterized by a subtle slowing or regression of development. Infants/young children aged 1 to 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]

Rett syndrome is most commonly caused by heterozygous *de novo* mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2).[6] Methyl-CpG-binding protein 2 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% to 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 the 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 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 with 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 the morphology of mitochondria and genes associated with these structures as well as redox balance have been demonstrated in patients with RTT, 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 cannabidiol (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.

Cannabidiol 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 describing the polypharmacology of CBD and its modulation of nonendocannabinoid system targets exist. 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 transient receptor potential cation channel subfamily V member 1 (TRPV1).[30,31,32] The second is inhibition of adenosine reuptake.[33,34,35]

Based on the 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 channels, benzodiazepine, and γ-aminobutryic acid (GABA) binding sites of the $GABA_A$ receptor.

Importantly, CBD does not produce THC-like euphoric effects. Furthermore, 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 the Lennox-Gastaut syndrome or the Dravet syndrome in patients 2 years of age and older.[36]

3.2.1 Nonclinical 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 subchronic 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 and 200 mg/kg i.p. and improved bicuculline-induced memory impairments in neonatal rats at 100 mg/kg i.p.[39] Cannabidiol 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 that 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] 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] Cannabidiol 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 the tissue production of chemical mediators of inflammation, such as tumor necrosis factor alpha and interleukin-2.[49] Cannabidiol (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 premotor region of the zebra finch brain results in a temporary disruption of vocal patterns that recovers over about 7 days and is dependent on the ability of birds to hear as part of sensorimotor learning. Cannabidiol 10 and 100 mg/kg (intramuscular) improved the phonology and syntax of the zebra finch song over the first 6 to 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 Safety Pharmacology

In a rat primary observation Irwin test of central nervous system function, no behavioral, physiological, or body temperature changes were observed following administration of CBD botanical drug substance (BDS) at 10 to 100 mg/kg.[52]

In the cardiovascular system, CBD as CBD BDS inhibited human ether-à-go-go-related gene tail current in a concentration-dependent manner[52] (no-observed-effect level [NOEL], 43 ng/mL) and had no effect on Purkinje fiber action potentials or QT interval changes[52] (NOEL, 22 ng/ml). Changes in cardiovascular parameters (heart rate, blood pressure, and electrocardiogram [ECG]) in the conscious dog were not considered to be adverse.[52]

In the respiratory system, CBD as CBD BDS had no biologically significant effect on respiratory parameters in conscious rats.[52]

3.2.1.3 Mechanism of Action

Cannabidiol 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 abnormal liver function tests 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, in addition to treating seizures, CBD may have beneficial effects on cognition and behavior as well as on patient QOL.[53,54]

This open-label extension (OLE) trial will evaluate the long-term safety of GWP42003-P in patients with RTT who carry a *MECP2* gene mutation.

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.

3.3.1.1 Choice of Primary Endpoints

Safety, selected as the primary endpoint, will be assessed by evaluating changes in AEs, clinical laboratory parameters, vital signs, physical examination procedures, 12-lead ECGs, effects on menstruation cycles, and suicidality. Change in growth and development will also be measured by height, weight, serum IGF-1 levels, and Tanner Staging (for patients aged ≥ 7 years or earlier, if clinically indicated by the onset of menarche or other signs of precocious puberty).

3.3.1.2 Choice of Secondary Endpoints

Secondary endpoints, scales, and assessments were selected to evaluate a wide range of symptoms observed in patients with RTT:

- RSBQ. This caregiver-completed assessment has been specifically developed for use in patients with RTT.[55] The RSBQ total score is used as a global measure to assess the patient's overall condition, whereas subscales of the RSBQ allow evaluation of more-specific domains (behavior and emotion, motor function, and breathing abnormalities).
- CGI-I and CGI-S. CGI-I was selected as a clinician-rated assessment that has been used extensively in neuropsychiatric disorders in both clinical practice and clinical trial settings[56,57,58] and reported to have successfully been implemented in the RTT patient population.[59] CGI-I is a global measure used to assess the

patient's overall condition. CGI-I assesses change in symptoms relative to the baseline CGI-S.

- MBA-9. This scale was selected as it provides a clinician assessment of a set of motor and behavior items of the original MBA[60,61] that are deemed amenable to change.
- CSHQ. This questionnaire was selected as sleep problems are reported for the majority of patients with RTT. CSHQ has been used to characterize sleep in other developmental disability populations (e.g., autism spectrum disorder[62]) and in a sample of patients with RTT.[63]

3.3.1.3 Choice of Exploratory Endpoints

The required constant care and supervision of patients with RTT places a significant burden on the 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 be assessed using CHQ-PF50. Information on health utilization will be assessed using the Hospital Services Use Questionnaire, which aims to analyze the frequency of patient hospitalizations and hospital visits.

The Caregiver Assessment of Rett Symptoms has been specifically developed for the proposed clinical trial with the intent of obtaining 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.

3.3.2 Choice of Dosing Regimen

Given that the objective of the trial is to monitor long-term safety, a flexible dose escalation based on efficacy and tolerability, as judged by the investigator, will be used. The maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) is set in accordance with the maximum dose per the United States (US) prescribing information for CBD.[64]

The GWP42003-P solution contains 7.9% w/v anhydrous ethanol, which is required as sucralose is not soluble in sesame oil. A dose of 15 mg/kg/day (administered as 7.5 mg/kg twice daily [b.i.d.]) in a 10 kg child will result in a blood alcohol content (BAC) of 0.0098 g/L, which equates to an ethanol ingestion of 5.93 mg/kg. Both these amounts are well under the threshold for a BAC of 0.125 g/L and an ethanol ingestion of 75 mg/kg for patients 6 years and older and also under the maximum BAC level of

0.01 g/L and ethanol ingestion of 6 mg/kg for children less than <6 years old.[65] At the highest recommended therapeutic dose of 20 mg/kg/day (administered as 10 mg/kg b.i.d.), a single dose of 10 mg/kg cannabidiol oral solution (CBD-OS) in a 10 kg child theoretically results in a BAC of 0.013 g/L and an ethanol ingestion of 7.9 mg/kg, slightly above the recommended threshold for BAC of 0.01 g/L for children less than 6 years old. In light of the wide safety margins observed in toxicology studies and taking the severity of the condition into account, this theoretical risk is judged to be acceptable.

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 Lennox-Gestaut Syndrome (LGS) and Dravet Syndrome (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 level (maximum dose of 20 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

There will be no formal hypothesis testing in this trial.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This is a multicenter, OLE trial for patients with RTT who have completed the randomized, double blind, placebo-controlled trial (GWND18064).

Entry to this OLE trial is recommended to be on the same day as Visit 9 of the randomized controlled trial (RCT), GWND18064; however, patients may enter the OLE up to the RCT follow-up visit (Visit 11).

All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1. Patients will be observed, and after 1 week, the dose may further be escalated, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.) in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.).

Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability, as deemed necessary by the investigator, until the optimal dose is found. Patients whose dose has been decreased can have their dose increased again if tolerability improves.

At the end of treatment (Visit 14 [Day 729]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period.

If a patient permanently discontinues treatment at any point during the trial, GWP42003-P should be gradually reduced over 10 days (unless inadvisable due to an AE). The patient should attend a withdrawal visit (Visit 14) as soon as possible after the decision is made to permanently discontinue GWP42003-P. If applicable, the patient will taper GWP42003-P, attend the End of Taper visit (Visit 15), 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

Safety:

The long-term safety profile of GWP42003-P will be assessed by evaluating changes in the following, relative to the prerandomization baseline of the RCT:

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

4.1.2 Secondary Endpoints

4.1.2.1 Secondary endpoints:

The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

- RSBQ
- CGI-I
- CGI-S
- MBA-9
- CSHQ

4.1.2.2 Exploratory endpoints:

The following will be assessed by evaluating changes relative to the prerandomization baseline of the RCT:

- SF-36
- CHQ-PF50

- Hospital Services Use Questionnaire
- Caregiver Assessment of Rett Symptoms

4.2 Number of Trial Centers

Approximately 25 trial centers are expected to participate in this trial. The number of centers may be reduced or increased depending on recruitment performance.

4.3 Number of Patients

All patients with RTT who complete the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and meet the eligibility criteria will transition to 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1 of the OLE. Approximately 252 patients will be enrolled.

5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate pharmacy manual for more detailed information on GWP42003-P.

5.1 GWP42003-P Oral Solution

The 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	Makes up to 1 mL

5.2 Packaging, Storage, and Drug Accountability

5.2.1 Packaging and Labeling

GWP42003-P will be manufactured, packaged, labeled, and/or distributed by GW or delegated contractors. GWP42003-P will be presented in 100 mL amber glass bottles with child-resistant screw caps and packed in cartons. GWP42003-P will be dispensed at each relevant visit. A unique identification number will be used to identify each carton and the GWP42003-P 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 GWP42003-P 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")
- 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 for use and the name, address, and telephone number of the investigator (or the 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.

5.2.2 Storage

GWP42003-P 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.

GWP42003-P must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve the storage location and facilities. Temperature records of the clinical center storage location must be maintained (recording a minimum of Monday to Friday, excluding public holidays) from the date of receipt of the first shipment until the end-of-trial dispensing period at each center. These records must contain at least the minimum and maximum daily temperatures and must be made available to the appropriate GW personnel for review throughout the trial. Temperature during the transit of GWP42003-P to the center must be checked on receipt and compliance/noncompliance to the minimum and maximum recorded.

Should storage conditions deviate from these specified requirements, the GW trial monitor must be contacted immediately to confirm if GWP42003-P remains suitable for use. GWP42003-P must be placed under quarantine until written confirmation is received that GWP42003-P is suitable for use.

Caregivers will be provided with instructions regarding home storage requirements for GWP42003-P.

5.2.3 Supply and Return of Investigational Medicinal Product

At trial initiation and as needed thereafter, GWP42003-P will be shipped to the identified responsible person, such as the pharmacist, at the investigator’s center, who will check

the amount received against the shipment request and the condition of the drug (i.e., integrity, physical appearance, and temperature during transit). Details of GWP42003-P received will be recorded in the GWP42003-P accountability record (see Section 5.2.4). The center will acknowledge the GWP42003-P receipt and will complete any receipt forms required. GWP42003-P 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 the GW/depot or destroyed at a GW-approved center if agreed in writing by the trial monitor.

5.2.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused GWP42003-P. A drug accountability record for GWP42003-P must be kept current and should contain the following:

- Trial code
- PRN, treatment number, date of receipt, and quantity of GWP42003-P received
- Patient's trial identification and/or treatment number
- Date and quantity of GWP42003-P dispensed
- The initials of the dispensing/dosing party
- Date and quantity of GWP42003-P returned to the investigator
- GWP42003-P expiry dates

GWP42003-P will be dispensed at visits as per the Schedule of Assessments in Appendix 1. Caregivers will be asked to return all GWP42003-P (used and unused) at each relevant visit. The center will check the returned GWP42003-P against the expected usage. 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 GWP42003-P.

A record of returned GWP42003-P must be completed and included in the shipment of used and unused GWP42003-P 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 GWP42003-P.

5.2.5 Post-trial Provision

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 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, and 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 has completed all scheduled visits of the treatment phase of the RCT, GWND18064, and has transitioned to OLE by the point of RCT follow-up (Visit 11).

6.1.2 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.

6.1.3 Patient and/or 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).

6.1.4 Patient must have the ability to swallow the IMP provided as a liquid solution or the ability for the IMP to be delivered via gastrostomy (G) or nasogastric (NG) feeding tube (only G- or NG-tubes made from polyurethane or silicon are allowed).

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

6.1.6 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 from the investigator.

6.2 Exclusion Criteria

If the RCT 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 reassessments (as applicable) raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE trial or if the patient should be withdrawn. The patient may not enter the trial if ANY of the following apply:

6.2.1 Patient meets the withdrawal criteria (including clinically significant abnormal laboratory values) in the investigator's opinion (refer to Section 10).

6.2.2 Patient met during the RCT the criteria for permanent IMP discontinuation (unless in case of an AE, if AE was not considered related with the IMP; patients that met ALT/AST elevations discontinuation criteria must be excluded).

6.2.3 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[a] 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 after the last dose.

6.2.4 Patient has been previously enrolled and dosed in this trial.

6.2.5 Patient is unwilling to abstain from donation of blood during the trial.

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

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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 trial 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 center'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). The nominated caregiver will be asked to consent to complete the QoL questionnaires. 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 patients with RTT, patients 18 years of age or older 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

As this is a single-group OLE trial, all patients will receive GWP42003-P. Patients will not be informed of their allocated treatment group in the RCT. Patients will retain the patient number allocated to them during the RCT.

7.2 Randomization

This is an OLE of the GWND18064 trial. Randomization will not occur. At the start of the GWND18064 trial, enrolled patients were allocated a unique patient number. Patients will retain this number during the OLE trial.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration, and Schedule

GWP42003-P will be presented as an oral solution containing 100 mg/mL CBD. For details regarding IMP formulations, see Section 5.

Before the patient undergoes any assessments or observations, the patient's parent(s)/legal representative is required to give written informed consent or assent (see Section 9.2.1 and Section 15.2). The nominated caregiver will be asked to consent to complete the QoL questionnaires.

8.1.1 Dose Administration

GWP42003-P will be administered orally (swallowed) b.i.d. (morning and evening) using the syringe(s) provided. GWP42003-P may be taken with other concomitant medications, as directed by the investigator. In patients with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in patients where oral dosing is not possible should GWP42003-P be administered via G- or NG-tubes made from polyurethane or silicon only. GWP42003-P 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 GWP42003-P administration in relation to food should be kept consistent throughout the trial The investigator should contact the medical monitor to review IMP administration guidelines if administration via G-or NG-tubes is planned.

8.1.2 Dose Escalation and Dose Adjustments

The daily volumes of the GWP42003-P 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 during the GWND18064 trial.

All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1. Patients will be observed, and after 1 week the dose may escalate further, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.) in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.).

Patients should then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be

decreased or increased if deemed necessary by the investigator, to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.).

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, until the event has resolved. 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 quicker 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 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 be withdrawn from treatment, unless a lower dose level is agreed in discussion with the medical monitor and can be accurately measured (minimum single-dose volume of 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.

Hepatic function monitoring should be carried out within 1 month following increases in GWP42003-P dose or introduction or dose increases of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change.

Transaminase elevations should be medically managed by the investigator either by reducing the GWP42003-P dose as described above or by reducing concomitant medications judged to be causing the elevation (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.

At the end of treatment (Visit 14 [Day 729]), the dose of GWP42003-P will be reduced over a 10-day taper period, and patients will enter the 4-week follow-up period.

Patients discontinuing GWP42003-P treatment at any other time should undergo a 10-day taper period (unless continued dosing is inadvisable, e.g., due to an AE). The decision on whether to taper GWP42003-P 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 antiepileptic drugs [AEDs]) administered concurrently, and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. 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. Cannabidiol has the potential to induce the expression of hepatic CYP 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 [52]. Any concerns regarding potential interactions with concomitant medications can be discussed with the trial medical monitor(s).

Changes in concomitant medications are allowed, but increases in dose of medications that affect liver function should be discussed with the medical monitor. Introduction of new medications is allowed, but introduction of new psychotropic and/or central acting agents intended as long-term treatment requires prior discussion with the medical monitor.

The use of rescue medication is allowed, when necessary (i.e., AED for transient exacerbation of seizures). Any medication, other than GWP42003-P, taken during the trial must be recorded on the electronic case report form (eCRF).

8.3 Prohibited Therapy During the Trial Period

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

- St John's wort
- Recreational or medicinal cannabis or cannabinoid-based medications (including Sativex or CBD oral solutions)
- Any other IMP

- Felbamate that has been taken for less than 1 year

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

GWP42003-P is dispensed to the patient at visits as per the Schedule of Assessments in Appendix 1. Further guidance on GWP42003-P dispensing will be provided in a separate pharmacy manual.

Caregivers will be asked to confirm dosing in the dosing schedule daily. Caregivers should return all GWP42003-P (used and unused) at each of the visits as per the Schedule of Assessments in Appendix 1. The returned medication will be checked against the expected usage, and any discrepancies will be 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 GWP42003-P administration in relation to meals.

The investigator must inform GW promptly of all missing or unaccountable GWP42003-P.

Records of GWP42003-P accountability will be maintained according to Section 5.2.4.

8.5 Access to Blinded Treatment Assignment

This is not applicable.

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 center, 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 patients with RTT, patients 18 years of age or older 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 ample time to discuss the trial with the investigator, nurse, relatives, or caregiver, as wished, patients for whom the parent(s)/legal representatives provide written informed consent, and in cases where the patient possesses adequate understanding, patients who give their assent will be screened for entry into the trial. The nominated caregiver will be asked to consent to complete the QoL questionnaires.

Each visit should be scheduled to take place at approximately the same time of day (i.e., morning or afternoon), whenever possible. Visits 2, 3, and 16 (safety follow-up) are to be conducted by telephone.

The investigator should use his/her judgment and knowledge of the patient to determine when to best 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 1)

Every effort should be made for this visit to take place on the same day as the RCT 'End of Treatment' visit. However, patients can still enter the OLE trial up to the point of the RCT follow-up (Visit 11).

OLE Visit 1 Assessments required for all patients:

- Informed consent and assent
- Eligibility check
- New medical history
- AE review
- GWP42003-P dispensing

OLE Visit 1 assessments required if OLE Visit 1 occurs on a different date than RCT Visit 9:

- Vital signs
- Hospital Services Use Questionnaire
- Suicidality assessment

OLE Visit 1 assessments required if OLE Visit 1 occurs > 28 days after RCT Visit 9:

- Physical examination (including weight)
- ECG
- Clinical laboratory blood sampling (hematology and biochemistry)
- Dipstick urinalysis (where possible)

Patients who satisfy all of the inclusion criteria and none of the exclusion criteria specified in Section 6 will begin the treatment period.

Patients will be dispensed sufficient GWP42003-P and a dosing schedule for the following 3 weeks. Caregivers will be instructed on how to use the dosing schedule and how to measure and administer the medication. At the next visit, all GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made.

Based on Section 9.1.3, assessments may be performed at unscheduled visits in the event of a safety concern, as deemed necessary by the investigator.

The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient will fail screening.

9.1.1.2 Visit 4 (Day 29 [± 7])

A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Vital sign assessments, physical examination (including body weight) and ECG assessments will be performed.

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

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 4 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.3 Visit 5 (Day 57 [± 7])

A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Vital sign assessments will be performed.

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

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be conducted via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 4 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.4 Visit 6 (Day 85 [± 7])

A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Vital sign assessments, physical examination (including body weight) and ECG assessments will be performed.

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

The caregiver will complete the RSBQ, CSHQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 8 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.5 Visit 7 (Day 141 [± 7])

A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. The investigator must assess adherence to the dosing schedule.

Vital sign assessments will be performed.

Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology and biochemistry for patients taking concomitant valproic acid, as well as for patients whose dose exceeds 15 mg/kg/day.

The caregiver will complete the RSBQ and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

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

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 8 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.6 Visit 8 (Day 197 [± 7]), Visit 10 (Day 365 [± 7]), and Visit 14 (Day 729 [± 7], End of Treatment/Withdrawal Visit)

A visit window of ± 7 days for Visits 8, 10, and 14 from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible.

The patient should attend a withdrawal visit (Visit 14) as soon as possible after the decision is made to permanently discontinue GWP42003-P.

Information regarding changes to concomitant medications, AEs, and menstruation cycle (where applicable) will be reviewed. Vital sign assessments, physical examination (including body weight), height, and ECG assessments will be performed.

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

- Hematology
- Biochemistry
- Dipstick urinalysis (provided urine can be obtained)
- Pregnancy test using a serum sample (as appropriate [Section 9.2.2])
- Determination of serum IGF-1 levels (Section 9.2.9)

The caregiver will complete the RSBQ, CSHQ, SF-36, CHQ-PF50, and Caregiver Assessment of Rett Symptoms.

The Hospital Services Use Questionnaire will be completed via interview.

The Tanner Stage will be recorded (where appropriate).

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

The investigator must assess adherence to the dosing schedule. All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the period until the next scheduled Visit.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

Visit 14 only: Patients will receive sufficient GWP42003-P for the 10-day taper period, as applicable. For patients who discontinue GWP42003-P early, the taper period should start at the time the decision is made to discontinue, unless tapering the dose of GWP42003-P is inadvisable (e.g., continued dosing is not possible due to an AE). For patients who discontinue GWP42003-P early, the decision on whether or not to taper GWP42003-P will be left to the investigator's clinical judgment.

9.1.1.7 Visit 9 (Day 281 [± 7])

A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed. Physical examination (including body weight) and vital sign assessments will be performed. Blood samples will be taken for the following:

- Hematology
- Biochemistry

The investigator must assess adherence to the dosing schedule.

The investigator will complete the suicidality assessment.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 12 weeks.

9.1.1.8 Visit 11 (Day 456 [± 7]) and Visit 13 (Day 638 [± 7])

Visits 11 and 13 are resupply visits. Patient's taking concomitant valproic acid or whose dose exceeds 15 mg/kg/day will need hepatic monitoring. All other patients do not need to attend in person. A visit window of ± 7 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 changes to concomitant medications and AEs will be reviewed.

The investigator must assess adherence to the dosing schedule.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Sufficient GWP42003-P and a dosing schedule will be provided for the following 13 weeks.

Based on Section 9.1.3, assessments may be performed at an unscheduled visit in the event of a safety concern, as deemed necessary by the investigator.

9.1.1.9 Visit 12 (Day 547 [± 7])

A visit window of ± 7 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 changes to concomitant medications, AEs will be reviewed. Vital sign assessments, physical examination (including body weight), height, and ECG assessments will be performed.

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

- Hematology
- Biochemistry
- Dipstick urinalysis (provided urine can be obtained)
- Pregnancy test using a serum sample (as appropriate [Section 9.2.2])

The investigator will complete suicidality assessment.

The investigator must assess adherence to the dosing schedule.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made. Patients will receive sufficient GWP42003-P and a dosing schedule for the following 13 weeks.

9.1.1.10 Visit 15 (Day 739 [+ 7], End of Taper)

A visit window of + 7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible. This visit marks the end of the taper period.

Information regarding changes to concomitant medications and AEs will be reviewed. Vital sign and suicidality assessments will be performed.

The investigator must assess adherence to the dosing schedule.

All GWP42003-P (used and unused) will be collected, and a check of the returned GWP42003-P against usage should be made.

The following assessments are not required but should be performed if clinically indicated:

- Physical examination (including body weight)
- ECG
- Clinical laboratory samples (urine [where possible] and blood) will be taken for the following:
  - Hematology
  - Biochemistry

9.1.2 Dipstick urinalysis (provided urine can be obtained)Telephone Visits

9.1.2.1 Visits 2 (Day 8 [± 3]) and 3 (Day 15 [± 3])

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.

Telephone visits will be conducted by a center nurse (the center investigator only needs to be involved if necessary, e.g., if any concerns are raised during the call). Information regarding changes to concomitant medications and AEs will be reviewed. The center (the nurse and, if necessary, the investigator) must assess adherence to the dosing schedule.

9.1.2.2 Visit 16 (28 days after last dose IMP [+ 7], Follow-up, End of Trial)

A visit window of + 7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible. This visit marks the end of the trial.

Visit 16 constitutes the last scheduled safety follow-up. The purpose of the visit is to ascertain the status of AEs continuing after the cessation of GWP42003-P or any new AEs commencing after discontinuation. All causally related AEs that result in a patient's early termination from the trial or are present at the end of the trial should be followed up until a satisfactory resolution occurs, i.e., until the AE resolves or is considered clinically insignificant, or until the investigator is satisfied that the AE is not related to GWP42003-P and needs no further investigation. Information regarding changes to concomitant medications will be reviewed.

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 are recorded for the trial. The nominated caregiver will be asked to consent to complete the QoL questionnaires.

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 signing, 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. Patients who cannot write 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. If a minor who is capable of forming an opinion and assessing the information provided makes an explicit wish to refuse participation in or to be withdrawn from the clinical trial at any time, this wish must be considered by the investigator. Given the severity of the condition, it is expected that the majority of patients will have an insufficient level of understanding of what is proposed, in which case solely parent(s)/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.

GW Research Ltd requires a physician to be present for consent and assent and to also sign the consent and assent forms. The original signed informed consent/assent forms should be retained, and a copy should be 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, male participants who are fertile (i.e., after puberty unless permanently sterile by bilateral orchidectomy) must agree that they are willing to use male contraception (e.g.,condom) or remain sexually abstinent during the trial and for 3 months after the last dose.

Where applicable, females 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 per the definition of woman of childbearing 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.[66] Such methods include:

- 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[b].
- Vasectomized partner[bb], provided that partner is the sole sexual partner of the patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Abstinence, as referenced above, is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.[67]

Serum pregnancy tests will be performed for any patients of childbearing potential at RCT Visit 9 and OLE Visit 8; 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.

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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
[b] Provided that partner is the sole sexual partner of the trial patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.

9.2.3 Concomitant Medication

Details of all current medications will be recorded during the RCT. Any changes in concomitant medication during the trial must be recorded on the eCRF at trial visits. Changes in concomitant medications are allowed, but increases in the dose of medications that affect liver function should be discussed with the medical monitor. Introduction of new medications is allowed, but introduction of new psychotropic and/or central acting agents intended as long-term treatment requires prior discussion with the medical monitor.

9.2.4 New Medical History

Any changes to medical history since the RCT will be recorded.

9.2.5 Menstruation

Any changes in menstrual cycles since the RCT will be captured at the end-of-treatment visit.

9.2.6 Physical Examination

Physical examinations will include body weight measurements. At Visits 8, 10, 12 and 14 height will be collected. If an accurate measurement of height is not possible, an estimate should be provided.

9.2.7 12-Lead Electrocardiogram

Triplicate ECGs will be performed after 5 minutes of rest. Triplicate ECGs should be taken as close together as possible. An ECG machine will be provided to all centers, 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 center in the case of clinically relevant abnormalities. The central reader will provide measurements and an overall assessment to support the investigator in his/her 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.

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 Clinical Laboratory Sampling

The investigator should use his/her judgment and knowledge of the patient to determine when to best 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.

Routine laboratory tests will include hematology, biochemistry, and urinalysis (provided urine can be obtained), IGF-1 levels, and a serum pregnancy test (if appropriate). Analysis of all clinical blood samples and pregnancy tests will be conducted at a central clinical laboratory.

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

The investigator and trial monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the trial and a statement of accreditation (or similar) for the laboratory.

The investigator should be aware of blood sampling volume restrictions, particularly for patients with low weight, and if additional monitoring is required (maximum total daily volume of 0.85mL/kg of body weight[68,69] maximum 4-week period volume of 2.55 mL/kg of body weight, and maximum 8-week period volume of 50 mL).

Clinical laboratory sample parameters are detailed in Table 9.2.9-1.

Table 9.2.9-1 Biochemistry, Hematology, and Urinalysis

Biochemistry (Serum)[1]	Hematology (Whole Blood)[1]	Urinalysis (Urine)[2]	Pregnancy Test (Serum)[1]
Alanine aminotransferase[3]	Hematocrit	Blood	Serum
Albumin[3]	Hemoglobin	Glucose	
Alkaline phosphatase[3]	Mean cell volume	Nitrites	
Aspartate aminotransferase[3]	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	Prothrombin time and INR (plasma)[5]	Ketones	
Gamma-glutamyl transferase[3]		Specific gravity	
Glucose		Urobilinogen	
Human chorionic gonadotropin			
HDL-cholesterol			
IGF-1[4]			
Potassium			
Prolactin			
Sodium			
Total bilirubin[3]			
Total protein[3]			
Triglycerides			
Urea (blood urea nitrogen)			

HDL = high-density lipoprotein; INR = international normalized ratio.
[1] Analyzed at a central laboratory.
[2] Analyzed at the trial center by use of a dipstick (if allowed per local regulations).
[3] Hepatic function monitoring panel.
[4] Visits 1, 8, 10 and 14 only; IGF-1 laboratory results to remain blinded throughout the trial.
[5] To be requested if ALT or AST > 3 × ULN after Visit 1 (to evaluate IMP discontinuation criteria)

Investigators at trial centers will be notified of laboratory test results. All laboratory results will be reviewed, and the reports will be signed and dated by the investigator. Any results considered to be of clinical significance must be addressed and followed up, as clinically appropriate. Per protocol requirements, in addition to the pre-scheduled biochemistry, further hepatic function monitoring may be needed. In cases where after Visit 1, ALT or AST are > 3 × ULN, international normalized ratio (INR) testing must be requested. If only the hepatic function monitoring panel was requested and ALT or AST > 3 × ULN, both INR and hematology panel (eosinophils) must be requested. 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 the investigator is satisfied that the abnormality is not related to GWP42003-P and needs no further investigation.

Additional samples may be collected, as needed, e.g., for monitoring of hepatic function (hepatic function monitoring panel) (see Section 8.1.2 and Table 9.2.9-1).

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 will be 2.55 mL/kg of body weight and will not exceed a total of 50 mL within any 8 week period[68,69] 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 the patient suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.10 Randomization and Trial Supply Management System

The RTSM system will be used to manage the IMP supply. 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 dispensing information (Visits 1, and 4 through 14 [end of treatment/withdrawal visit]).
- Provide completion/taper/early termination information (Visit 14/the end of treatment/withdrawal visit, or Visit 15 [end of taper], as applicable).

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

9.2.11 Dosing Schedule/Compliance Review

Caregivers will be provided with a dosing schedule. Caregivers will be asked to confirm dosing in the dosing schedule daily from Visit 1 through Visit 15 (end of taper). 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 GWP42003-P administration in relation to meals.

9.2.12 Questionnaires and Assessments Completed at Scheduled Visits

Caregiver questionnaires should be completed by the identified caregiver, nominated at Visit 1 of the RCT. The same person should answer/complete the questionnaires/assessments in order to maintain consistency. Questionnaires should be completed during the scheduled visits. The nominated caregiver must have given consent to complete the QoL questionnaires prior to the completion of the questionnaires.

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.

9.2.12.1 Rett Syndrome Behaviour 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. Each item is rated on a 3-point numerical scale; 0 indicates an item that is 'not true as far as you know,' 1 indicates an item is 'somewhat or sometimes true,' and 2 indicates 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.[55]

9.2.12.2 Children's Sleep Habit Questionnaire

This is a caregiver-completed sleep screening instrument designed for school-aged children.[70] CSHQ includes 33 items within 8 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; and 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; and "Rarely" if it occurs never or 1 time in a week. Some items should be reversed in scoring, so a higher score reflects more-disturbed sleep behavior. The caregiver is also asked to indicate for each item if the sleep item is a problem.

9.2.12.3 36-Item Short Form

Caregivers' health-related QoL will be assessed using the SF-36 questionnaire. SF-36 measures 8 domains of health-related QoL 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 SF-36 are based on a 0-to-100 scale; 0 represents the lowest possible score, and 100 represents the highest possible score, with a higher score indicating a better health state.

9.2.12.4 Child Health Questionnaire Parent Form 50

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 the 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 mutlidimensional 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; a higher score indicates better QoL.

9.2.12.5 Hospital Services Use Questionnaire

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

9.2.12.6 Caregiver Assessment of Rett Symptoms

Caregivers will be asked to rate, on a 0-to-10 numerical rating scale, the patient's condition and performance/severity of symptoms in terms of breathing, hand stereotypies, interactions, problem behaviors, constipation, seizures, and sleep. This assessment

corresponds to the symptom diary completed weekly in the RCT but will be completed at trial visits only in the OLE.

9.2.12.7 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. The severity of the 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; or 4 = very severe or constant. The total maximum score is 36, and higher total scores represent greater severity.[61] The MBA-9 items address the core symptoms of RTT.

9.2.12.8 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.[56]

The CGI questionnaire is split into 2 scales: the CGI-S scale and the CGI-I scale. 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 the total clinical experience, a patient will be assessed on the severity of illness at the time of rating. This is rated as follows: 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 scale, 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 (RCT Visit 2). This is rated as follows: 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 predefined set of anchors developed specifically for the use of CGI in RTT.[59]

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

9.2.12.9 Suicidality Assessment

The profound cognitive impairment of patients with RTT 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.

9.2.13 Tanner Staging

The pubic hair growth and breast development of all adolescent patients (i.e., ≥ 7 years of age[71] at the time of signing the ICF or earlier, if clinically indicated by the onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging.[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.

9.2.14 Investigational Medicinal Product Accountability

Records of GWP42003-P accountability will be maintained according to Section 5.2.4.

GWP42003-P will be dispensed at Visit 1 (Day 1) and every scheduled visit thereafter (Visit 4 through Visit 14 [end of treatment/withdrawal visit]).

Caregivers will be asked to return all GWP42003-P (used and unused) at each relevant visit (Visits 4 through Visit 15 [end of taper]). The center will check the returned GWP42003-P against the expected usage. Any discrepancies will be discussed with the caregiver at the time of the visit and documented accordingly within the patient's source documents.

9.2.15 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 16), whether or not attributed to GWP42003-P 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 a 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 that meets SAE criteria should still be reported as a SAE.

Serious adverse events 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.

10 IMP WITHDRAWAL

In accordance with the Declaration of Helsinki[73] the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2)[74] the FDA regulations relating to GCP and clinical trials[75,76,77] the EU Clinical Trials Directive[78] the EU GCP Directive[79] 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/her future medical care by the physician or at the institution.

The patient must be withdrawn permanently discontinued from the trial 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** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5)

  Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where the transaminase elevation withdrawal 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 withdrawn permanently from the trial for any of the following:

- Patient or caregiver noncompliance
- AE (including clinically significant laboratory result) that, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial
- Failure to meet the eligibility criteria
- Any evidence of the use of drugs of abuse or drug diversion
- Suicidal ideation or behavior during the treatment period

The patient should attend a withdrawal visit (Visit 14) as soon as possible after the decision is made to permanently discontinue GWP42003-P. Patients who discontinue the 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 who discontinue the IMP and complete tapering of the 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. All assessments required at the withdrawal visit should be conducted, if possible. If the tapered dose is administered, patients should return for Visit 15 (End of taper), if possible. Wherever possible, a safety follow-up visit should take place 28 days from the date of last dose of IMP. 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 follows:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant) or diagnosis or worsening of a pre-existing condition that occurs at any point up to the post-treatment, final safety follow-up visit (Visit 16), which may or may not be considered to be related to GWP42003-P. 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 pretrial existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization that prolongs the scheduled hospital stay, in which case it would be considered an SAE (refer to Section 12.2).

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

12.1.2 Investigator

The term "investigator" refers to the trial principal investigator (PI) or a formally delegated trial physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur, which if suspected to be GWP42003-P-related, might be significant enough to lead to important changes in the way GWP42003-P 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., an SAE, when the event falls into one of the following criteria:

- Results in death
- Is life threatening*

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

* The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that, 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 Research Ltd 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 that occur up to the last formal safety follow-up (Visit 16). If the investigator subsequently becomes aware of any deaths or a new GWP42003-P-related SAE after the last formal follow-up period of the trial, these should still be reported to GW PVD.

Any other problem discovered after Visit 10 that 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 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 the final trial data lock. GW Research Ltd PVD may request safety follow-up information after the final trial visit in order to investigate a potential safety issue.

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

12.4 Pregnancy

Any patient, or patient's partner, who has become pregnant while receiving GWP42003-P or within 90 days of the last dose of GWP42003-P must be reported to 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 awareness. 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 GWP42003-P. However, if the investigator becomes aware of a new pregnancy outside this time limit, then he/she should report it as above. 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 GWP42003-P 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 GWP42003-P:

"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 the IMP (pretreatment) should be considered as not causally related. Where a pretreatment event worsens in severity following the first dose of the 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, especially SAEs, it is important that the investigator assess not only the possible role of GWP42003-P but also other potential contributing factors. Factors for consideration of the underlying cause may include the following:

- 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 safety follow-up visit (Visit 16), whether or not attributed to GWP42003-P 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 a change in the pattern or severity of seizures, should be documented in the CRF if deemed to meet the definition of an AE, in the investigator's opinion.

Any AE that meets the SAE criteria should still be reported as an 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 the 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., the month and year or, in exceptional circumstances, just the year). When the actual start date becomes known, the eCRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one 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 the AE start and stop dates relating to the overall event duration, regardless of severity.

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

E) Causality

See Section 12.5.

F) Action Taken with IMP

This question refers to the action taken with GWP42003-P due to an AE. The action with GWP42003-P must be classified as follows:

- None
- Dose reduced temporarily
- Dose reduced
- IMP interrupted
- IMP stopped

12.7 Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur post follow-up Visit 16, after the trial.

Adverse events considered related to GWP42003-P 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 he/she perceives 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 centers are required to submit to GW PVD the laboratory results for any patient after randomization who 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 GW PVD via e-mail (see Appendix 2.2) within 24 hours of becoming aware of the results. In addition, a copy of the patient's baseline laboratory results with all reports should be sent to 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 center as soon as possible (within 24 to 48 hours of notice of abnormal results) for a repeat assessment of ALT, AST, TBL, alkaline phosphatase, gamma-glutamyl transferase levels, eosinophils as well as for testing INR (prothrombin time), detailed history; and physical examination. Patients should be followed 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 be withdrawn from the trial.

Elevations in ALT or AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury but will be followed as detailed above, within 72 hours' notice of abnormal results. In cases where after Visit 1, ALT or AST are > 3 × ULN, INR testing must be requested. If only the hepatic function monitoring panel was requested and ALT or AST > 3 × ULN, both INR and hematology panel (eosinophils) must be requested. If the patient cannot return to the investigational center, repeat assessments may be done at a local laboratory, and the results should be 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[78] relevant parts of the FDA Code of Federal Regulations[80] and any national regulations, GW will inform the 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[52]: A compilation of the clinical and nonclinical safety data available on the IMP that are 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 ethics committees that have approved the trial, and the investigators. As required, the investigators should notify their regional IRBs/IECs of SAEs or SUSARs occurring at their center and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the 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[75] 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, were 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[80] states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multicenter trial may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW Research Ltd will inform the 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 the 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, as well as relevant updates between the period from ethical approval and the final database lock.

13 STATISTICAL CONSIDERATIONS

Further details of the proposed statistical analysis will be documented in a statistical analysis plan (SAP). Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power, and Significance Levels

There is no formal sample size calculation for this trial. All patients with RTT who completed the randomized, double-blind, placebo-controlled trial (GWND18064) who wish to take GWP42003-P and who meet eligibility criteria can be included in this trial.

Approximately 252 patients will be enrolled.

13.2 Interim Analysis

No formal interim analysis will be conducted.

13.3 Analysis Sets

For this trial there will be 1 analysis set:

Safety Analysis Set

- All patients who receive at least 1 dose of GWP42003-P in the trial will be included. Only patients for whom it has been confirmed that they did not take any GWP42003-P will be excluded from this safety analysis set. This analysis set will be used to report the safety data.

13.3.1 Protocol Deviations

Protocol deviations will be listed.

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of nonmissing values (n), mean, standard deviation, 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 in the RCT.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, randomized, prematurely terminated IMP, etc.) will be accounted for in the enrollment 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 Clinical Severity Scale score and *MECP2* mutation (confirmation and definition) will be summarized.

13.5.3 Concomitant Medication

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

13.6 Endpoints and Statistical Methods

The primary safety endpoint will be analyzed as detailed in Section 13.6.2. Secondary endpoints will be analyzed as detailed in Section 13.6.3. Exploratory endpoints will be analyzed as detailed in Section 13.6.4.

13.6.1 Evaluable Period

The start of the evaluable period of the OLE trial (Day 1) is defined as the date the patient took his/her first dose of IMP in the clinic at Visit 1. All data that will be collected during this trial will be summarized over time using appropriate descriptive statistics. Changes from baseline of the RCT will also be presented where appropriate.

13.6.2 Primary Safety Endpoints

The safety endpoints are listed below and will be evaluated as detailed in the following sections:

- AEs.
- Clinical laboratory parameters.
- Vital signs.
- Physical examination procedures.
- 12-lead 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).

13.6.2.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.2.2 Adverse Events

AEs 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 system organ class. 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.

13.6.2.3 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 each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and serum IGF-1 levels from baseline of the RCT to end of treatment will be summarized.

13.6.2.4 Clinical Laboratory Data

Clinical laboratory data at the end of treatment in the OLE and the change from baseline of the RCT to end of treatment will be summarized using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range.

13.6.2.5 Menstruation

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

13.6.2.5.1 Suicidality

Suicidality assessment responses will be summarized and listed as appropriate.

13.6.3 Secondary Endpoint(s)

There are several secondary endpoints. For each endpoint, the change from baseline of the RCT will be derived. For visit-based endpoints, baseline will be taken as the last measurement prior to the first dose of IMP (e.g. Visit 1 of the RCT).

The following secondary endpoints will be assessed by evaluating changes relative to the prerandomization baseline of the RCT and will be summarized using appropriate descriptive statistics:

- RSBQ.
- CGI-I.
- CGI-S.
- MBA-9.
- CSHQ.

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 trial visit (see Appendix 1). However, patients who withdraw from the trial are required to complete the procedures at Visit 14 at the time of withdrawal. For these patients, their Visit 14 data will be assigned to the nearest visit (for which the assessment is scheduled to be performed), based on the day of the visit. Further details will be specified in the SAP.

13.6.4 Exploratory Endpoint(s)

The following exploratory endpoints for the trial will be assessed by evaluating changes relative to the prerandomization baseline of the RCT and will be summarized by time point:

- SF-36.
- CHQ-PF50.
- Hospital Services Use Questionnaire
- Caregiver Assessment of Rett Symptoms.

13.6.5 Handling of Missing Data

There will be no imputation of missing data, and all observed data will be summarized.

14 SAFETY MONITORING COMMITTEE

No safety monitoring committee will be used in this trial.

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[73] the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] the EU Clinical Trials Directive[78] the EU GCP Directive[79] and the clinical trial regulations adopting European Commission Directives into national legislation.[81,82,83,84,85]

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 center by adding the center'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. The nominated caregiver will be asked to consent to complete the QoL questionnaires. In cases where the patient possesses adequate understanding, assent will be taken (if allowed per local regulations) along with parent(s)/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 enforced 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/nominated caregiver (as applicable) and by the person who conducted the informed consent/assent discussion. GW Research Ltd also requires a physician to be present for consent/assent and to sign the consent/assent forms. The original signed informed consent/assent forms should be retained and a copy

provided to the patients' parent(s)/legal representative/nominated caregiver (see Section 9.2.1).

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 center, 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 Pretrial 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[75,76,77,86] the EU Clinical Trials Directive[78] the EU GCP Directive[79] or the ICH Harmonised

Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] 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 will ensure that the center is informed of when screening of patients can commence.

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the eCRFs or other documents submitted to GW, patients should be identified by their 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[75,76,77,86] and the EU Clinical Trials Directive[78]and the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] 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 center, will be agreed with each center 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 trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related, essential documentation (as outlined in ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6[R2], Section 8.2[74]), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include the following:

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

In addition, all original source documents supporting entries in the eCRFs 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 on the 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[79] or if needed by GW.

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

16.3 Trial Monitoring and Data Collection

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

The GW trial monitor, or designee, is responsible for inspecting the eCRFs, questionnaires, and dosing schedule at regular intervals throughout the trial to verify

adherence to the protocol, completeness, accuracy and consistency of the data, and adherence to local regulations on the conduct of clinical research. The trial monitor must have 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 trial monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a 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[75,76,77,86] ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2)[74] and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable. 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[75,76,77,86] the EU Clinical Trials Directive[78], the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2),[74] and the sponsor's audit plans, representatives from GW's Clinical Quality Assurance Department may select this trial for audit. Inspection of center facilities, e.g. pharmacy, drug storage areas, and laboratories and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, the EU Clinical Trials Directive,[78] the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2),[74] and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the trial center in the event of any claim in respect of personal injury arising due to a patient's involvement in the trial, provided 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, provided that there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

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

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

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

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

16.7 Intellectual Property Rights

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

16.8 Confidential Information

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

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Appendix 1 Schedule of Assessments

Visit Number	1	2[a]	3[a]	4	5	6	7	8	9	10	11	12	13	14[b,c] EoT/ Withdrawal	15 (end of taper)	16[a] (follow-up)
Day Number (Visit Window)	**1**	**8 (±3)**	**15 (± 3)**	**29 (± 7)**	**57 (± 7)**	**85 (± 7)**	**141 (± 7)**	**197 (± 7)**	**281 (± 7)**	**365 (± 7)**	**456 (± 7)**	**547 (± 7)**	**638 (± 7)**	**729 (± 7)**	**739 (+ 7)**	**767 (+ 7)**
Informed consent and assent[d]	X[e]															
Eligibility check	X[e]															
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
New medical history	X[e]															
Adverse events	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Menstruation question (where appropriate)								X		X				X		
Physical examination (including body weight)	X[f]			X		X		X	X	X		X		X	(X)	
Height								X		X		X		X		
ECG	X[f]			X		X		X		X		X		X	(X)	
Vital signs	X[g]			X	X	X	X	X	X	X		X		X	X	
Clinical laboratory blood sampling (hematology and biochemistry)[h]	X[f]			X	X	X		X	X	X		X		X	(X)	
Hepatic function monitoring panel[i]							X[i]				X[i]		X[i]			
Dipstick urinalysis (where possible)	X[f]							X		X		X		X	(X)	

Visit Number		**1**	**2**[a]	**3**[a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**[b,c] **EoT/ Withdrawal**	**15 (end of taper)**	**16**[a] **(follow-up)**
Day Number (Visit Window)		**1**	**8 (±3)**	**15 (± 3)**	**29 (± 7)**	**57 (± 7)**	**85 (± 7)**	**141 (± 7)**	**197 (± 7)**	**281 (± 7)**	**365 (± 7)**	**456 (± 7)**	**547 (± 7)**	**638 (± 7)**	**729 (± 7)**	**739 (+ 7)**	**767 (+ 7)**
Serum pregnancy test (if appropriate)									X		X		X		X		
Caregiver completed questionnaire/assessment	RSBQ				X	X	X	X	X		X				X		
	CSHQ						X		X		X				X		
	Caregiver QoL questionnaire (SF-36)								X		X				X		
	Patient QoL questionnaire (CHQ-PF50)								X		X				X		
	Hospital Services Use Questionnaire	X[g]			X	X	X	X	X		X				X		
	Tanner Staging (where appropriate)								X		X				X		
	Caregiver Assessment of Rett Symptoms				X	X	X	X	X		X				X		
MBA-9							X		X		X				X		
CGI-S					X	X	X	X	X		X				X		
CGI-I					X	X	X	X	X		X				X		
Suicidality assessment		X[g]			X	X	X	X	X	X	X		X		X	X	
GWP42003-P dispensing		X[e]			X	X	X	X	X	X	X	X	X	X	X		
GWP42003-P collection and compliance review					X	X	X	X	X	X	X	X	X	X	X	X	
Dosing schedule[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

(X) = if clinically indicated; EoT = end of treatment

a Visit to be conducted by telephone.

b To be performed to all patients completing or withdrawing from the trial. Patients who withdraw early should commence the 10-day GWP42003-P taper period, if possible.

c A safety follow-up Visit 4 weeks after last GWP42003-P dose is required for all patients who withdraw from the trial or complete the trial.

d 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 parent(s)/legal representative consent. The nominated caregiver will be asked to complete the quality of life questionnaires.

e Always required.

f Required only if OLE Visit 1 is > 28 days after RCT Visit 9.

g Required if OLE Visit 1 does not occur on the same day as RCT Visit 9.

h Determination of serum IGF-1 levels at Visits 1, 8, 10, and 14 only; IGF-1 laboratory results will remain blinded throughout the trial.

i Hepatic function monitoring is required following increases in GWP42003-P dose or introduction of medications that are known to impact liver function. If the concerned change does not occur within 1 month of a scheduled biochemistry assessment, the investigator should perform an additional hepatic monitoring within 1 month of the change. Hepatic monitoring at Visit 7, 11 and 13 is required for patients taking concomitant valproic acid or whose dose exceeds 15 mg/kg/day.

j The dosing schedule is to be completed by the caregiver daily throughout the trial and reviewed at Visits 2 through 15.

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 Research Ltd (GW) master files (electronically and added to the trial master file at the end of the trial).

Appendix 2.2 Sponsor Contact Details

PI	**Email:** PI Tel: PI Fax: PI USA Toll-free Fax: PI
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1223 266 800 Fax: +44 (0) 1223 235 667

At the time of protocol production, the contract research organizations (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):

Trial Conduct	Premier Research Europe 1st Floor, Rubra 2 Mulberry Business Park Fishponds Road Wokingham, RG41 2GY United Kingdom Tel: PI

AN OPEN-LABEL EXTENSION TRIAL TO INVESTIGATE THE LONG-TERM SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME

Study Code: GWND19002

EudraCT Number: 2019-001605-24

CLINICAL PROTOCOL ANNEX 1

The purpose of this protocol annex is to detail changes which are applicable **only** to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064

GW Research Ltd
Sovereign House
Vision Park
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Histon
Cambridge CB24 9BZ
United Kingdom
Tel: +44 (0) 1223 266 800
Fax: +44 (0) 1223 235 667

Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol annex 1 entitled An Open-label Extension Trial to Investigate the Long-term Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome, dated 28 May 2020 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to Good Clinical Practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the trial and for all trial-related medical decisions.

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

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

Center No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

PI

Date: 02 June 2020

(DD Month YYYY)

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List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBD	Cannabidiol
COVID-19	Coronavirus disease 2019
EU	European Union
GCP	Good clinical practice
GW	GW Research Ltd
IMP	Investigational medicinal product
OLE	Open-label extension
RCT	Randomized controlled trial
TBL	Total bilirubin
ULN	Upper limit of normal

Definition of Terms

Term	Definition
Caregiver	An assigned patient's parent or designated care provider.
Day 1	The day a participant first receives investigational medicinal product in this trial.
End of treatment	Completion of the treatment period (Visit 14 [Day 729]), or withdrawal.
End of trial	Last participant last visit/telephone call.
Enrolled participant	Any patient whose parent(s)/legal representative has provided written informed consent for the patient 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.

1 RATIONALE

This addendum covers protocol changes which are applicable to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064:

- Allowance for patients to enroll into GWND19002 after the point of GWND18064 follow-up (Visit 11).
- Allowance for patients who withdrew from GWND18064 due to COVID-19 pandemic containment measures to enroll into GWND19002 at a later date, when appropriate.

There are no implications for the conduct of the GWND19002 trial for patients that were not affected by the COVID-19 pandemic containment measures, and no changes are required to the Clinical Protocol currently approved at each territory. Please see Section 3 for full details of changes.

2 SUMMARY OF THE ANNEX

2.1 Objective

Due to the COVID-19 pandemic situation, patients may have been unable to attend the scheduled clinic visits or local safety assessments deemed required for the safe continuation of investigational medicinal product (IMP) dosing. This situation may have resulted in the inability to complete GWND18064 or enroll into GWND19002 within the timeline stipulated in the protocol (up to GWND18064 Visit 11).

The objective of this annex is to define when patients whose participation in Study GWND18064 was disrupted by COVID-19 pandemic containment measures are allowed to take part in GWND19002 despite not meeting the criterion 'Patient has completed all scheduled visits of the treatment phase of the randomized controlled trial (RCT), GWND18064, and has transitioned to open-label extension (OLE) by the point of RCT follow-up (Visit 11)' defined in the GWND19002 protocol. The measures implemented via this protocol annex do not affect the primary objective of GWND19002, which is to evaluate the long-term safety of GWP42003-P in patients with Rett Syndrome.

3 DESIGN AND PROCEDURES

3.1 Patient Eligibility

With the exception of the inclusion criterion that requires patients must have completed all scheduled visits of the treatment phase of the RCT, GWND18064, and transitioned to OLE by the point of RCT follow-up (Visit 11), all inclusion and exclusion criteria defined in the GWND19002 protocol must be met. In addition, the following inclusion criteria apply:

Inclusion criteria

- Patient has completed all scheduled visits of the treatment phase of the RCT, either in clinic or completed as many scheduled assessments as feasible remotely, or has withdrawn from GWND18064 after discussion with the medical monitor due to inability to adequately monitor safety and benefit risk.
- Visit 1 is taking place no later than 3 months after screening of new subjects for study GWND18064 has reopened at their trial site.

Exclusion criteria

- Any history of suicidal behavior or any suicidal ideation in the last month or at Visit 1.
- Patient has clinically relevant abnormalities in the electrocardiogram measured at Visit 1 (including QT interval, corrected by Bazett's correction formula [QTcB] > 450 msec, average of 3 measurements).
- 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. If Visit 1 laboratory results indicate the patient is not eligible, the patient must be withdrawn. Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, international normalized ratio, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.
- Patient has received an IMP (other than GWND18064 IMP) since participation in GWND18064.
- Patient has been taking felbamate for less than 1 year prior to Visit 1

- Patient is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex® [nabiximols]) or cannabidiol oral solutions (excluding GWND18064 IMP) within the 3 months prior to Visit 1 and is unwilling to abstain for the duration of the trial.
- 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 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.
- Female patient is pregnant (positive pregnancy test) or lactating.

3.2 Trial Procedures

3.2.1 Visit 1 Procedures

Visit 1 must include the Visit 1 assessments listed in the GWND19002 protocol as required for patients for whom OLE Visit 1 occurs > 28 days after RCT Visit 9.

In addition the following assessments are required:

- Concomitant medications review (details of all current and recent medication; i.e., those taken within the previous 14 days of Visit 1)
- Menstruation question (where appropriate)
- Height
- Serum pregnancy test (if appropriate)
- Rett Syndrome Behaviour Questionnaire
- Children's Sleep Habits Questionnaire
- Caregiver QoL questionnaire (SF-36)
- Patient QoL questionnaire (CHQ-PF50)
- Tanner Staging (where appropriate)
- Caregiver Assessment of Rett Symptoms
- 9-items Motor Behavioral Assessment
- Clinical Global Impressions - Severity
- Clinical Global Impressions - Improvement (completed in relation to the baseline of the RCT, GWND18064 Visit 2)

4 DATA ANALYSIS

All Visit 1 data will be summarized for patients enrolling in the OLE under this protocol annex. Their data will be summarized in the same way as that of patients enrolling in the OLE under the GWND19002 protocol. The summary tables will present data from patients enrolling in the OLE under this protocol annex combined with that of patients enrolling in the OLE under the GWND19002 protocol. Their data will also be presented separately.

5 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol to country/sites affected by the COVID-19 pandemic containment situation. 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.

6 REFERENCES

No changes.

AN OPEN-LABEL EXTENSION TRIAL TO INVESTIGATE THE LONG-TERM SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME

Study Code: GWND19002

EudraCT Number: 2019-001605-24

CLINICAL PROTOCOL ANNEX 1

The purpose of this protocol annex is to detail changes which are applicable **only** to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064 or withdrew from GWND18064 due to sponsor administrative decision

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Fax: +44 (0) 1223 235 667

Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol annex 1 entitled An Open-label Extension Trial to Investigate the Long-term Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome, dated 11 Nov 2020 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation (ICH) Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the trial and for all trial-related medical decisions.

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

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

Center No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization PI

PI

Table of Contents

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBD	Cannabidiol
COVID-19	Coronavirus disease 2019
EU	European Union
GCP	Good clinical practice
GW	GW Research Ltd
IMP	Investigational medicinal product
OLE	Open-label extension
RCT	Randomized controlled trial
TBL	Total bilirubin
ULN	Upper limit of normal

Definition of Terms

Term	Definition
Caregiver	An assigned patient's parent or designated care provider.
Day 1	The day a participant first receives investigational medicinal product in this trial.
End of treatment	Completion of the treatment period (Visit 14 [Day 729]), or withdrawal.
End of trial	Last participant last visit/telephone call.
Enrolled participant	Any patient whose parent(s)/legal representative has provided written informed consent for the patient 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.

1 RATIONALE

This annex covers protocol changes which are applicable to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064 or withdrew from GWND18064 due to sponsor administrative decision:

- Allowance for patients to enroll into GWND19002 after the point of GWND18064 follow-up (Visit 11).
- Allowance for patients who withdrew from GWND18064 due to COVID-19 pandemic containment measures or withdrew from GWND18064 due to sponsor administrative decision to enroll into GWND19002 at a later date, when appropriate.

There are no implications for the conduct of the GWND19002 trial for patients who were not affected by the COVID-19 pandemic containment measures or administrative withdrawal, and no changes are required to the Clinical Protocol currently approved at each territory. Please see Section 3 for full details of changes.

2 SUMMARY OF THE ANNEX

2.1 Objective

Due to the COVID-19 pandemic situation, patients may have been unable to attend the scheduled clinic visits or local safety assessments deemed required for the safe continuation of investigational medicinal product (IMP) dosing. This situation may have resulted in the inability to complete GWND18064 or enroll into GWND19002 within the timeline stipulated in the protocol (up to GWND18064 Visit 11).

The objective of this annex is to define when patients whose participation in Study GWND18064 was disrupted by COVID-19 pandemic containment measures are allowed to take part in GWND19002 despite not meeting the criterion 'Patient has completed all scheduled visits of the treatment phase of the randomized controlled trial (RCT), GWND18064, and has transitioned to open-label extension (OLE) by the point of RCT follow-up (Visit 11)' defined in the GWND19002 protocol. This annex also applies to patients who withdrew from GWND18064 due to sponsor administrative decision. The measures implemented via this protocol annex do not affect the primary objective of GWND19002, which is to evaluate the long-term safety of GWP42003-P in patients with Rett Syndrome.

3 DESIGN AND PROCEDURES

3.1 Patient Eligibility

With the exception of the inclusion criterion that requires patients must have completed all scheduled visits of the treatment phase of the RCT, GWND18064, and transitioned to OLE by the point of RCT follow-up (Visit 11), all inclusion and exclusion criteria defined in the GWND19002 protocol must be met.

In addition, the following inclusion criteria apply:

Inclusion criteria

- Patient has completed all scheduled visits of the treatment phase of the RCT, either in clinic or completed as many scheduled assessments as feasible remotely, or has withdrawn from GWND18064 after discussion with the medical monitor due to inability to adequately monitor safety and benefit risk, or has withdrawn from GWND18064 due to sponsor administrative decision.

For patients who enroll after the point of RCT follow-up (Visit 11) the following additional exclusion criteria must be confirmed:

Exclusion criteria

- Any history of suicidal behavior or any suicidal ideation in the last month or at Visit 1.
- Patient has clinically relevant abnormalities in the electrocardiogram measured at Visit 1 (including QT interval, corrected by Bazett's correction formula [QTcB] > 450 msec, average of 3 measurements).
- 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. If Visit 1 laboratory results indicate the patient is not eligible, the patient must be withdrawn. Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, international normalized ratio, % eosinophils, gamma-glutamyl transferase, alkaline phosphatase, and eosinophils. Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.
- Patient has received an IMP (other than GWND18064 IMP) since participation in GWND18064.

- Patient has been taking felbamate for less than 1 year prior to Visit 1
- Patient is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex® [nabiximols]) or cannabidiol oral solutions (excluding GWND18064 IMP) within the 3 months prior to Visit 1 and is unwilling to abstain for the duration of the trial.
- 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 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.
- Female patient is pregnant (positive pregnancy test) or lactating.

3.2 Trial Procedures

3.2.1 Visit 1 Procedures

For patients who enroll after the point of RCT Visit 11, GWND19002 Visit 1 must include the Visit 1 assessments listed in the GWND19002 protocol as required for patients for whom OLE Visit 1 occurs > 28 days after RCT Visit 9 and, in addition, the following assessments are required:

- Concomitant medications review (details of all current and recent medication; i.e., those taken within the previous 14 days of Visit 1)
- Menstruation question (where appropriate)
- Height
- Serum pregnancy test (if appropriate)
- Rett Syndrome Behaviour Questionnaire
- Children's Sleep Habits Questionnaire
- Caregiver QoL questionnaire (SF-36)
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- Tanner Staging (where appropriate)
- Caregiver Assessment of Rett Symptoms
- 9-items Motor Behavioral Assessment
- Clinical Global Impressions - Severity
- Clinical Global Impressions - Improvement (completed in relation to the baseline of the RCT, GWND18064 Visit 2)

4 DATA ANALYSIS

All Visit 1 data will be summarized for patients enrolling in the OLE under this protocol annex. Their data will be summarized in the same way as that of patients enrolling in the OLE under the GWND19002 protocol. The summary tables will present data from patients enrolling in the OLE under this protocol annex combined with that of patients enrolling in the OLE under the GWND19002 protocol. Their data will also be presented separately.

5 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol to applicable country/sites. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

6 REFERENCES

No changes.

AN OPEN-LABEL EXTENSION TRIAL TO INVESTIGATE THE LONG-TERM SAFETY OF CANNABIDIOL ORAL SOLUTION (GWP42003-P, CBD-OS) IN PATIENTS WITH RETT SYNDROME

Study Code: GWND19002

EudraCT Number: 2019-001605-24

CLINICAL PROTOCOL ANNEX 1 AMENDMENT NUMBER 1

to be incorporated into the Protocol Annex, creating

CLINICAL PROTOCOL ANNEX 1 VERSION 2, DATE 11 NOVEMBER 2020

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Fax: +44 (0) 1223 235 667

Confidentiality Statement

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1 RATIONALE

This clinical protocol annex amendment 1 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 1 Version 2, Date 11 November 2020) addresses the following issue(s): Extension of annex scope to patients who withdraw from GWND18064 due to sponsor administrative decision (as a result of GWND18064 study termination)

- Removal of requirement for GWND18064 screening to have reopened at site within the last 3 months (given screening for GWND18064 is closed)

2 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 1 Version 2, Date 11 November 2020. It will be kept in the trial master file at GW as well as in each applicable investigational center file and, if applicable, pharmacy site file.

3 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 Version 1, Date 28 May 2020** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 Amendment 1 (Clinical Protocol Annex 1 Version 2 Date 11 November 2020)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Title Page p. 1	The purpose of this protocol annex is to detail changes which are applicable only to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064	The purpose of this protocol annex is to detail changes which are applicable only to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064 **or withdrew from GWND18064 due to sponsor administrative decision**	See Section 1
Section 1 Rationale p. 6	This addendum covers protocol changes which are applicable to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064: • Allowance for patients to enroll into GWND19002 after the point of GWND18064 follow-up (Visit 11). • Allowance for patients who withdrew from GWND18064 due to COVID-19 pandemic	This addendum covers protocol changes which are applicable to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064 **or withdrew from GWND18064 due to sponsor administrative decision**: • Allowance for patients to enroll into GWND19002 after the point of GWND18064 follow-up (Visit 11).	See Section 1

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 Version 1, Date 28 May 2020 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 Amendment 1 (Clinical Protocol Annex 1 Version 2 Date 11 November 2020) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Rationale p. 6 (continued)	containment measures to enroll into GWND19002 at a later date, when appropriate. There are no implications for the conduct of the GWND19002 trial for patients ~~**that**~~ were not affected by the COVID-19 pandemic containment measures, and no changes are required to the Clinical Protocol currently approved at each territory. Please see Section 3 for full details of changes.	• Allowance for patients who withdrew from GWND18064 due to COVID-19 pandemic containment measures **or withdrew from GWND18064 due to sponsor administrative decision** to enroll into GWND19002 at a later date, when appropriate. There are no implications for the conduct of the GWND19002 trial for patients **who** were not affected by the COVID-19 pandemic containment measures **or administrative withdrawal**, and no changes are required to the Clinical Protocol currently approved at each territory. Please see Section 3 for full details of changes.	

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 Version 1, Date 28 May 2020** *(Deleted wording is struck through and in bold)*	**Revised Wording from Clinical Protocol Annex 1 Amendment 1 (Clinical Protocol Annex 1 Version 2 Date 11 November 2020)** *(Revised wording is underscored and in bold)*	**Rationale for the amendment**
Section 2.1 Objective p. 7	(…) The objective of this annex is to define when patients whose participation in Study GWND18064 was disrupted by COVID-19 pandemic containment measures are allowed to take part in GWND19002 despite not meeting the criterion 'Patient has completed all scheduled visits of the treatment phase of the randomized controlled trial (RCT), GWND18064, and has transitioned to open-label extension (OLE) by the point of RCT follow-up (Visit 11)' defined in the GWND19002 protocol. (…)	(…) The objective of this annex is to define when patients whose participation in Study GWND18064 was disrupted by COVID-19 pandemic containment measures are allowed to take part in GWND19002 despite not meeting the criterion 'Patient has completed all scheduled visits of the treatment phase of the randomized controlled trial (RCT), GWND18064, and has transitioned to open-label extension (OLE) by the point of RCT follow-up (Visit 11)' defined in the GWND19002 protocol. **This annex also applies to patients who withdrew from GWND18064 due to sponsor administrative decision**. (…)	See Section 1

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 Version 1, Date 28 May 2020 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 Amendment 1 (Clinical Protocol Annex 1 Version 2 Date 11 November 2020) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 3.1 Patient Eligibility p. 8	Inclusion criteria • Patient has completed all scheduled visits of the treatment phase of the RCT, either in clinic or completed as many scheduled assessments as feasible remotely, or has withdrawn from GWND18064 after discussion with the medical monitor due to inability to adequately monitor safety and benefit risk. • ~~**Visit 1 is taking place no later than 3 months after screening of new subjects for study GWND18064 has reopened at their trial site.**~~ Exclusion criteria (…)	Inclusion criteria • Patient has completed all scheduled visits of the treatment phase of the RCT, either in clinic or completed as many scheduled assessments as feasible remotely, or has withdrawn from GWND18064 after discussion with the medical monitor due to inability to adequately monitor safety and benefit risk**, or has withdrawn from GWND18064 due to sponsor administrative decision**. **For patients who enroll after the point of RCT follow-up (Visit 11) the following additional exclusion criteria must be confirmed:** Exclusion criteria (…)	See Section 1

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 Version 1, Date 28 May 2020** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 Amendment 1 (Clinical Protocol Annex 1 Version 2 Date 11 November 2020)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 3.2.1 Visit 1 Procedures p. 9	Visit 1 must include the Visit 1 assessments listed in the GWND19002 protocol as required for patients for whom OLE Visit 1 occurs > 28 days after RCT Visit 9. **~~I~~**n addition, the following assessments are required: (…)	**For patients who enroll after the point of RCT Visit 11, GWND19002** Visit 1 must include the Visit 1 assessments listed in the GWND19002 protocol as required for patients for whom OLE Visit 1 occurs > 28 days after RCT Visit 9 **and, i**n addition, the following assessments are required: (…)	See Section 1
Section 5 Implementation of the Annex p. 11	This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol to country/sites **~~affected by the COVID-19 pandemic containment situation~~**. 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.	This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol to **applicable** country/sites. It will be kept in the trial master file at GW as well as in each investigational **center** file and, if applicable, pharmacy site file.	See Section 1

4 REFERENCES

N/A