SPONSOR: GW PHARMA LIMITED

A Double-blind, Randomized, Placebo-controlled, Parallel-group Trial of the Efficacy and Safety of Nabiximols Oromucosal Spray as Add-on Therapy in Patients with Spasticity Due to Multiple Sclerosis

Study Code: GWSP18023

EudraCT Number: 2019-002623-14

CLINICAL PROTOCOL

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol entitled "A Double-blind, Randomized, Placebo-controlled, Parallel-group Trial of the Efficacy and Safety of Nabiximols Oromucosal Spray as Add-on Therapy in Patients with Spasticity Due to Multiple Sclerosis", dated 01Jun2021 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s), the United States 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 patients during the trial and for all trial-related medical decisions.

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

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

Trial site No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: [redacted] Date: 01-Jul-2021 | 21:27 PDT

Clinical Operations Director (DD Month YYYY)

Signature: [redacted]

1 PROTOCOL SYNOPSIS

Trial Title	A Double-blind, Randomized, Placebo-controlled, Parallel-group Trial of the Efficacy and Safety of Nabiximols Oromucosal Spray as Add-on Therapy in Patients with Spasticity Due to Multiple Sclerosis
Clinical Trial Type	Phase 3
Indication	Symptomatic treatment of spasticity in patients with multiple sclerosis (MS)
Primary Objective	To establish the efficacy of nabiximols relative to placebo in reducing spasm count as part of the presentation of spasticity when used as adjunctive therapy in patients with MS who have not achieved adequate relief from other antispasticity agents
Secondary Objective(s)	• To evaluate the effect of nabiximols relative to placebo using the following patient-reported outcome measure of spasticity: – The MS Spasticity Scale (MSSS-88) total score • To evaluate the safety and tolerability of nabiximols • To evaluate the pharmacokinetics (PK) of nabiximols
Exploratory Objective(s)	To evaluate the effect of nabiximols relative to placebo using the following patient-reported outcome measures and clinician-administered assessments of spasticity: – The 8 MS Spasticity Scale (MSSS-88) subscale scores – The 11-point Numerical Rating Scale (NRS) for spasm severity – The 11-point NRS for spasticity • To evaluate the effect of nabiximols relative to placebo on health-related quality of life (QoL), as reflected by the 36-Item Short Form Health Survey (SF-36) • To evaluate the effect of nabiximols relative to placebo on functional outcome as reflected by walking ability using the Timed 25-Foot Walk (T25FW) test
Trial Design	This multicenter, double-blind, placebo-controlled trial includes a 28-day baseline period, a 12-week treatment period (comprising a 2-week titration phase and a 10-week maintenance phase), and 2-week follow-up period. Eligible patients will enter a 28-day baseline period. During baseline, patients will maintain their optimized oral antispasticity medication regimen (that must include at least 1 of baclofen, tizanidine or dantrolene) and record spasm count, 11-point NRS

	spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications once daily, around the same time of day, preferably in the evening before retiring to sleep, using an electronic daily diary. At Visit 2 (Day 1), eligible patients will be randomized to either nabiximols or placebo in a 1:1 ratio. Patients will initiate investigational medicinal product (IMP) treatment as a single spray in the evening on the first day of the titration phase. Patients will be advised to titrate IMP, beginning with 1 spray/day, to an optimized dose or to a maximum of 12 sprays/day over the first 14 days of treatment. Patients may leave a gap between sprays of approximately 15 minutes. Patients should continue at the same dose level achieved at the end of the titration phase (i.e., their daily optimized dose) ± 1 spray divided into a morning dose and an evening dose for the remainder of the treatment period. For the first 14 days of administering stable doses of IMP following titration, patients should be instructed to gradually decrease the interval between sprays to a target interval of approximately 1 minute between sprays. Patients will be advised to administer IMP at approximately the same time each day in a consistent manner in relation to food consumption. Morning and evening doses should be administered around the same time within 30 minutes after starting a snack or meal. Daily spasm count, the patient's symptom experiences, functional outcomes, health-related quality of life, safety, tolerability, and PK will be evaluated during the treatment period. Following randomization (Visit 2 [Day 1]), patients will attend the trial site on Visit 3 (Day 15), Visit 4 (Day 29), and Visit 5 (Day 57). The End of Treatment Visit (Visit 6) will occur on Day 85 (± 7 days). Participants who are permanently discontinued from receiving IMP will be recommended to continue the study and follow the original visit schedule and requirements (e.g. eDiary data entry) without taking IMP. If a participant discontinues from the IMP and is unwilling or unable to follow the original visit schedule and requirements without taking IMP, he or she should be asked, at the discretion of the investigator, to return to the study site for the Early Withdrawal Visit (see Schedule of Assessment table). Where possible, the Early Withdrawal Visit should be within 14 days from last IMP dose, unless consent is withdrawn from further study participant, or the participant is lost to follow-up. A Safety Follow-up Visit (Visit 7 [Day 99]) will take place 14 (± 4) days after the End of Treatment Visit or Withdrawal Visit for all patients.

	Patients who complete the trial will participate for a total of approximately 18 weeks (127 days), including the 28-day baseline period. Patients will have a maximum duration of 85 (± 7) days on IMP treatment.
Primary Endpoint	Change from baseline in the average daily spasm count (from Days 57 to 84 compared to the average daily spasm count for the baseline period).
Secondary Endpoints	Efficacy: • Change from baseline in total score of the MSSS-88 at Visit 6 Safety: • Frequency of treatment-emergent adverse events (AEs) • Change from baseline to each assessment timepoint by treatment arm for the following: – Clinical laboratory tests – Vital signs – 12-lead electrocardiograms (ECGs) Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, and at each subsequent timepoint with reference to the last assessment (since last visit) Pharmacokinetics: • Plasma concentrations for Δ^9-tetrahydrocannabinol (THC) and its relevant metabolites (11-hydroxy-Δ^9-tetrahydrocannabinol [11-OH-THC] and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol [11-COOH-THC]) and cannabidiol (CBD) and its relevant metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]) at Visits 2 (predose), 3, 4, 5, and 6
Exploratory Endpoints	Efficacy: • Change from baseline in the 8 subscale scores of the MSSS-88 at Visit 6 • Change from baseline in average daily 11-point NRS spasm severity score to Days 57 to 84 • Change from the last 7 days of baseline in average daily 11-point NRS spasticity score to Days 78 to 84 • Change from baseline in the SF-36 total score at Visit 6 (Day 85) • Change from baseline in Timed 25-Foot Walk (T25FW) test at Visit 6 (Day 85)

Sample Size	The trial will consist of 2 treatment arms: a nabiximols treatment arm and a placebo treatment arm. 446 patients (223 patients per treatment arm) will be randomized to nabiximols or placebo in a 1:1 ratio.
Summary of Patient Eligibility Criteria	**Inclusion Criteria** *Screening (Visit 1)* For inclusion in the trial, patient must fulfill ALL of the following criteria: • Male or female aged 18 years or above • Willing and able to give informed consent for participation in the trial • Willing and able (in the investigator's opinion) to comply with all trial requirements. (With the exception of the T25FW test, if the patient is non-ambulatory) • Has had a diagnosis with any disease subtype of MS, by revised 2017 McDonald criteria, for at least 12 months prior to Visit 1 and is expected to remain stable for the duration of the trial • Has had treatment with at least 1optimized oral antispasticity therapy prior to Visit 1 that must include either oral baclofen or oral tizanidine (monotherapy or combination therapy) • Currently receiving optimized treatment with at least 1 oral antispasticity medication (baclofen, tizanidine or dantrolene) and has been stable for at least 30 days prior to Visit 1. Despite optimization, the patient does not have adequate relief of spasticity signs and symptoms, including muscle spasms. Optimization of antispasticity medications is defined as having reached the most efficacious and best tolerated dose according to the relevant local prescribing information. The patient must be willing to maintain the same antispasticity medication and not plan to initiate a new course of physiotherapy for the duration of the trial • If currently receiving an MS disease-modifying therapy, it must be at a stable dose for at least 3 months prior to Visit 1 and is expected to remain stable for the duration of the trial • If currently receiving dalfampridine or fampridine, it must be at a stable dose for at least 3 months prior to Visit 1 and is expected to remain stable for the duration of the trial

	• Willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law • Willing to allow his or her primary care practitioner (if he or she has one) and/or treating neurologist (if he or she has one) to be notified of participation in the trial, if the primary care practitioner/treating neurologist is different than the investigator *Additional Inclusion Criteria at Randomization (Visit 2)* The patient is eligible for randomization in the trial if, in addition to continuing to meet the Screening (Visit 1) inclusion criteria, they also meet ALL of the following criteria during the first 28 days of the baseline period (Note: patients are expected to start completing their electronic diary in the evening of their screening visit): • In the opinion of the investigator, the patient is able to interpret and report spasm count data accurately • Completed their electronic diary for at least 25 of the first 28 days of the baseline period • Has an average daily spasm count of ≥ 4 during the first 28 days of the baseline period, as recorded by the patient • Has no more than 35 spasms on any single day of the first 28 days of the baseline period, as recorded by the patient • Does not have > 7 consecutive days without experiencing any spasm during the first 28 days of the baseline period If, for any reason, the patient is unable to attend the site for randomization within the visit window, the site should contact the Medical Monitor or the sponsor to discuss.

	In addition to meeting the Screening (Visit 1) inclusion criteria and additional inclusion criteria above, any patient with more than 28 days between Visit 1 and Visit 2 would need to meet ALL of the following criteria prior to randomization: • Completed their electronic diary for at least 85% of days between Visit 1 and Visit 2 • Has an average daily spasm count of ≥ 4 between Visit 1 and Visit 2 (randomization), as recorded by the patient • Has no more than 35 spasms on any single day between Visit 1 and Visit 2, as recorded by the patient • Does not have > 7 consecutive days without experiencing any spasm between Visit 1 and Visit 2 **Exclusion Criteria** The patient may not enter the trial if ANY of the following apply: • Previously participated in a clinical trial of nabiximols or has had a poor previous response or intolerance to nabiximols or other cannabinoid-containing products used for therapeutic purposes • Any concomitant disease or disorder that has spasticity-like symptoms or that may influence the patient's level of spasticity • Medical history suggests that relapse/remission is likely to occur during the trial, which, in the opinion of the investigator, is expected to influence the patient's spasticity • Has had a relapse of MS within the 60 days prior to Visit 1 • Has taken cannabis, or a cannabis-derived product for medicinal or recreational use within the 30 days prior to screening (Visit 1) or a positive blood drug test for THC at screening (Visit 1) • Is unwilling to abstain from use of cannabis, or a cannabis-derived product for medicinal or recreational purposes for the duration of the trial • Currently using botulinum toxin injection for the relief of spasticity (within 6 months of Visit 1) • Is unwilling to abstain from the use of botulinum toxin injection for the relief of spasticity for the duration of the trial • Currently taking antipsychotic medication • Currently taking benzodiazepines, unless the doses and dosing regimen have been stable for at least 30 days prior to Visit 1

	• Has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP • Has experienced myocardial infarction or clinically significant cardiac dysfunction within the 12 months prior to Visit 1 or has a cardiac disorder that, in the opinion of the investigator, would put the patient at risk of a clinically significant arrhythmia or myocardial infarction • Has a diastolic blood pressure of < 50 mmHg or > 105 mmHg or systolic blood pressure < 90 mmHg or > 150 mmHg (when measured in a supine position at rest for 5 minutes), or a postural drop in the systolic blood pressure of ≥ 20 mmHg or in diastolic blood pressure of ≥ 10 mmHg at Visit 1. All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant • Has clinically significant impaired renal function at Visit 1, as evidenced by an estimated creatinine clearance lower than 50 mL/min. All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant • Has moderately impaired hepatic function at Visit 1, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN). All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant • Male and fertile (i.e., after puberty unless permanently sterile by bilateral orchiectomy) unless willing to ensure that he uses male contraception (condom or vasectomy) or remains sexually abstinent during the trial and for 3 months thereafter

	• Female and of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months with a follicle stimulating hormone (FSH) ≥ 30 mIU/mL unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless willing to ensure that she uses a highly effective method of birth control (e.g., intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner, other highly effective hormonal methods or sexual abstinence) during the trial and for 3 months thereafter. Patients using combined hormonal methods or a progestogen-only pill or injection or implant should use an additional barrier method such as a condom or diaphragm during the trial and for 3 months thereafter • Female and pregnant (positive pregnancy test at Visit 1 or Visit 2 [predose]), lactating, or planning pregnancy during the course of the trial or within 3 months thereafter • Received an IMP within the 30 days prior to Visit 1 • Has any other clinically significant disease or disorder (including seizure disorder) that, in the opinion of the investigator, may put the patient, other patients, or site staff at risk because of participation in the trial, influence the interpretation of trial results, or may affect the patient's ability to take part in the trial • Has any abnormalities identified following a physical examination, clinical laboratory, serology, or other applicable screen procedures that, in the opinion of the investigator, would jeopardize the safety of the patient or the conduct of the study if he or she took part in the trial • Has any history of suicidal behavior in the 5 years prior to Visit 1 or a suicidal ideation score of 3, 4, or 5 on the C-SSRS in the month prior to Visit 1 • Has a history of severe psychiatric disorder that may be exacerbated by the use of a cannabinoid-containing product • Has donated blood during the 3 months prior to Visit 1 and is unwilling to abstain from donation of blood during the trial • Has been previously randomized into this trial

	• Has any known or suspected history of alcohol or substance use disorder within 1 year prior to Visit 1. Patients with nicotine use disorder are allowed to enroll • Currently using an illicit drug or current nonprescribed use of any prescription drug. A positive drug test at Visits 1 or 2 for a prescribed medication is not exclusionary at the investigator's discretion. A positive drug test at Visit 1 or predose at Visit 2 for illicit drugs may be repeated locally at the investigator's discretion • Has any planned clinical interventions or intends to change any or all medications that may have an effect on spasticity or MS during the trial • Currently taking drugs that are solely metabolized by UGT1A9 and UGT2B7 • Currently taking strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) • There is an expectation that the participant will require a new course of treatment with strong CYP3A4 inhibitors during the study duration (e.g., participant with recurrent fungal infections requiring intermittent treatment with itraconazole) • Patients who receive a positive coronavirus disease 2019 (COVID-19) antigen test result, potentially suggesting infective status, before randomization may be screen failed, at the discretion of the investigator Individuals who do not meet the criteria for participation in this trial (screen failure) because of, for example, fever due to a brief acute upper respiratory illness, having taken a prohibited over the counter medication within the excluded period, recent blood donation, due to the inclusion criterion related to the ability to interpret and report spasm count data accurately, or who could not be randomized for logistical reasons, can be rescreened once, at the discretion of the investigator or designee, with sponsor approval. Rescreened participants should be assigned a new screening number.

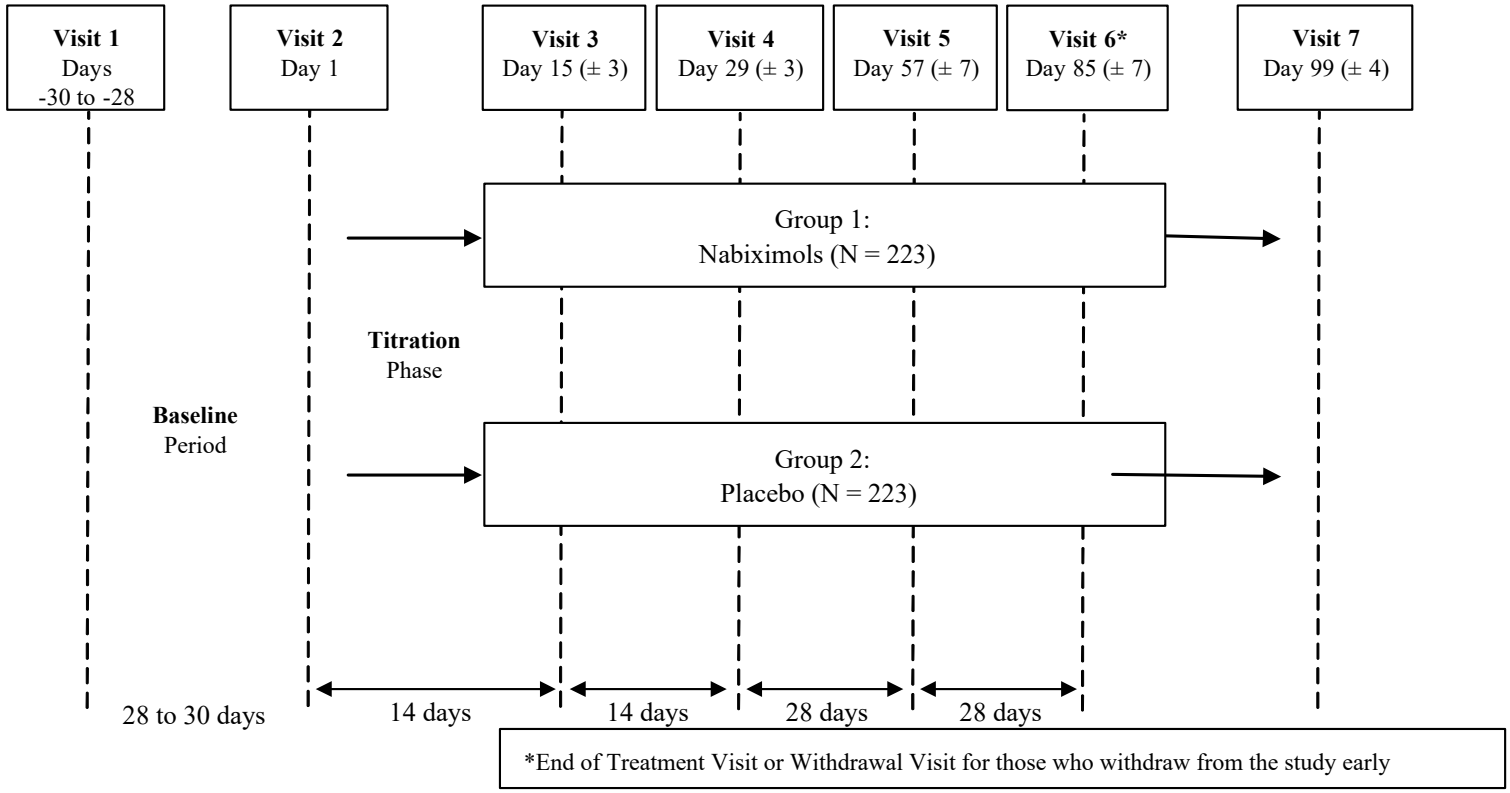
Criteria for Withdrawal	The patient must be withdrawn from the trial if any of the following apply: • Administrative decision by the investigator, GW Pharma Ltd, or regulatory authority • Withdrawal of patient consent • Lost to follow-up The patient must cease IMP and should remain in the trial if any of the following apply: • Pregnancy • Protocol deviation that is considered to potentially compromise the safety of the patient • Suicidal behavior, or a suicidal ideation score of 4 or 5 during the treatment period, as evaluated with the C-SSRS • 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 > 5 × ULN • ALT or AST > 3 × ULN **and** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5) • Any prohibited medication after Visit 1 The patient may be required to cease IMP at the discretion of the investigator and should remain in the trial for any of the following reasons: • Did not meet eligibility criteria • Patient 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 • Any evidence of drug abuse or diversion • Disease progression (defined as a relapse of MS requiring a change in treatment) • A positive COVID-19 test result after randomization

Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen	Nabiximols oromucosal spray (GW-1000-02) is a mixture of THC and CBD extracts derived from *Cannabis sativa* L. Each of the botanical extracts contains a cannabinoid as the major constituent (i.e., THC or CBD) and minor constituents, including other cannabinoid and noncannabinoid plant components, such as terpenes, sterols, and triglycerides. Nabiximols is presented as an oromucosal spray containing THC (27 mg/mL):CBD (25 mg/mL), dissolved in ethanol:propylene glycol (50% v/v) excipients with peppermint oil (0.05% v/v) flavoring. Each 100 µL spray delivers 2.7 mg THC and 2.5 mg CBD. Placebo to match nabiximols is presented as an oromucosal spray containing the excipients ethanol and propylene glycol (50% v/v) with colorings and flavored with peppermint oil (0.05% v/v). Each spray delivers 100 µL containing no active ingredients. Treatment will be initiated as a single spray in the evening on the first day of the titration phase (normally the day of Visit 2 [Day 1]). Patients will be advised to administer IMP at approximately the same time each day in a consistent manner in relation to food consumption. Morning and evening doses should be administered around the same time within 30 minutes after starting a snack or meal. Patients will gradually titrate their daily dose by 1 additional spray/day to an individually determined optimized dose, balancing efficacy and tolerability, or to a maximum number of 12 sprays/day. Patients may leave a gap between sprays of approximately 15 minutes. Patients should complete titration within 14 days of their first dose of IMP and should continue at the same dose level achieved at the end of titration (i.e., their daily optimized dose) ± 1 spray divided into a morning dose and an evening dose for the remainder of the treatment period. For the first 14 days of administering stable doses of IMP following titration, patients should be instructed to gradually decrease the interval between sprays to a target interval of approximately 1 minute between sprays. The total daily dose should be administered as a morning dose and an evening dose, which may be composed of a different number of sprays. Patients may take their morning dose spread out during the morning and their evening dose spread out during the evening, with a minimum interval between sprays as specified above (i.e., 15 minutes during the titration phase and a target of approximately 1 minute during the maintenance phase).
Control Arm	The control arm will receive matching placebo (excipients alone).

Procedures	Assessments/procedures include the following: • Informed consent, demographics, previous cannabis use, medical history, and electronic diary training (Visit 1) • Eligibility check and urine drug screen (Visit 1 and 2) • Blood THC test (Visit 1) • Randomization, urine pregnancy test (if appropriate), and IMP dosing training (Visit 2 [predose]) • Concomitant medications review, AE review, and vital signs measurement (Visits 1 through 7) • Physical examination (including height measurement at Visit 1 only) (Visits 1, 2 [predose], and 6) • Examination of oral mucosa and C-SSRS assessment (Visits 1 through 6) • Body weight measurement, 12-lead ECG, and clinical laboratory blood sampling (hematology and biochemistry) (Visits 1, 2 [predose], 4, and 6) • Dipstick urinalysis and serum pregnancy test (if appropriate) (Visits 1 and 6) • PK blood sampling – patients can choose the sparse PK sampling option or the semi-intensive PK sampling option: o Sparse option (Visit 2 [predose], and one sample will be collected at any time during Visits 3, 4, 5, and 6) o Semi-intensive option (Visit 2 [predose] and at just one of Visits 3, or 4, or 5 but not during Visit 6, at predose [collected upon arrival], and then at 2, 4, and 6 hours postdose during the clinic visit). • MSSS-88 assessment (Visits 2 [predose], 5, and 6) • T25FW test in ambulatory patients, and SF-36 assessment (Visits 2 [predose] and 6) • Medication Use Survey (Visit 6) • IMP dispensing (Visits 2 [predose], 3, 4, and 5) • IMP collection and compliance review (Visits 3, 4, 5, and 6)

	Electronic Patient Diary Patients will complete their electronic diary once daily, around the same time each day, during the baseline period prior to Visit 2 and throughout the trial until Visit 7, unless otherwise indicated, and the following assessments will be conducted: • Spasm count • 11-point NRS for spasm severity • 11-point NRS for spasticity • Use of antispasticity medications • IMP dosing record (Visits 2 through 6) • Dosing in relation to food intake (applicable only to the days preceding Visits 3, 4, 5, and 6) • Additional procedures to screen for the presence of or immunity against infectious diseases may be conducted according to local guidance and policy. In cases where patients are not able to attend study visits due to the presence of an infectious disease or other transmissible condition (such as COVID-19/other pandemic restrictions), the investigator will discuss with the Sponsor potential mitigation approaches.
Statistical Considerations	The primary and secondary endpoints will be compared between treatment arms, using appropriate statistical methods, through the 12-week double-blind treatment period. Statistical hypothesis testing will be 2-sided and carried out at the 5% level of significance. To control for Type 1 error, the primary endpoint and secondary efficacy endpoints will be tested hierarchically, starting with the primary endpoint, then the change from baseline in total score of MSSS-88. No additional adjustments for multiplicity will be made for the exploratory endpoints. Safety data will be summarized using appropriate statistical methods.
Sponsor	GW Pharma 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

11-COOH-THC	11-nor-9-carboxy-Δ^9-tetrahydrocannabinol
11-OH-THC	11-hydroxy-Δ^9-tetrahydrocannabinol
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy-cannabidiol
AD	Assistive device
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDS	Botanical drug substance
CBD	Cannabidiol
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
ECG	12-lead electrocardiogram
EDSS	Expanded Disability Status Scale
eCRF	Electronic case report form
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GW	GW Pharma Ltd
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board

IRT	Interactive response technology
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MS	Multiple sclerosis
MSSS-88	Multiple Sclerosis Spasticity Scale
MUS	Medication Use Survey
NRS	Numerical Rating Scale
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per protocol
PRN	As-needed
PT	Preferred term
PVD	Pharmacovigilance department
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	36-Item Short Form Health Survey
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
T25FW	Timed 25-Foot Walk
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
ULN	Upper limit of normal
US	United States

Definition of Terms

Term	Definition
Baseline period	The 28 (+2)-day period from screening (Visit 1 [Day -28(-2)] to the day before randomization (Visit 2 [Day 1]).
Clonus	A clinical manifestation of spasticity described as self-sustained rhythmic involuntary muscular contractions and relaxations in response to a muscle stretch.
Day 1	The day a patient is randomized and first receives investigational medicinal product in this trial.
End of trial	Last patient last visit or last contact, whichever occurs last.
Enrolled patient	Any patient who has provided written informed consent to take part in the trial.
International normalized ratio	A calculation made to standardize prothrombin time.
Investigational medicinal product	Term used to describe both investigational active product and reference therapy (placebo).
Investigator	Trial principal investigator or a formally delegated trial physician.
Spasm	A clinical manifestation of spasticity described as a sudden, involuntary contraction of a muscle.
Spasticity	A velocity-dependent increase in muscle tone resulting from an upper motor neuron lesion. Clinically, spasticity manifests as muscle stiffness or tightness, increased tendon reflexes, clonus, and flexor and extensor spasms.

2 OBJECTIVES

2.1 Objectives and Endpoints

An overview of objectives and endpoints is shown in Table 2-1.

Table 2-1 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To establish the efficacy of nabiximols relative to placebo in reducing spasm count as part of the presentation of spasticity when used as adjunctive therapy in patients with multiple sclerosis (MS) who have not achieved adequate relief from other antispasticity agents	• Change from baseline in average daily spasm count (from Days 57 to 84 compared to the average daily spasm count for the baseline period)
Secondary Objectives	**Secondary Endpoints**
The secondary endpoints are change in MS Spasticity Scale (MSSS-88) total score, safety, tolerability, and pharmacokinetics (PK).	
• To evaluate the effect of nabiximols relative to placebo using the following patient-reported outcome measure of spasticity: o The MSSS-88 total score	Efficacy: • Change from baseline in total score of the MSSS-88 at Visit 6
• To evaluate the safety and tolerability of nabiximols	The following outcomes will be assessed at distinct time points during the 12 weeks of the double-blind treatment period. • Frequency of treatment-emergent adverse events (TEAEs) • Change from baseline to each assessment timepoint by treatment arm for the following: o Clinical laboratory tests o Vital signs o 12-lead electrocardiograms (ECGs) • Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, and at each subsequent timepoint with reference to the last assessment (since last visit)

Table 2-1 Objectives and Endpoints	
• To evaluate the PK of nabiximols	• Plasma concentrations for THC and its relevant metabolites (11-hydroxy-Δ9-tetrahydrocannabinol [11-OH-THC] and 11-nor-9-carboxy Δ9 tetrahydrocannabinol [11-COOH-THC]) and CBD and its relevant metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]) at Visits 2 (predose), 3, 4, 5, and 6
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of nabiximols relative to placebo using the following patient-reported outcome measures and clinician-administered assessments of spasticity: o The 8 MS Spasticity Scale (MSSS-88) subscale scores o The 11-point Numerical Rating Scale (NRS) for spasm severity o The 11-point NRS for spasticity • To evaluate the effect of nabiximols relative to placebo on health-related QoL, as reflected by the 36-Item Short Form Health Survey (SF-36) • To evaluate the effect of nabiximols relative to placebo on functional outcome as reflected by walking ability using the Timed 25-Foot Walk (T25FW) test	• The change from baseline in the 8 subscale scores of the MSSS-88 at Visit 6 • Change from baseline in average daily 11-point NRS spasm severity score to Days 57 to 84 • Change from the last 7 days of baseline in average daily 11-point NRS spasticity score to Days 78 to 84 • Change from baseline in the SF-36 total score at Visit 6 (Day 85) • Change from baseline in Timed 25-Foot Walk (T25FW) test at Visit 6 (Day 85)

Table 2-1 Objectives and Endpoints
Primary Estimand: The primary estimand for this study is defined by the following 3 components: • Target population: patients with spasticity due to MS who have not achieved adequate relief from other antispasticity agents but have optimized treatment • Endpoint: change from baseline in average daily spasm frequency count (from Days 57 to 84 compared to the average daily spasm count for the baseline period) • Measure of intervention effect: mean difference in change from baseline between patients randomized to nabiximols compared to patients randomized to placebo, regardless of treatment compliance and change of other antispasticity medications; following a treatment policy strategy for handling intercurrent events. All randomized patients and all measurements collected after treatment discontinuation and after change in antispasticity medication will be included in the primary analysis.

3 BACKGROUND AND RATIONALE

3.1 Disease

Multiple sclerosis is a progressive, chronic, immune-mediated disease of the central nervous system[1,2], diagnosed predominantly in young adults with more than 2.3 million people affected worldwide[3]. It is the most common neurological disease in young and middle-aged adults, resulting in marked physical disability, inability to work or early retirement, significantly impaired QoL, and a substantial burden on society in terms of associated costs as the disease evolves[4,5]. Multiple sclerosis is clinically characterized by a broad range of signs and symptoms, the most common being restricted mobility, spasticity, fatigue, sensory deficits, weakness, pain, bladder dysfunction, cognitive dysfunction, and visual impairment[6,7].

The pathology of MS is characterized by autoimmune damage of neuronal axons and destruction of the protective myelin sheath (demyelination). Several signs and symptoms may occur as a consequence of the nerve damage; muscle spasticity (a velocity-dependent increase in muscle tone resulting from an upper motor neuron lesion) is one of the most common manifestations of MS, affecting more than 80% of patients with MS during the course of the disease[6,8,9]. Multiple sclerosis spasticity clinically manifests as symptoms, such as muscle stiffness or tightness, and signs including increased tendon reflexes, clonus, and flexor and extensor spasms mainly in the extensor muscles of the lower limbs and flexor muscles of the upper limbs. On a daily basis, severity may be exacerbated by a range of concurrent medical conditions, such as urinary infections. The QoL of patients with MS worsens as spasticity severity increases[5,10,11].

The most important goals in the treatment of patients with MS-induced spasticity are to avoid or eliminate triggers that may elicit spasms or enhance spasticity, to reduce pain and symptoms of spasticity, to improve or maintain functional abilities and QoL, and to facilitate nursing. If physiotherapy, as a generally accepted first basic treatment option, is not sufficient, antispasticity medications should be tried[12]. Depending on the severity of generalized spasticity, drug treatment varies widely, reliant on approved drugs that may differ between geographical regions. Commonly used medications such as baclofen, tizanidine, or dantrolene are taken orally. Their mode of action varies, but all cause muscle relaxation.

Both incidence and severity of MS spasticity increase as the disease evolves, appearing in more than 80% of patients with MS and reaching a moderate or severe intensity in over a third of cases despite available treatments[6,13,14]. Multiple sclerosis spasticity of at least

moderate severity is present in approximately a third of patients with a 10-year history of the disease[14].

3.2 Nabiximols Background

The investigational medicinal product (IMP) nabiximols (GW-1000-02) (named Sativex® in Canada, Spain, and the United Kingdom and also named Sativex oromucosal spray; United States [US] Adopted Name: Nabiximols; World Health Organization Anatomical Therapeutic Chemical Code: N02BG10) is formulated from 2 genetically distinct varieties of the *Cannabis sativa* L. plant, which are defined by their chemical profiles (chemotypes). GW Pharma Ltd (GW) produces chemotypes of *Cannabis sativa* L. that contain principally 1 of the 2 major cannabinoids, Δ^9-tetrahydrocannabinol (THC) or cannabidiol (CBD). Production under controlled conditions ensures consistency in the starting materials. Dried plant material is extracted and further processed to yield the THC botanical drug substance (BDS) and CBD BDS. The extracts also contain smaller amounts of minor cannabinoids and other plant-derived compounds.

Nabiximols contains amounts of both THC BDS and CBD BDS to yield similar concentrations of THC and CBD, dissolved in the excipients ethanol and propylene glycol and delivered as an oromucosal spray. Peppermint oil is used in the spray preparation as a flavoring agent to mask the taste and odor of plant-based components present in the product. The oromucosal spray is administered under the tongue or inside the cheeks and delivers 2.7 mg THC and 2.5 mg CBD per 100 µL spray.

For details on the pharmacological activity of nabiximols, please refer to the investigator's brochure (IB)[15].

3.3 Rationale

Nabiximols is currently authorized across 28 countries for the symptomatic improvement of patients with moderate to severe spasticity due to MS who have not responded adequately to other antispasticity medications on the basis of favorable treatment effects on the NRS spasticity compared to placebo. The data to establish a favorable benefit-risk ratio for nabiximols and to support the registration for this indication globally were generated in a series of Phase 3 trials with and without enrichment design, with change from baseline in NRS spasticity score at the end of treatment as the primary endpoint.

The effects of nabiximols on muscle spasms were evaluated in some of the pivotal trials; however, changes in spasms were not the main focus of these trials. Hence, different outcome measures were used for the assessment of spasm frequency across trials, and data were collected with different means (e.g., paper diary and interactive voice response system). There was evidence of efficacy of nabiximols in reducing spasm frequency

based on post-hoc analyses; however, no nabiximols trial evaluated the effect on muscle spasms as a primary or secondary endpoint. Muscle spasms are quantifiable and represent 1 of the 3 cardinal features of spasticity in patients with MS (i.e., increase in muscle tone, spasms, and clonus). Demonstration of efficacy in reducing spasm count should support the overall benefit-risk ratio of nabiximols in the treatment of spasticity associated with MS.

Trial GWSP18023 is being conducted to demonstrate the efficacy of nabiximols in the treatment of muscle spasms associated with MS and the data generated may support registration or labeling of nabiximols worldwide.

3.4 Clinical Hypothesis

The primary clinical hypothesis is that there will be a difference between nabiximols and placebo in their effect on spasm count as measured by the change from baseline in the average daily spasm count from Days 57 to 84 relative to the average daily spasm count for the baseline period.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This multicenter, double-blind, placebo-controlled trial includes a 28-day baseline period, a 12-week treatment period (comprising a 2-week titration phase and a 10-week maintenance phase), and a 2-week follow-up period.

Eligible patients will enter a 28-day baseline period. During baseline, patients will maintain their optimized oral antispasticity medication regimen (that must include at least 1 of baclofen, tizanidine, or dantrolene) and record spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications once daily, around the same time of day, preferably in the evening before retiring to sleep, using an electronic daily diary. At Visit 2 (Day 1), eligible patients will be randomized to either nabiximols or placebo in a 1:1 ratio.

Patients will initiate IMP treatment as a single spray in the evening on the first day of the titration phase. Patients will be advised to titrate IMP, beginning with 1 spray/day, to an optimized dose or to a maximum of 12 sprays/day over the first 14 days of treatment. Patients may leave a gap between sprays of approximately 15 minutes. Patients should continue at the same dose level achieved at the end of the titration phase (i.e., their daily optimized dose) ± 1 spray divided into a morning dose and an evening dose for the remainder of the treatment period. For the first 14 days of administering stable doses of IMP following titration, patients should be instructed to gradually decrease the interval between sprays to a target interval of approximately 1 minute between sprays. Patients will be advised to administer IMP at approximately the same time each day in a consistent manner in relation to food consumption. Morning and evening doses should be administered around the same time within 30 minutes after starting a snack or meal.

Daily spasm count, the patient's symptom experiences, functional outcomes, health-related QoL, safety, tolerability, and PK will be evaluated during the treatment period.

Following randomization (Visit 2 [Day 1]), patients will attend the trial site on Visit 3 (Day 15), Visit 4 (Day 29), and Visit 5 (Day 57). The End of Treatment Visit (Visit 6) will occur on Day 85 (±7 days). Participants who are permanently discontinued from receiving IMP will be recommended to continue the study and follow the original visit schedule and requirements (e.g., eDiary data entry) without taking IMP.

If a participant discontinues from the IMP and is unwilling or unable to follow the original visit schedule and requirements without taking IMP, he or she should be asked, at the discretion of the investigator, to return to the study site for the Early Withdrawal Visit (see Schedule of Assessment table [APPENDIX 1]). Where possible, the Early

Withdrawal Visit should be within 14 days from last IMP dose, unless consent is withdrawn from further study participant, or the participant is lost to follow-up.

A Safety Follow-up Visit (Visit 7 [Day 99]) will take place 14 (± 4) days after the End of Treatment Visit or Withdrawal Visit for all patients.

Patients who complete the trial will participate for a total of approximately 18 weeks (127 days), including the 28-day baseline period. Patients will have a maximum duration of 85 (± 7) days on IMP treatment.

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.

4.2 Number of Sites

Approximately 65 sites (US and Europe) are expected to participate in this trial. Additional trial sites may be used in order to supplement recruitment.

4.3 Number of Patients

A total of 446 patients (223 patients per treatment arm) will be randomized to nabiximols or placebo in a 1:1 ratio.

5 INVESTIGATIONAL MEDICINAL PRODUCT

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

5.1 Nabiximols

Product code: GW-1000-02

Nabiximols is presented as an oromucosal spray containing THC (27 mg/mL):CBD (25 mg/mL) dissolved in ethanol:propylene glycol (50% v/v) excipients with peppermint oil (0.05% v/v) flavoring. Each 100 µL spray delivers 2.7 mg THC and 2.5 mg CBD.

5.2 Placebo

Placebo to match nabiximols is presented as an oromucosal spray containing the excipients ethanol and propylene glycol (50% v/v) with colorings (FD&C Yellow No.5 [0.0260% v/v], FD&C Yellow No.6 [0.038% v/v], FD&C Red No.40 [0.0033% v/v], and FD&C Blue No.1 [0.00058% v/v]) and flavored with peppermint oil (0.05% v/v). Each spray delivers 100 µL containing no active ingredients.

5.3 Packaging, Storage, and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled, and/or distributed by GW or delegated contractors. The IMP will be presented as an oromucosal spray in a brown plastic-coated, glass vial. The IMP will be dispensed at each relevant visit. A unique identification number will be used to identify each box and the IMP it contains. The unique identification number, together with the packaging reference number, will permit full traceability of manufacture, pack, and label activities conducted at or on behalf of GW and the IMP information held on the interactive response technology (IRT). GW will ensure that all IMP provided is fully labeled and packaged.

Label text will include the following information, as a minimum:

- Sponsor’s name and address
- Product identification (e.g., “Nabiximols or Placebo”)
- Product details
- Dose and potency
- Vial number
- Batch number
- Trial code
- Site details
- 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 patient.

5.3.2 Storage

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

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

Patients will be instructed to store IMP in a refrigerator (2°C to 8°C). Once the spray container is opened and in use, refrigerated storage is not necessary, but the IMP should not be stored above 25°C. The spray container should be stored upright. Patients will be provided with further instructions regarding home storage requirements for the IMP.

5.3.3 Supply and Return of Investigational Medicinal Product

IMP will be transported to approved country depots and trial sites in compliance with good distribution practice guidelines. All IMP will be shipped with a product release certificate that includes a physical description of the product for confirmation of identity on receipt.

Once a trial site has been activated via the IRT at trial initiation, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator’s site, who will check the amount received (against the IRT Shipment Request) and condition of the

drug (i.e., integrity, physical appearance, and temperature during transit). Details of the IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The site will acknowledge the IMP receipt via the IRT and will complete any receipt forms required. The IMP will be dispensed and returned as detailed in Section 8.4 with further IMP shipments to be initiated by IRT. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GW/depot or destroyed at a GW approved site if agreed in writing by the trial monitor.

5.3.4 Investigational Medicinal Product Accountability

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

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

IMP will be dispensed at Visits 2, 3, 4, and 5. Patients will be asked to return all IMP (used and unused) at each subsequent visit (Visits 3, 4, 5, and 6). The trial site will check the returned IMP against the usage recorded in the electronic diary via electronic Clinical Report Form (eCRF) accountability calculations. Any discrepancies will be discussed with the patient at the time of the visit and documented accordingly within the patient's source documents. Refer to Section 9.2.18.2.1 for the list of triggering drug accountability discrepancies associated with monitoring of drug abuse liability.

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

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

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

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

5.3.5 Post-trial Provision

There will be no post-trial provision of nabiximols.

A summary of the results of this trial will be made available on https://www.clinicaltrials.gov as required by US law and on https://www.clinicaltrialsregister.eu/ of the European Union (EU) Clinical Trials Register.

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, race, and sex; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

Screening (Visit 1)

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

1. Male or female aged 18 years or above.
2. Willing and able to give informed consent for participation in the trial (see Section 15.2).
3. Willing and able (in the investigator's opinion) to comply with all trial requirements. (With the exception of the T25FW test, if the patient is non-ambulatory).
4. Has had a diagnosis with any disease subtype of MS, by revised 2017 McDonald criteria, for at least 12 months prior to Visit 1 and is expected to remain stable for the duration of the trial.
5. Has had treatment with at least 1 optimized oral antispasticity therapy prior to Visit 1 that must include either oral baclofen or oral tizanidine (monotherapy or combination therapy).
6. Currently receiving optimized treatment with at least 1 oral antispasticity medication (baclofen, tizanidine, or dantrolene) and has been stable for at least 30 days prior to Visit 1. Despite optimization, the patient does not have adequate relief of spasticity signs and symptoms, including muscle spasms. Optimization of antispasticity medications is defined as having reached the most efficacious and best tolerated dose according to the relevant local prescribing information. The patient must be willing to maintain the same antispasticity medication and not plan to initiate a new course of physiotherapy for the duration of the trial.
7. If currently receiving an MS disease-modifying therapy, it must be at a stable dose for at least 3 months prior to Visit 1 and is expected to remain stable for the duration of the trial.
8. If currently receiving dalfampridine or fampridine, it must be at a stable dose for at least 3 months prior to Visit 1 and is expected to remain stable for the duration of the trial.
9. Willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law.
10. Willing to allow his or her primary care practitioner (if he or she has one) and/or treating neurologist (if he or she has one) to be notified of participation in the trial, if the primary care practitioner/treating neurologist is different than the investigator.

Additional Inclusion Criteria at Randomization (Visit 2)

Patients are eligible for randomization in the trial if, in addition to continuing to meet the Screening (Visit 1) inclusion criteria, they also meet ALL of the following criteria during the first 28 days of the baseline period. (Note: patients are expected to start completing their electronic diary in the evening of their screening visit):

11. In the opinion of the investigator, the patient is able to interpret and report spasm count data accurately
12. Completed their electronic diary for at least 25 of the first 28 days of the baseline period
13. Has an average daily spasm count of ≥ 4 during the first 28 days of the baseline period, as recorded by the patient
14. Has no more than 35 spasms on any single day of the first 28 days of the baseline period, as recorded by the patient
15. Does not have > 7 consecutive days without experiencing any spasm during the first 28 days of the baseline period

If, for any reason, the patient is unable to attend the site for randomization within the visit window, the site should contact the Medical Monitor or the sponsor to discuss.

In addition to meeting the Screening (Visit 1) inclusion criteria and additional inclusion criteria 11 to 14, any patient with more than 28 days between Visit 1 and Visit 2 would need to meet ALL of the following criteria prior to randomization:

16. Completed their electronic diary for at least 85% of days between Visit 1 and Visit 2
17. Has an average daily spasm count of ≥ 4 between Visit 1 and Visit 2 (randomization), as recorded by the patient
18. Has no more than 35 spasms on any single day between Visit 1 and Visit 2, as recorded by the patient
19. Does not have > 7 consecutive days without experiencing any spasm between Visit 1 and Visit 2

6.2 Exclusion Criteria

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

1. Previously participated in a clinical trial of nabiximols or has had a poor previous response or intolerance to nabiximols or other cannabinoid-containing products used for therapeutic purposes.
2. Any concomitant disease or disorder that has spasticity-like symptoms or that may influence the patient's level of spasticity.
3. Medical history suggests that relapse/remission is likely to occur during the trial, which, in the opinion of the investigator, is expected to influence the patient's spasticity.

4. Has had a relapse of MS within the 60 days prior to Visit 1.
5. Has taken cannabis, or a cannabis-derived product for medicinal or recreational use within the 30 days prior to screening (Visit 1) or a positive blood drug test for THC at screening (Visit 1).
6. Is unwilling to abstain from use of cannabis, or a cannabis-derived product for medicinal or recreational purposes for the duration of the trial.
7. Currently using botulinum toxin injection for the relief of spasticity (within 6 months of Visit 1)
8. Is unwilling to abstain from the use of botulinum toxin injection for the relief of spasticity for the duration of the trial.
9. Currently taking antipsychotic medication.
10. Currently taking benzodiazepines, unless doses and dosing regimen have been stable for at least 30 days prior to Visit 1.
11. Has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP.
12. Has experienced myocardial infarction or clinically significant cardiac dysfunction within the 12 months prior to Visit 1 or has a cardiac disorder that, in the opinion of the investigator, would put the patient at risk of a clinically significant arrhythmia or myocardial infarction.
13. Has a diastolic blood pressure of < 50 mmHg or > 105 mmHg or systolic blood pressure < 90 mmHg or > 150 mmHg (when measured in a supine position at rest for 5 minutes), or a postural drop in the systolic blood pressure of ≥ 20 mmHg or in diastolic blood pressure of ≥ 10 mmHg at Visit 1. All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant.
14. Has clinically significant impaired renal function at Visit 1, as evidenced by an estimated creatinine clearance lower than 50 mL/min. All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant.
15. Has moderately impaired hepatic function at Visit 1, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 × upper limit of normal (ULN). All measurements will be performed singly and can be repeated once, if any are outside the reference range but not considered clinically significant.
16. Male and fertile (i.e., after puberty unless permanently sterile by bilateral orchiectomy) unless willing to ensure that he uses male contraception (condom or vasectomy) or remains sexually abstinent during the trial and for 3 months thereafter.
17. Female and of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months with a follicle stimulating hormone (FSH) ≥ 30 mIU/mL unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) unless willing to ensure that she uses a highly effective method of birth control (e.g., intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner, other highly effective hormonal methods or sexual

abstinence) during the trial and for 3 months thereafter. Patients using combined hormonal methods or a progestogen-only pill or injection or implant should use an additional barrier method such as a condom or diaphragm during the trial and for 3 months thereafter (see Section 9.2.2).

18. Female and pregnant (positive pregnancy test at Visit 1 or Visit 2 [predose]), lactating, or planning pregnancy during the course of the trial or within 3 months thereafter.
19. Received an IMP within the 30 days prior to Visit 1.
20. Has any other clinically significant disease or disorder (including seizure disorder) that, in the opinion of the investigator, may put the patient, other patients, or site staff at risk because of participation in the trial, influence the interpretation of trial results, or may affect the patient's ability to take part in the trial.
21. Has any abnormalities identified following a physical examination, clinical laboratory, serology, or other applicable screen procedures that, in the opinion of the investigator, would jeopardize the safety of the patient or the conduct of the study if he or she took part in the trial.
22. Has any history of suicidal behavior in the 5 years prior to Visit 1 or a suicidal ideation score of 3, 4, or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) in the month prior to Visit 1.
23. Has a history of severe psychiatric disorder that may be exacerbated by the use of a cannabinoid-containing product.
24. Has donated blood during the 3 months prior to Visit 1 and is unwilling to abstain from donation of blood during the trial.
25. Has been previously randomized into this trial.
26. Has any known or suspected history of alcohol or substance use disorder within 1 year prior to Visit 1. Patients with nicotine use disorder are allowed to enroll.
27. Currently using an illicit drug or current nonprescribed use of any prescription drug. A positive drug test at Visits 1 or 2 for a prescribed medication is not exclusionary at the investigator's discretion. A positive drug test at Visit 1 or predose at Visit 2 for illicit drugs may be repeated locally at the investigator's discretion.
28. Has any planned clinical interventions or intends to change any or all medications that may have an effect on spasticity or MS during the trial.
29. Currently taking drugs that are solely metabolized by UGT1A9 and UGT2B7 (see APPENDIX 4).
30. Currently taking strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort).
31. There is an expectation that the participant will require a new course of treatment with strong CYP3A4 inhibitors during the study duration (e.g., participant with recurrent fungal infections requiring intermittent treatment with itraconazole).

32. Patients who receive a positive coronavirus disease 2019 (COVID-19) antigen test result, potentially suggesting infective status, before randomization may be screen failed, at the discretion of the investigator.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of, for example, fever due to a brief acute upper respiratory illness, having taken a prohibited over the counter medication within the excluded period, recent blood donation, due to the inclusion criterion related to the ability to interpret and report spasm count data accurately, or who could not be randomized for logistical reasons, can be rescreened once, at the discretion of the investigator or designee with sponsor approval. Rescreened participants should be assigned a new screening number.

7 PATIENT ENROLLMENT

Before patients may be entered into the trial, GW requires a copy of the relevant site's institutional review board (IRB) or independent ethics committee (IEC) written approval of the protocol, informed consent form (ICF), and other patient information material. Patients will be considered enrolled in the trial from the time of providing written informed consent. All patients must personally sign and date the consent form prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2).

7.1 Treatment Assignment

At the start of Visit 1, enrolled patients will be allocated a unique patient number in a sequential order by trial site. Following randomization, GW will provide all IMP in a packed and labeled state, and the IRT will identify the pack number to be dispensed to the patient at each relevant visit according to the treatment arm assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The treatment allocation schedule will have balanced randomly permuted blocks, stratified by region (US versus non-US) and prior cannabis use defined as any pattern of recreational or medicinal use, which would typically exclude isolated, unintentional, or passive exposures. Investigator judgment should be applied during the clinical interview to determine if there is a history of intentional, repeated use of cannabis or cannabinoid products. The randomization schedule will be held centrally on the IRT and not divulged to any other person involved in the trial until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5. Patients who withdraw from the trial will not be replaced.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration, and Schedule

The IMP will be presented as a pump oromucosal spray. Nabiximols oromucosal spray is a mixture of THC and CBD extracts derived from *Cannabis sativa* L. Each of the botanical extracts contains a cannabinoid as the major constituent (i.e., THC or CBD) and minor constituents, including other cannabinoid and noncannabinoid plant components, such as terpenes, sterols, and triglycerides.

The use of placebo in the current trial is deemed necessary to determine the efficacy or safety of the current intervention(s), since the best proven intervention has already been tried/is being given as background treatment and has failed to/does not fully alleviate the patient's symptoms. Placebo to match nabiximols is presented as an oromucosal spray containing excipients, coloring, and flavoring, with no active ingredients.

For details regarding IMP formulations, see Section 5.

8.1.1 Dose Administration

For all treatment arms, IMP will be administered by the patient via a pump oromucosal spray. The IMP will be self-administered to the oral mucosa. Patients will receive IMP dosing training from site staff on Visit 2 (Day 1 predose). Patients will be advised to administer IMP at approximately the same time each day in a consistent manner in relation to food consumption. Morning and evening doses should be administered around the same time within 30 minutes after starting a snack or meal. Patients should divide doses greater than 1 spray/day into a morning dose and an evening dose.

Following the titration phase (see Section 8.1.2), IMP will be administered as 1 spray (100 µL per spray) with a target interval of approximately 1 minute until the patient's specific optimized dose has been administered. Patients should be advised to direct each spray at a different site on the oromucosal surface, changing the application site for each spray of the IMP, and patients should divide doses greater than 2 sprays/day into a morning dose and an evening dose. If lesions are observed or persistent soreness is reported, the IMP administration must be interrupted until complete resolution occurs. Events of this nature are to be recorded according to the adverse event (AE) procedures (see Section 12).

8.1.2 Dose Escalation and Dose Adjustments

After IMP dosing training and IMP dispensing, site staff will provide patients with an example titration schedule and instructions to record IMP dosing information in the patient electronic diary. Patients will initiate IMP treatment as a single spray in the

evening on the first day of the titration phase. Patients will be advised to titrate IMP, to the maximally acceptable dose, balancing efficacy and tolerability, beginning with 1 spray/day, to an optimized dose or to a maximum number of 12 sprays/day over the first 14 days of treatment. During the titration phase, there should be an approximately 15-minute interval between sprays. Patients may temporarily pause or slightly reduce the number of sprays upon the emergence of AEs, the titration may be resumed when the AEs resolve. No further dose adjustments should take place after 14 days unless advised by the investigator. An example titration regimen is presented in Table 8.1.2-1.

Patients should not take more than 12 sprays/day of IMP at any time during the trial. Patients should consult the dosing instructions provided and contact the investigational site when in doubt about changes in the daily dose of IMP at any time during the study.

Table 8.1.2-1 Example Titration Schedule

Day	Number of Sprays in the Morning	Number of Sprays in the Evening	Total Number of Sprays/Day
1	0	1	1
2	1	1	2
3	1	2	3
4	2	2	4
5	3	2	5
6	3	3	6
7	4	3	7
8	4	4	8
9	5	4	9
10	5	5	10
11	6	5	11
12	6	6	12
13	6	6	12
14	6	6	12

Patients should complete titration within 14 days of their first dose of IMP and should continue at the same dose level achieved at the end of titration (i.e., their daily optimized dose) ± 1 spray divided into a morning dose and an evening dose for the remainder of the treatment period. This guidance applies unless patients agree with the investigator to lower the dose of IMP to address poor tolerability that emerges during the period of stable dosing. For the first 14 days of administering stable doses of IMP following titration, patients should be instructed to gradually decrease the interval between sprays to a target interval of approximately 1 minute between sprays.

The total daily dose should be administered as a morning dose and an evening dose, which may be composed of a different number of sprays. Patients may take their morning dose spread out during the morning and their evening dose spread out during the evening, with a minimum interval between sprays as specified above (i.e., 15 minutes during the titration phase and a target of approximately 1 minute during the maintenance phase).

8.2 Concomitant Therapy

From Screening (Visit 1) forward, any new treatments taken or any change to ongoing medications during the patient's participation in the trial will be recorded on the appropriate electronic case report form (eCRF) page by the investigator or designee. Similarly, any ongoing physiotherapy as part of the management of spasticity at the time of enrollment will be documented in the eCRF as well as any changes in physiotherapy regimen that occur in the course of the study (e.g., discharge from physiotherapy).

For details about the potential for interactions from initiating IMP with prior medications, refer to the guidance for the investigator and potential drug interactions within the IB[15].

8.2.1 Concomitant Optimized Multiple Sclerosis Antispasticity Medications

As nabiximols is being investigated as therapy in patients with spasticity due to MS, all patients must currently be taking at least 1 optimized oral antispasticity medication. Optimized oral antispasticity medications will include at least baclofen, tizanidine, or dantrolene (monotherapy or combination therapy). Their antispasticity medication must have been stable for at least 30 days prior to Screening (Visit 1) and the medication is expected to remain stable through the duration of the trial. However, despite this optimization, eligible patients do not have adequate relief of their spasticity symptoms, including muscle spasms. Optimization of antispasticity medications is defined as having reached the most efficacious and best tolerated dose according to the relevant local prescribing information. The patient must be willing to maintain the same antispasticity therapy for the duration of the trial.

Benzodiazepine use is allowed if doses and dosing regimen have been stable for at least 30 days prior to Visit 1.

If the patient is currently receiving an MS disease-modifying therapy or dalfampridine or fampridine, it must be at a stable dose for at least 3 months prior to Visit 1 and is expected to remain stable for the duration of the trial.

8.3 Prohibited Therapy During Trial Period

The following medications are prohibited for the duration of the trial:

- Cannabis use for medical or recreational purposes or any cannabinoid-based medication within 30 days of Visit 1 and for the duration of the trial
- Botulinum toxin injection for the relief of spasticity within 6 months of Visit 1 and for the duration of the trial
- Antipsychotic medication
- Any benzodiazepines use on an as-needed (PRN) basis

- Drugs that are solely metabolized by UGT1A9 and UGT2B7 (See APPENDIX 4)
- Strong CYP3A4 inhibitors or inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort)

Any patient taking these medications after Visit 1 must cease IMP and should remain in the trial.

The use of psychotropic medications other than those specified above would be allowed provided the medication is used on a daily basis, has been at a stable dose for at least 30 days or 5 half-lives (whichever is longer) prior to Visit 1 and is expected to remain stable throughout the trial.

8.4 Compliance in Investigational Medicinal Product Administration

The patient will record the number of sprays administered on each treatment day in the electronic diary.

Patients should return all IMP (used and unused) at each of Visits 3, 4, 5, and 6. The electronic diary-reported dosing information will be checked and any discrepancies discussed with the patient at the time of the visit and documented accordingly within the patient's source documents. Refer to Section 9.2.18.2.1 for the list of triggering drug accountability discrepancies associated with monitoring of drug abuse liability.

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

8.5 Access to Blinded Treatment Assignment

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

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

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

9 TRIAL PROCEDURES

A list of the required trial procedures is provided in the subsections that follow; refer also to the schedule of assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the eCRF. Additional procedures to screen for the presence of immunity against infectious diseases (such as body temperature, sampling of nasal or pharyngeal mucosa or serology) may be conducted at screening, at the beginning of each visit or as needed, according to local guidance and policy.

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

In cases where patients are not able to attend study visits due to the presence of an infectious disease or other transmissible condition (such as COVID-19/other pandemic restrictions), the investigator will discuss with the Sponsor potential mitigation approaches (including but not limited to extending the visit window, conducting evaluations via video link or phone call, allowing for safety procedures to be conducted at the patient's home or local facility, or implementing potential mitigation approaches for IMP dispensing, secure delivery, and collection). The rationale (e.g., the specific limitation imposed by the infectious disease that led to the inability to perform the protocol-specified assessment) and outcome of the discussion will be documented in the medical record.

In keeping with ICH Good Clinical Practice (ICH GCP) E6 Guideline, it is the investigator's responsibility to provide oversight of data provided by patients, including daily spasm count entered in the eDiary, to ensure completeness and reliability. If the investigator has concerns about the reliability of the spasm count data, they may discuss this with the sponsor or sponsor's representative.

9.1 Trial Procedures by Visit

Patients will be invited to take part in the trial and will be issued with the patient information and informed consent. Following adequate time to discuss the trial with the investigator, nurse, relatives or caregiver, as wished, patients who provide written informed consent will be screened for entry into the trial.

9.1.1 Visit 1 (Days −30 to −28, Screening)

Informed consent (see Section 9.2.1) must be obtained from the patient prior to beginning any trial-related procedures.

The following assessments/procedures will be performed:

- Eligibility check (Section 6)
- Demographics (Section 9.2.3)
- Previous cannabis use (Section 9.2.4)
- Medical history (Section 9.2.5), including current Expanded Disability Status Scale (EDSS) score (if known) or ambulatory status
- Electronic diary training (Section 9.2.14.1)
- Concomitant medications review (Section 9.2.6)
- AE review (Section 9.2.17)
- Physical and oral mucosa examinations (including height measurement) (Section 9.2.7 & 9.2.8)
- Body weight measurement (Section 9.2.9)
- Vital signs measurement (Section 9.2.10)
- 12-lead ECG (Section 9.2.11)
- Clinical laboratory blood sampling (hematology and biochemistry) (Section 9.2.12)
- Dipstick urinalysis (Section 9.2.12)
- Urine drug screen (including THC) (Section 9.2.12)
- Serum pregnancy test (if appropriate) (Sections 9.2.2 and 9.2.12)
- Confirmatory FSH test for postmenopausal state (see Sections 6.2 and 9.2.2)
- Blood THC test (Section 9.2.12)
- C-SSRS assessment (Section 9.2.15.3)

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

Following Visit 1, there will be no changes in the dose of the patient's current oral antispasticity medications. Patients will enter a 28-day baseline period, during which they will be required to take their optimized oral antispasticity medication (that must include at least 1 of baclofen, tizanidine, or dantrolene) and complete an electronic daily diary to record spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications once daily, around the same time of day, preferably in the evening before retiring to sleep. Patients are expected to start completing their electronic diary in the evening of their screening visit (first day of the 28-day baseline period).

At the discretion of the investigator, patients who receive a positive COVID-19 antigen test result, suggesting potentially infective status, before randomization may be screen failed. At the discretion of the investigator, patients who receive a positive COVID-19

test result after randomization may be discontinued from IMP but kept in the trial. See Section 9.2.6 for the data to be collected from those patients who received a COVID-19 vaccination in the 12 months prior to Screening.

9.1.1.1 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to trial intervention. A minimal set of screen failure information is required to ensure transparent reporting of individuals who failed screening in order to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. The minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Rescreening of Participants:

Individuals who do not meet the criteria for participation in this trial (screen failure) because of, for example, fever due to a brief acute upper respiratory illness, having taken a prohibited over the counter medication within the excluded period, recent blood donation, due to the inclusion criterion related to the ability to interpret and report spasm count data accurately, or who could not be randomized within the screening window for logistical reasons, can be rescreened once, at the discretion of the investigator or designee with sponsor approval. Rescreened participants should be assigned a new screening number.

9.1.2 Visit 2 (Day 1, Randomization)

Following the 28-day baseline period, patients will attend the site for Visit 2 on Day 29, a visit window of +2 days is permitted but it is preferred that the visit is performed on the scheduled visit day, where possible. If, for any reason, the patient is unable to attend the site for randomization within the visit window, the site should contact the Medical Monitor or the sponsor to discuss; please note the eligibility criteria the patient needs to meet should this occur.

The following assessments/procedures will be performed:

- Eligibility check
- Randomization (Section 7.2)
- Concomitant medications review
- AE review
- Physical and oral mucosa examinations
- Body weight measurement
- Vital signs measurement

- 12-lead ECG
- Clinical laboratory blood sampling (hematology and biochemistry)
- Urine drug screen (including THC)
- Urine pregnancy test (if appropriate)
- PK blood sampling (Section 9.2.12.1)
- MSSS-88 assessment (Section 9.2.15.2)
- C-SSRS assessment
- T25FW test (Section 9.2.15.4)
- SF-36 assessment (Section 9.2.15.6)
- IMP dosing training and dispensing (Section 9.2.14.4)

Following predose assessments and after IMP dosing training and IMP dispensing, site staff will provide patients with an example titration schedule and instructions to record IMP dosing information in the patient electronic diary. Patients will take the first dose of IMP on the evening of Visit 2 (Day 1).

See Section 8.1.1 and Section 8.1.2 for IMP dosing and administration information.

Patients should be reminded to record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications in the electronic diary once daily, around the same time of the day, preferably in the evening before retiring to sleep. In addition, on the day before Visits 3, 4, and 5 patients will be prompted to record whether they started their morning and evening doses of IMP within 30 minutes of a meal.

Each site will have the option to follow up with the patient through telephone calls during the titration phase to monitor the patient's titration, safety and tolerance, and electronic daily diary reporting.

9.1.3 Visit 3 (Day 15), Visit 4 (Day 29), and Visit 5 (Day 57)

Visits 3, 4, and 5 will occur 14, 28, and 56 days after the first dose of IMP, respectively. A visit window of ± 3 days for Visits 3 and 4 and ± 7 days for Visit 5 is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible.

The following assessments/procedures will be performed at these visits, unless otherwise indicated:

- Concomitant medications review
- AE review
- Oral mucosa examination
- Body weight measurement (Visit 4 only)
- Vital signs measurement

- 12-lead ECG (Visit 4 only)
- Clinical laboratory blood sampling (hematology and biochemistry) (Visit 4 only)
- PK blood sampling (see Section 9.2.12.1)
- MSSS-88 assessment (Visit 5 only)
- C-SSRS assessment
- IMP collection and compliance review (Section 8.4)
- IMP dispensing

See Section 8.1.1 and Section 8.1.2 for IMP dosing and administration information.

Patients should be reminded to record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, use of antispasticity medications, and IMP dosing in the electronic diary once daily, around the same time of the day, preferably in the evening before retiring to sleep. In addition, on the day before Visit 6, patients will be prompted to record whether they started their morning and evening doses of IMP within 30 minutes of a meal.

9.1.4 Visit 6 (Day 85, End of Treatment Visit/Withdrawal Visit)

This visit will occur 84 days after the first dose of IMP 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.

Patients who discontinue IMP treatment early will be encouraged to continue (off treatment) in the trial and to complete all remaining trial procedures to Visit 6 (Day 85), where possible.

The following assessments/procedures will be performed:

- Concomitant medications review
- AE review
- Physical and oral mucosa examinations
- Body weight measurement
- Vital signs measurement
- 12-lead ECG
- Clinical laboratory blood sampling (hematology and biochemistry)
- PK blood sampling (see Section 9.2.12.1)
- Dipstick urinalysis
- Serum pregnancy test (if appropriate)
- MSSS-88 assessment
- C-SSRS assessment
- T25FW test

- Medication Use Survey (MUS [Section 9.2.15.5])
- SF-36 assessment
- IMP collection and compliance review

Patients should be reminded to record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications in the electronic diary once daily, around the same time of the day, preferably in the evening before retiring to sleep.

9.1.5 Visit 7 (Day 99, Safety Follow-up Visit)

The Safety Follow-up Visit will occur 14 days after the End of Treatment Visit or Withdrawal Visit. A visit window of ± 4 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day, where possible. Patients who discontinue IMP but complete scheduled trial visits are not required to complete the Safety Follow-up Visit.

The following assessments/procedures will be performed:

- Concomitant medications review
- AE review
- Vital signs measurement

9.2 Trial Procedure Listing

9.2.1 Informed Consent

Adult patients with an adequate level of understanding must personally sign and date the IRB/IEC-approved ICF before any trial-specific procedures are performed or any patient-related data are recorded for the trial. If an adult patient is unable to read (illiterate or visually impaired), or is physically unable to speak or write, an impartial witness should be present during the entire informed consent discussion. After the ICF is read and explained to the patient and after the patient has orally consented to participation in the trial and has signed and dated the ICF (if capable of doing so), the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to and apparently understood by the patient and that informed consent was freely given by the patient (as outlined in the International Council for Harmonisation [ICH] Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice [GCP] E6(R2), Section 4.8.9).

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

The original signed ICF should be retained and a copy provided to the patient. Patients 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 regarding the informed consent, see Section 15.2.

9.2.2 Contraception Requirements

To be eligible for the trial, female patients of childbearing potential (i.e., following menarche and until becoming postmenopausal for ≥ 12 consecutive months with a FSH ≥ 30 mIU/mL unless permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must have agreed that they are willing to use highly effective contraception for the duration of the trial and for 3 months thereafter. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraception, an intrauterine device/hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence. Due to the possible interaction of the IMP with contraceptive steroids, the use of hormonal contraception must be supplemented with a barrier method (preferably male condom or diaphragm).

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

Abstinence, as referenced above, is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhea method are not acceptable methods of contraception.

9.2.3 Demographics

At Screening (Visit 1), the following information will be obtained for each patient: date of birth, sex, and race (as allowed per local regulations).

9.2.4 Previous Cannabis Use

At Screening (Visit 1), any intermittent or regular previous use of cannabis or cannabinoid products for medicinal or recreational purposes will be recorded.

9.2.5 Medical History

Relevant, significant medical history, including current EDSS score (if known) or ambulatory status, will be obtained at Screening (Visit 1) and is defined as any condition or disease that:

- May affect the condition under study in this trial
- Is ongoing on entry into the trial
- Has occurred within 1 year prior to Screening (Visit 1)

9.2.6 Concomitant Medication

Details of all current medications will be recorded. Any changes in concomitant medication during the trial must be recorded on the eCRF at trial visits. Patients should stop taking any prohibited therapy prior to Screening (Visit 1), as defined in Section 8.3.

Please note: Any vaccination related to COVID-19, that was received within the 12 months prior to Screening should be recorded as a concomitant medication. The information recorded should include the vaccine manufacturer and the dates of administration; differing start and end dates denoting two doses being received, if applicable.

9.2.7 Physical Examination

A full physical examination will be performed at the timepoints specified in the Schedule of Assessments (see APPENDIX 1); height will be recorded at Screening (Visit 1) only.

9.2.8 Examination of Oral Mucosa

Examination of the oral mucosa will occur at relevant visits (see APPENDIX 1).

9.2.9 Body Weight Measurements

Body weight measurements will be recorded at relevant visits (see APPENDIX 1).

9.2.10 Vital Signs

As part of the screening procedures at Visit 1, vital signs (systolic and diastolic blood pressure and pulse rate) will first be measured after the patient assumed a supine position for 5 minutes. Where postural blood pressure is required at Visit 1 it should be measured within 2 minutes of assuming a standing position in ambulatory patients only. At all subsequent time points, vital sign measurements will be completed in a sitting position at rest for 5 minutes. Blood pressure must be recorded using the same arm throughout the trial, where possible.

Additional vital signs measurements may be taken during the trial if clinically indicated.

9.2.11 12-Lead Electrocardiogram

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

9.2.12 Clinical Laboratory Sampling

The investigator and trial monitor will be provided with a list of the normal ranges used by the central laboratory for all variables assayed during the trial and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in Table 9.2.12-1.

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

Table 9.2.12-1 Biochemistry, Hematology, Urinalysis, Pregnancy Test, and Drug Screen

Biochemistry (Serum[1])	Hematology (Whole Blood[1])	Urinalysis (Urine[2])	Pregnancy Test (Serum[1], Urine[2])	Drug Screen (Serum[1], Urine[3])
Alanine aminotransferase	Hematocrit	Blood	Serum and urine	THC
Albumin	Hemoglobin	Glucose		Drugs of abuse
Alkaline phosphatase	Mean cell volume	Nitrites		
Aspartate aminotransferase	Mean corpuscular hemoglobin	pH		
Calcium	Platelets	Protein		
Creatinine	Red blood cell count	White blood cells		
Follicle stimulating hormone			Serum[4]	
Gamma-glutamyl transferase	White blood cell count with automated differential	Specific gravity		
Potassium		Ketones		
Prothrombin time (plasma)[5]				
Sodium		Urobilinogen		
Total bilirubin		Bilirubin		
Total protein				

Table 9.2.12-1	**Biochemistry, Hematology, Urinalysis, Pregnancy Test, and Drug Screen**			
Biochemistry (Serum[1])	**Hematology (Whole Blood[1])**	**Urinalysis (Urine[2])**	**Pregnancy Test (Serum[1], Urine[2])**	**Drug Screen (Serum[1], Urine[3])**
Urea (blood urea nitrogen)				

[1]Analyzed at a central laboratory

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

[3]The standard drugs of abuse screen, including THC, will be analyzed by use of a urine dipstick at Visits 1 and 2. All patients will undergo a separate blood THC test at Visit 1.

[4]Confirmatory test for postmenopausal state.

[5]Analyzed as Screening (Visit 1) only.

Investigators at trial sites will be notified of safety laboratory test results. All laboratory results will be reviewed and the reports signed and dated by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. The results of blood THC testing at Visit 1 will be reported back to the trial site for confirmation of eligibility. All laboratory results considered to represent an AE must be documented on the eCRF. For reporting and follow-up of potential cases of drug-induced liver injury, see Section 12.8.

Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation. Blood sample volume requirements and processing procedures will be detailed in a separate laboratory manual; the maximum amount of blood taken during the course of the trial, including PK blood samples, will be approximately 67 mL, taking into account possible repeat tests.

9.2.12.1 Pharmacokinetic Blood Sampling

Plasma concentrations will be obtained for THC and its relevant metabolites (11-OH-THC and 11-COOH-THC) and CBD and its relevant metabolites (7-OH-CBD and 7-COOH-CBD). There will be 2 options for the collection of PK samples:

1) For patients choosing the sparse PK sampling option, blood samples will be taken as follows:
   - Visit 2 – 1 sample predose
   - Visits 3, 4, 5, and 6 – 1 sample collected at any time during the visit
   - During the visits, the exact time of PK blood sampling and the time of the patient's snacks and meals should be recorded

2) For patients choosing the semi-intensive PK sampling option, blood samples will be taken as follows:
    - Visit 2 – 1 sample predose
    - At 1 visit (either Visit 3, 4, or 5):
        - 1 sample predose (i.e., prior to administration of IMP at the investigational site)
        - 1 sample between 2 and 3 hours postdose
        - 1 sample between 4 and 6 hours postdose
        - 1 sample between 6 and 8 hours postdose
    - There must be a minimum period of at least 2 hours between each of the 4 blood sampling time points
    - The predose sample will be taken prior to the morning IMP dose. On the day of the semi-intensive PK sampling the patient must bring their study medication with them to the visit and not take their morning IMP dose until instructed to do so by the site staff
    - During the visits the exact time of PK blood sampling and the time of the patient's snacks and meals should be recorded

Analysis of all PK samples will be conducted at a central bioanalytical laboratory. Blood sample volume requirements and processing procedures will also be detailed in a separate laboratory manual; the maximum amount of blood taken for PK analyses during the course of the trial will be approximately 30 mL, taking into account possible repeat tests. The patient must be advised that it may not be safe for the patient to undertake further blood tests within 1 month of any trial-related blood draws and to inform the investigator if they suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.13 Interactive Response Technology

The IRT will be used to assign patients to treatment arms, manage IMP supply, and to provide treatment allocation information in the event of patient unblinding.

A member of the trial team must contact the IRT at each clinic visit in order to perform the following:

- Randomize a patient (Visit 2)
- Obtain IMP dispensing information (Visits 2, 3, 4, and 5)
- Provide completion/premature termination information (Visit 6)

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

9.2.14 Electronic Patient Diary

As part of the baseline period, patients will record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications in the electronic diary once daily, around the same time each day, during the baseline period prior to Visit 2 and throughout the trial until Visit 7, unless otherwise indicated. Patients are expected to start completing their electronic diary in the evening of their screening visit (first day of the 28-day baseline period).

In addition, on the day before PK blood sampling, patients will be prompted to record whether they started their morning and evening doses of IMP within 30 minutes of a meal.

9.2.14.1 Electronic Diary Training

Patients will be trained by the site staff on the use of the electronic diary at Screening (Visit 1) and will be instructed on how to record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications once daily, around the same time of day, preferably in the evening before retiring to sleep, during the baseline period prior to Visit 2 and throughout the trial until Visit 7. Following randomization during Visit 2, patients will be instructed to log their daily IMP dosing in the electronic diary throughout the treatment period until Visit 6.

9.2.14.2 Spasm Severity Numerical Rating Scale

The 11-point NRS is considered a valid and reliable method to assess overall spasticity in patients with MS. It is the standardized patient-related outcome that best identifies a clinically important difference and a minimum clinically important difference.

Patients will be asked to make a daily assessment, at bedtime, to read the question, and to tick the most appropriate number to indicate the severity of his or her spasms over the last 24 hours. The patients will be given a definition of spasm and the question will be phrased as follows:

On a scale of 0 to 10, how severe were your spasms on average over the last 24 hours? Considering 0 as "No spasms" and 10 as "Worst possible spasms".

This information will be recorded in the patient electronic diary.

9.2.14.3 Spasticity Numerical Rating Scale

Patients will be asked to make a daily assessment, at bedtime, to read the instruction, and to tick the most appropriate number to indicate the severity of his or her spasticity over the last 24 hours. The patients will be given a definition of spasticity and the question will be phrased as follows:

On a scale of 0 to 10, please indicate your level of spasticity over the last 24 hours, considering 0 as "No spasticity" and 10 as "Worst possible spasticity."

This information will be recorded in the patient electronic diary.

9.2.14.4 Use of Antispasticity Medications and Investigational Medicinal Product Dosing Record

Patients will be instructed to record their use of antispasticity medications, including their use of baclofen, tizanidine or dantrolene as part of their optimized oral antispasticity therapy, and their IMP dosing daily in their electronic diary.

9.2.15 Questionnaires and Assessments Completed at Scheduled Visits

Questionnaires should be completed by the patient, unless otherwise specified. The same person should administer/complete the questionnaires/assessments in order to maintain consistency, unless otherwise stated. The C-SSRS and T25FW will be administered by a trained assessor.

9.2.15.1 Multiple Sclerosis Spasticity Scale

The MSSS-88 is a patient self-report measure of the impact of spasticity (muscle stiffness and spasms) in MS. This 88-item scale captures the patient experience and impact of spasticity, including muscle stiffness, pain and discomfort, muscle spasms, effect on daily activities, ability to walk, body movement, patient feelings, and social functioning. Responses to individual questions can range from "not at all bothered" to "extremely bothered."

9.2.15.2 Columbia-Suicide Severity Rating Scale

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

The C-SSRS is to be administered by the investigator or his/her qualified designee at Visits 1 through 6 as indicated in the schedule of assessments (see APPENDIX 1); "qualified designee" is defined as anyone who has completed the C-SSRS training within the past 2 years or has continually administered C-SSRS assessments throughout the trial since obtaining the training certificate. The survey should be completed by the same assessor, where possible, throughout the trial. Assessments will be conducted only if patients are capable of understanding and answering the questions, in the investigator's opinion.

9.2.15.3 Timed 25-Foot Walk

The T25FW is a quantitative measure of lower extremity function and should be performed by a trained assessor. The same assessor should administer the T25FW test throughout the trial where possible. If ambulatory, the patient will be instructed to begin at one end of a clearly marked 25-foot course. They will be instructed to walk the 25 feet as quickly as possible, but safely, and to not slow down until after they have passed the finish line. The task will be immediately administered a second time following the first trial by having the patient walk back the same distance.

Patients will be permitted to use their customary, nonmotorized assistive device (AD) (cane, walking sticks, walker, and rollator) during the T25FW test. The same AD must be used at each assessment and its use documented in the patient record.

9.2.15.4 Medication Use Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or trial coordinator will complete this survey as an interview with the patient at the End of Treatment Visit or Withdrawal Visit (Visit 6).

The MUS will be completed for all patients in the trial and not only those who have reported a triggering AE or drug accountability discrepancy, although only those with triggering AEs/drug accountability events will be adjudicated for abuse potential (see Section 9.2.18).

9.2.15.5 36-Item Short Form Health Survey

The SF-36 is a generic multipurpose, short-form QoL health survey comprising 36 questions self-reported by the patient. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures and a preference-based health utility index[17].

The SF-36 differentiates between physical and mental health and consists of 8 different dimensions (physical functioning, vitality, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) and is validated for bodily pain and physical function.

The SF-36 scores for each dimension can range between 0 and 100, where higher scores indicate better functional health and well-being.

9.2.16 Investigational Medicinal Product Accountability

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

9.2.17 Adverse Events

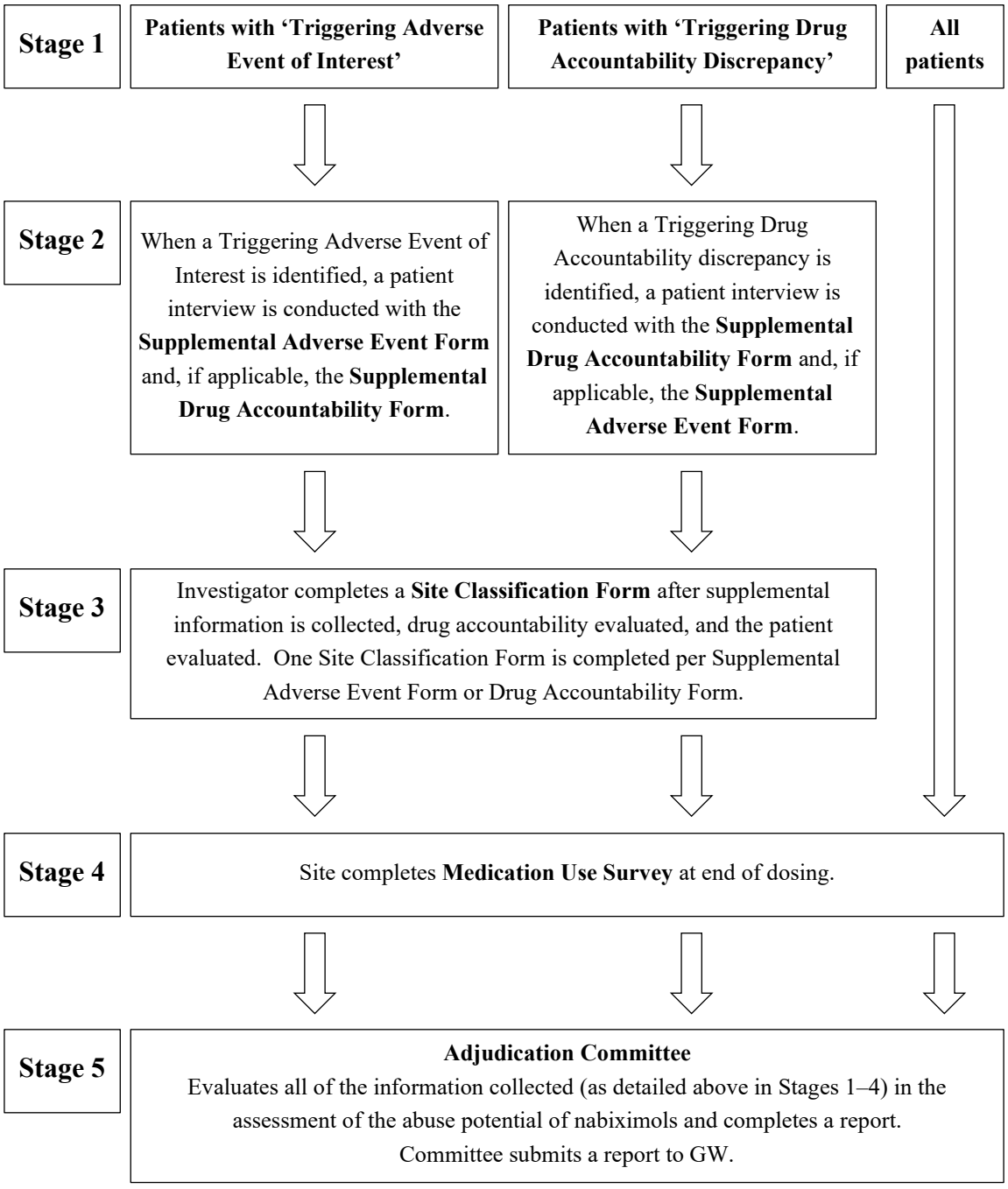
Refer to Section 12 for definitions, procedures, and further information on AE reporting.

Refer to Section 9.2.18.1.1 for the list of triggering AEs of interest associated with monitoring of drug abuse liability.

9.2.18 Monitoring of Drug Abuse Liability

There are 2 triggers that will require the investigator or trial coordinator to discuss abuse potential signals with the patient. These are either AEs of interest that may be reported by the patient or drug accountability issues regarding overuse of the IMP or missing vials. Different questionnaires will be completed by the trial site depending upon which trigger occurs (see Figure 9.2.18-1). Irrespective of the above, all patients will be interviewed at the End of Treatment Visit or Withdrawal Visit (Visit 6) and a MUS will be completed by the investigator or trial coordinator (see Section 9.2.15.4). Investigators and trial coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at the trial site.

Figure 9.2.18-1 Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data through Systematic Categorization, Tabulation, and Analysis which can Illuminate an Abuse Potential Signal



9.2.18.1 Monitoring of Adverse Events (Abuse Liability)

AE information will be collected according to Section 12.6.

9.2.18.1.1 List of Triggering Adverse Events of Interest (Abuse Liability)

During the collection of AEs, if the patient reports an AE consistent with any of the following categories, then the investigator or trial coordinator is required to complete a Supplemental Adverse Event Form (see Section 9.2.18.1.2) and a Site Classification Form (investigator only; see Section 9.2.18.3) following further discussion of the event(s) with the patient. The categories are:

- Addiction
- Disturbance in cognition, memory, or attention
- Drug abuse
- Drug withdrawal or drug withdrawal syndrome
- Drunk, high or intoxicated
- Euphoria or inappropriate elation
- Hallucinations (visual or auditory), dissociations, disorientation, agitation
- Inappropriate laughter or exhilaration
- Misuse of IMP
- Mood changes
- Overdose
- Thoughts of suicide, attempted suicide, or suicide

An AE that is consistent with the above categories will be known as a 'triggering AE of interest' for the purposes of this trial.

9.2.18.1.2 Supplemental Adverse Event Form (Abuse Liability)

This form consists of 12 questions regarding the AE and the use of IMP. It is completed as part of an interview with the patient when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or trial coordinator with the patient present. The answers on the Supplemental Adverse Event Form will then be entered into the patient's eCRF for the trial. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the trial site should contact the patient to obtain the required answers as soon as possible. The time and date of collection must be recorded in the patient's notes and on the eCRF.

9.2.18.2 Monitoring Drug Accountability Discrepancies (Abuse Liability)

Any time after randomization until final collection of trial data, drug accountability discrepancies are monitored as follows:

- At routine drug accountability collection times (i.e., Visits 3, 4, 5, and 6)
  - The site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the electronic diary
- At any time that the trial site is informed by the patient about any overuse of IMP, suspected misuse, abuse, or diversion

9.2.18.2.1 List of Triggering Drug Accountability Discrepancies (Abuse Liability)

If there are any discrepancies in drug accountability as outlined by the criteria below, known as 'triggering drug accountability discrepancies', then the trained investigator or trial coordinator will complete a Supplemental Drug Accountability Form (see Section 9.2.18.2.2) and a Site Classification Form (investigator only; see Section 9.2.18.3) following further discussion of the event(s) with the patient. The triggering drug accountability discrepancies are as follows:

- Compliance issues where 1 or more vials are used compared to the expected use, according to the electronic diary entries and drug accountability calculations in eCRF
- Greater than the target daily dose as recorded in the electronic diary
- Missing vial(s)
- Returned IMP supply with evidence of tampering

9.2.18.2.2 Supplemental Drug Accountability Form (Abuse Liability)

This form consists of 10 questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or trial coordinator with the patient present. The answers on the Supplemental Drug Accountability Form will then be entered into the patient's eCRF for the trial. The accountability reporting procedures will still occur (see Section 5.3.4). If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the trial site should contact the patient by telephone to obtain the required answers as soon as possible. (Note: IMP refers to nabiximols or placebo, not other concomitant medications).

9.2.18.3 Site Classification Form (Abuse Liability)

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and should then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of certainty of the classification. The answers from the Site Classification Form will then be entered into the patient's eCRF for the trial.

9.2.18.4 Adjudication Committee: Assessment of Abuse Potential of Nabiximols

A formal adjudication committee will be appointed and assigned to this initiative to classify triggered cases. The adjudication committee will meet on a periodic basis to review and assess all of the information collected on triggered cases. Only data from patients who have completed the trial will be assessed.

A detailed charter will be agreed, which will describe the roles, responsibilities, and duties of the members of adjudication committee. The adjudication committee will review all of the information collected in the process and in the assessment of the abuse potential of nabiximols, such as:

- Additional information from trial site(s) as requested by the adjudication committee
- All triggering AE information
- All triggering drug accountability discrepancies
- Site Classification Form
- MUS
- Supplemental Adverse Event Form (if applicable)
- Supplemental Drug Accountability Form (if applicable)

The adjudication committee will assess all of the information. It will form an opinion on the classification of each event and will write a trial-related report, detailing the conclusions and recommendations.

The overall process is summarized in Figure 9.2.18-1.

10 WITHDRAWAL

In accordance with the Declaration of Helsinki, the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), the US FDA regulations relating to GCP and clinical trials , the EU Clinical Trials Directive, the EU GCP Directive, and/or other applicable regulations, a patient has the right to withdraw from the trial at any time and for any reason, with no obligation to provide a reason, and without prejudice to his or her future medical care by the physician or at the institution.

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

- Administrative decision by the investigator, GW, or a regulatory authority
- Withdrawal of patient consent
- Lost to follow-up

The patient must cease IMP and should remain in the trial if any of the following apply:

- Pregnancy
- Protocol deviation that is considered to potentially compromise the safety of the patient
- Suicidal behavior, or suicidal ideation score of 4 or 5 during the treatment period, as evaluated with the C-SSRS
- 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 > 5 × ULN
- ALT or AST > 3 × ULN and (total bilirubin [TBL] > 2 × ULN or international normalized ratio [INR] > 1.5)
- Any prohibited medication after Visit 1

The patient may be required to cease IMP at the discretion of the investigator and should remain in the trial for any of the following reasons:

- Did not meet eligibility criteria
- Patient 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
- Any evidence of drug abuse or diversion

- Disease progression (defined as a relapse of MS requiring a change in treatment)
- A positive COVID-19 test result after randomization

Should a patient request or decide to withdraw consent 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 according to Section 12.7. All information should be reported on the applicable eCRF pages (refer to Section 9.2). A Safety Follow-up Visit should take place 14 (± 4) days after the End of Treatment Visit (Visit 6) or Withdrawal Visit if the patient does not complete the remaining trial visits after discontinuing IMP (refer to Section 9.1.5). If withdrawing patients decline to give a reason for withdrawal of consent, the investigator must respect the patients' wishes.

Patients who withdraw from the trial will not be replaced.

11 URGENT SAFETY MEASURES

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

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

- Safety follow-up may be done by a telephone call, other means of virtual contact or home visit, if appropriate.
- Patient and/or clinician-rated outcomes assessments may be done by videoconference, telephone call, other means of virtual contact, if possible.
- An alternative approach for IMP dispensing, secure delivery and collection may be sought.
- Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with documentation of the means of communication (e.g., phone call or videoconference).
- Biological samples may be collected and analyzed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.
- If it is not possible to collect the biological samples or safety assessments (e.g., ECG, vital signs) within the interval predefined in the protocol (see the Schedule of Assessments in APPENDIX 1), then the interval may be extended up to a maximum duration of 3 days.
- If a safety assessment cannot be performed within the modified window, the investigator must review the benefit-risk for patient continuation in the study and record this in the medical records.

The rationale (e.g., the specific reasons behind the changes) and outcome of the discussion with the medical monitor will be documented in the medical record. Information on how each visit was performed will be recorded in the eCRF.

GW will report urgent safety measures to regulatory authorities and will provide a written report to the regulatory authorities and IRB/IEC within 3 days. Exceptional measures taken in response to COVID-19/other pandemic conditions and their impact on study results, such as tests done in a local laboratory, will be justified, assessed, and reported in the clinical study report in keeping with ICH E3.

The remote visit should include all protocol assessments that can be performed remotely (see minimum requirements, Table 11-1) and should take place within the original visit window, if possible. The investigator should make reasonable efforts to obtain these assessments which may include local clinicians, local laboratories and other resources. If these assessments cannot be obtained within a reasonable time outside the window of the scheduled visit date, the benefit-risk ratio for the patient to continue in the study should be reassessed.

The decision to replace a site visit with a remote visit will be made by the investigator, on a case-by-case basis, in consultation with GW, who should be informed of each visit to be rescheduled as early as possible.

If a telephone contact takes place at the time of stopping IMP, all safety data which can be obtained remotely should be collected as close as possible to the time of stopping IMP.

Table 11-1 Assessments Required at Minimum in the Event of Pandemic Conditions

	Visit					
	2	**3**	**4**	**5**	**6**	**7**
	Day 1 (Randomization)	**Day 15 14 days from Day 1 (± 3 days)**	**Day 29 28 days from Day 1 (± 3 days)**	**Day 57 56 days from Day 1 (± 7 days)**	**End of Treatment /Early Withdrawal Day 85 84 days from Day 1 (± 7 days)**	**Day 99 14 days from Visit 6 (± 4 days)**
C-SSRS	X	X	X	X	X	
Review of concomitant medications	X	X	X	X	X	X
Review of AEs	X	X	X	X	X	X
MSSS-88	X				X	
MUS					X	
Clinical laboratory blood sampling (hematology and biochemistry)	X		X		X	
Vital Signs	X	X	X	X	X	X
12-lead ECG	X		X		X	
Dipstick pregnancy test (if appropriate)	X				X	
eDiary completion	X	X	X	X	X	X
IMP dosing training	X					
IMP collection and compliance review		X	X	X	X	
IMP dispensing	X	X	X	X		

AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; COVID-19 = coronavirus disease 2019; ECG = 12-lead electrocardiogram; IMP = investigational medicinal product; MSSS-88 = Multiple Sclerosis Spasticity Scale; MUS = Medication Use Survey

Notes:

[1] During pandemic conditions only, sites may use local laboratories for safety assessments noted above, following consultation with the Sponsor.

[2] Methodology for some assessments performed at locations other than the site (e.g., blood pressure cuff) will need to be pre-approved.

[3] Under pandemic conditions, an initial IMP dosing training would be given at the site at Visit 1, with a refresher training given remotely at Visit 2. A training video would be supplied for IMP dosing training should pandemic conditions begin between Visits 1 and 2.

[4] In cases where patients are not able to attend study visits due to COVID-19/other pandemic restrictions, the investigator will discuss with the Sponsor potential mitigation approaches for IMP dispensing and collection.

[5] Data for the day of Visit 7 should not be entered in the electronic diary. Site staff will confirm that data that relates to the day prior to attending the site for Visit 7 has been entered in the electronic diary prior to completion of the trial.

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 following Screening (Visit 1) and at any point up to the post-treatment Safety Follow-up Visit (Visit 7), which may or may not be considered related to the IMP. Any event that is the result of a trial procedure must be recorded as an AE.

Surgical/investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-trial existing conditions or elective procedures are not AEs. An exception may be if the patient has an AE during hospitalization that prolongs his/her 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 the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

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

12.2 Serious Adverse Events

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

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

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

*The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event 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 drug abuse. In addition, a positive test result for COVID-19 is to be recorded as an SAE.

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 reported in the eCRF within 24 hours of discovery or notification of the event (see APPENDIX 2). The GW Pharmacovigilance Department (PVD) will be automatically notified that an SAE has been recorded. Any additional information required for a case (follow-up of corrections to the original case) will be requested by GW PVD through eCRF queries.

The investigator is not obliged to actively monitor for any new SAEs that occurred after the last formal Safety Follow-up Visit (Visit 7). However, if the investigator becomes aware of any deaths or a new IMP-related SAE occurring within 28 days of the final dose of IMP, these should be reported to the GW PVD.

Any other problem discovered after Visit 7 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 the GW PVD. Such post-trial SAEs do not need to be recorded on the patient's eCRF if editing rights to the eCRF have been removed due to final trial data lock. The GW PVD may request safety follow-up information after the final trial visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the site files for all trial sites and on the GW SAE report form.

12.4 Pregnancy

Any patient, or patient's partner, who becomes pregnant while receiving the IMP, or within 3 months of the last dose of IMP, must be reported to the GW PVD using the GW Pregnancy Monitoring forms provided. Where possible, the investigator should provide the outcome of the pregnancy.

All pregnancies must be recorded in the eCRF within 24 hours of becoming aware. The GW PVD will be automatically notified that a pregnancy has been recorded. Any additional information required for a case (follow-up or corrections to the original case) will be requested by GW PVD through eCRF queries where data is entered in EDC.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 3 months after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit, then he/she should report it as above. The GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

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

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

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

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

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

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

12.6 Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the trial will be reported on the running logs in the AE section of the eCRF. This includes all events from the time following Screening (Visit 1) up to and including the Safety Follow-up Visit (Visit 7), whether or not attributed to the IMP and observed by the investigator or patient.

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

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

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the eCRF. Once a diagnosis has been determined, the AE section of 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., symptom due to disease (i.e., weakness due to cancer, tremor due to MS, headache and fever due to pneumonia, and generalized weakness due to hepatic cancer progression).

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, as much information as possible (i.e., month and year or, in exceptional circumstances, just year) should be recorded. When the actual start date becomes known, the eCRF must be updated to replace the previously recorded date.

C) Outcome

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

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Not Recovered/Not Resolved
- Fatal

D) Severity

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

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

A severe AE is not the same as 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 above.

F) Action Taken with Trial Medication

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

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

12.7 Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur after Visit 7, after the trial.

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

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

12.8 Potential Cases of Drug-induced Liver Injury

All trial sites are required to submit to the GW PVD the laboratory results for any patient after randomization who meets the criteria for the following selected laboratory parameters:

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

These reports must be sent to the GW PVD via email within 24 hours of becoming aware of the results (see APPENDIX 2 for GW PVD contact details). In addition, a copy of the patient's baseline laboratory results together with all reports to the GW PVD. Any laboratory results that constitute an AE in the investigator's opinion must be recorded in the eCRF. Where the results are considered to be SAEs, these must be recorded in the eCRF within 24 hours of becoming aware of the result, in line with reporting procedures for SAEs (Section 12.3).

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 IMP discontinuation and important medical events. The investigator will arrange for the patient to return to the trial site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase, gamma-glutamyl transferase, INR, and hematology parameter levels; detailed history; and physical examination. Patients should be followed in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

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

12.9 Notification of Safety Information to Investigators, Regulatory Authorities, and Institutional Review Boards/Independent Ethics Committees

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

This information will be provided through 3 sources:

1) IB[15]: This document is a compilation of the clinical and non-clinical safety data available on the IMP that are relevant to the trial. The IB is updated annually.
2) Development core safety information: this document forms the safety section of the IB[15] or is updated as an addendum to the IB[15]. This document is revised, if necessary, when new important safety information becomes available.
3) 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 investigator should notify their regional IRBs/IECs of SAEs or SUSARs occurring at their trial site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

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

In general, an AE observed during the conduct of a trial should be considered an unanticipated problem involving risk to patients and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the trial (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed

consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the trial cannot be understood.

The FDA guidance states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a 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 will inform investigators, regulatory authorities, and relevant IRBs/IECs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the trial does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

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

13 STATISTICAL CONSIDERATIONS

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

13.1 Sample Size, Power, and Significance Levels

446 patients will be randomized to the nabiximols or placebo treatment arms on a 1:1 basis.

The following assumptions have been used for the sample size:

- Common standard deviation of 6.5 for the change from baseline in average daily spasm count for nabiximols and placebo treatment arms
- True mean difference of −2 between the mean change from baseline in average daily spasm count in the nabiximols treatment arm compared to the placebo treatment arm

Using the above assumptions, the total sample size of 446 patients (223 patients per treatment arm) will have 90% power to detect a difference between treatment arms in change from baseline in average spasm count of −2 using a 2-sided hypothesis test at the 5% significance level.

13.2 Interim Analysis

No formal interim analysis is planned.

13.3 Analysis Sets

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

Full Analysis Set

- All patients who sign the informed consent, and are randomized will be included and analyzed according to their randomized treatment arm
- The full analysis set (FAS) is the primary analysis set for all efficacy endpoints

Safety Analysis Set

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

Per Protocol Analysis Set

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

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

13.3.1 Protocol Deviations

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

13.4 General Considerations

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

For the primary endpoint of spasm count and the exploratory endpoint of 11-point NRS spasm severity score, baseline is defined as the average of all data collected between Visit 1 and the day before Visit 2.

For the exploratory endpoint of 11-point NRS spasticity score, baseline is defined as the average of the last 7 days of electronic diary entries prior to randomization.

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

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (signed informed consent, received IMP, 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), and other demographic or baseline characteristics will be summarized by treatment arm using appropriate summary statistics. There will be no formal comparison of baseline data.

13.5.3 Medical History

Previous and current medical conditions will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) by treatment arm.

13.5.4 Concomitant Medication

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

13.6 Endpoints and Statistical Methods

The primary endpoint will be analyzed as detailed in Section 13.6.1. The secondary endpoints will be analyzed as detailed in Section 13.6.2. The exploratory endpoints will be analyzed as detailed in Section 13.6.3. PK data will be summarized as detailed in Section 13.6.4. Safety endpoints will be summarized as detailed in Section 13.6.5.

13.6.1 Primary Endpoint

The primary endpoint is the change from baseline in average daily spasm count (the average daily spasm count from Days 57 to 84 compared to the average daily spasm count for the baseline period) for all randomized patients regardless of treatment compliance.

The average daily spasm count will be calculated for the baseline period and each 28-day period corresponding to Days 1 to 28, Days 29 to 56, and Days 57 to 84. The change from baseline for average daily spasm count will be calculated for Days 1 to 28, Days 29 to 56, and Days 57 to 84.

Average daily spasm count for each period is defined as follows:

$$\frac{Total\ spasm\ count\ for\ the\ period}{Number\ of\ days\ in\ which\ the\ daily\ diary\ was\ completed\ during\ the\ period}$$

For post-randomization data, the average daily spasm count over the 28-day period will only be calculated if there are ≥ 15 days of non-missing data and < 10 consecutive days of missing data. If there are < 15 days of non-missing data or ≥ 10 consecutive days of missing data then the average daily spasm count for the 28-day period will be set to missing.

The average daily spasm count and change from baseline will be summarized by treatment for each 28-day period.

The change from baseline will be analyzed using mixed model repeated measures (MMRM), using data for each 28-day period. The model will include baseline average daily spasm count, prior cannabis use, region (US versus non-US), period, treatment arm,

period by treatment arm interaction, and period by baseline interaction as fixed effects. Period repeated within each patient will be included as a repeated effect. Denominator degrees of freedom adjustment will be performed using the Kenward-Roger method.

The within-patient correlation structure will be modelled using an unstructured covariance matrix. If the model does not converge the following structures will be used in order of preference Toeplitz, first-order autoregressive and Compound symmetry.

The least squares mean estimates for each treatment arm and period, along with the standard error and 95% confidence intervals (CIs), will be presented. In addition, estimates of the treatment difference at each period in change from baseline will be presented along with standard errors of the difference and 95% CIs. The primary comparison is the estimate of the treatment difference for the Days 57 to 84 period.

If the data appear to not be normally distributed, alternative approaches such as transformation of the data and nonparametric analyses may be considered to express treatment effects. This will be specified in detail in the SAP along with other further details on the statistical analysis.

13.6.1.1 Sensitivity Analyses for the Primary Efficacy Analysis

The following sensitivity analysis will be conducted for the primary endpoint to assess the impact on the primary estimand:

- MMRM using multiple imputation to impute missing data under the missing not at random (MNAR) assumption. MMRM assumes that missing data are missing at random (MAR), a pattern mixture model with control-based imputation using multiple imputation methodology will be used to assess the impact of MNAR on the MAR assumption. Further details of this analysis will be specified in the SAP.

13.6.1.2 Supplemental Analyses

- Primary efficacy analysis repeated for the PP analysis set

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

13.6.2 Secondary Endpoint(s)

The secondary efficacy endpoints are as follows:

- Change from baseline in total score of the MSSS-88 at Visit 6

Other secondary endpoints:

- To evaluate the safety and tolerability of nabiximols
  To evaluate the PK of nabiximols

Total score of MSSS-88 will be analyzed using the MMRM methods used for the primary endpoint described in Section 13.6.1, using visit instead of period. Patients who withdraw from the trial are required to complete the procedures scheduled for Visit 6 at the time of withdrawal. For these patients, their Visit 6 data will be assigned to the nearest post-baseline Visit (for which the assessment is scheduled to be performed) based on the trial day of the visit. Further details will be specified in the SAP.

To control for Type 1 error, the primary endpoint and secondary efficacy endpoint will be tested hierarchically, starting with the primary endpoint, then the change from baseline in total score of MSSS-88. No additional adjustments for multiplicity will be made for the exploratory endpoints.

13.6.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- Change from baseline in the 8 subscale scores of the MSSS-88 at Visit 6
- Change from baseline in average daily 11-point NRS spasm severity score to Days 57 to 84
- Change from the last 7 days of baseline in average daily 11-point NRS spasticity score to Days 78 to 84
- Change from baseline in the SF-36 total score at Visit 6 (Day 85)
- Change from baseline in T25FW (measured in seconds) test at Visit 6 (Day 85)

The NRS and MSSS-88 endpoints will be analyzed using the methods used for the primary endpoint described in Section 13.6.1 and secondary endpoints described in Section 13.6.2, respectively.

The T25FW and SF-36 endpoints will be analyzed using analysis of covariance models with baseline as a covariate and treatment, prior cannabis use and region (US versus non-US) effects.

Each endpoint will be summarized by treatment arm and visit/period.

13.6.4 Pharmacokinetics

Plasma concentrations for THC and its relevant metabolites (11-OH-THC and 11-COOH-THC) and CBD and its relevant metabolites (7-OH-CBD and 7-COOH-CBD) will be summarized by visit together with any estimates of PK parameters.

This data will undergo a population PK analysis and will be presented in a stand-alone report.

13.6.5 Safety

The safety endpoints are listed below and will be compared with placebo as detailed in the following subsections:

- Frequency of TEAEs
- Change from baseline to each assessment timepoint by treatment arm for the following:
  - Clinical laboratory tests
  - Vital signs
  - 12-lead ECGs
- Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, and at each subsequent timepoint with reference to the last assessment (since last visit)

13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.5.2 Adverse Events

AEs will be coded according to the MedDRA.

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

Descriptive presentations of TEAEs will be given by PT and SOC for the safety analysis set. The number of patients reporting at least 1 TEAE will be provided.

The following summaries will be produced at a minimum:

- All-causality TEAEs
- Treatment-related TEAEs
- 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

13.6.5.3 Clinical Laboratory Data

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

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

Vital signs, 12-lead ECG, and C-SSRS data will be summarized for the safety analysis set at screening, baseline, and at each time point during the treatment period using appropriate summary statistics, as applicable. Changes in vital signs from baseline to the End of Treatment Visit or Withdrawal Visit (Visit 6) will also be summarized.

13.6.6 Handling of Missing Data

Analyses using MMRM account for missing data under the assumption that the missing data are missing at random. In addition, for the primary endpoint, a sensitivity analysis is proposed to impute missing data under the missing not at random assumption.

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

14 DATA SAFETY MONITORING COMMITTEE

There will not be a data safety monitoring committee involved 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, the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), the EU Clinical Trials Directive, the EU GCP Directive, and the clinical trial regulations adopting European Commission Directives into national legislation.

15.2 Informed Consent

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

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

The acquisition of informed consent must be documented in the patient's medical records, and the ICF must be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The original signed ICF should be retained and a copy provided to the patient.

15.3 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICFs, master ICF, 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 ICF 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 document. The investigator must notify the IRB/IEC of deviations from the protocol, SAEs occurring at the trial site, and other AE reports received from GW, in accordance with local procedures.

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

15.4 Pre-trial Documentation Requirements

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

- Signed and dated protocol signature page
- Copy of IRB/IEC-approved ICF (including version number and date) and other patient information material
- Copy of the IRB/IEC approval of the protocol, ICF (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 subinvestigators
- The IRB/IEC composition and/or written statement of the IRB/IEC in compliance with the FDA regulations relating to GCP and clinical trials, the EU Clinical Trials Directive, the EU GCP Directive, or the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), where the EU Clinical Trials and GCP Directives do not apply
- Signed and dated laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW
- Signed and dated clinical trial agreement (including patient/investigator indemnity insurance and financial agreement)
- Form FDA 1572, if required
- Drug Enforcement Administration license (where applicable)
- Completed financial disclosure statements for the PI and all subinvestigators, if relevant

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

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the eCRFs and within electronic data capture databases used to collect the trial data 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 ICF, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to GCP and clinical trials and the EU Clinical Trials Directive/ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), it is required that the investigator and institution permit authorized representatives of the company, the regulatory authorities, and the IRB/IEC to 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 will remain the sole property of the company. The investigator will agree to use this information only in accomplishing the trial and will not use it for any other purposes without the written consent of the company.

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Trial or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/IEC and regulatory authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrative 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 trial site, will be agreed with each trial site prior to patient recruitment. In the rare situations of data being recorded directly into the eCRF in error, then the source data from the eCRF should be transcribed into the patient's notes with appropriate signature and date to provide a full audit trail.

The investigator and trial staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related, essential documentation (as outlined in the ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP Topic R6(R2), Section 8.2), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed eCRFs, ICFs, and supporting copies of source documentation
- Trial files containing the protocol with all amendments, IB, copies of pre-trial documentation (see Section 15.4), and all correspondence to and from the IRB/IEC and GW
- Enrollment log of all patients who consented to take part in the trial

- Screening and recruitment log of all patients screened and whether or not they were recruited into the trial (i.e., randomized and/or dosed with IMP)
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement, and all drug-related correspondence

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

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

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

16.3 Trial Monitoring and Data Collection

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

The GW trial monitor, or designee, is responsible for inspecting onsite or remotely the eCRFs and available electronic diary data at regular intervals throughout the trial to verify adherence to the protocol, completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of clinical research. The trial monitor must have direct or remote access to patient medical records and other trial-related records needed to verify the entries on the 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 trial sites, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations, ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the trial site for completion and then returned to GW or the CRO, as applicable.

16.4 Quality Assurance

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

16.5 Compensation

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

16.6 Publication Policy

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

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

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

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

16.7 Intellectual Property Rights

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

16.8 Confidential Information

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

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Appendix 1 SCHEDULE OF ASSESSMENTS

	Screening	Treatment Period					Safety Follow-up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day Number (Visit Window)	**Days -28**	**Day 1/Randomization[1] (+2)**	**Day 15 14 days from Day 1 (± 3 days)**	**Day 29 28 days from Day 1 (± 3 days)**	**Day 57 56 days from Day 1 (± 7 days)**	**End of Treatment /Early Withdrawal Day 85 84 days from Day 1 (± 7 days)**	**Day 99 14 days from Visit 6 (± 4 days)**
Informed consent	X						
Eligibility check	X	X					
Demographics	X						
Previous cannabis use	X						
Medical history	X						
Electronic diary training	X						
Randomization		X					
Concomitant medications	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Physical examination	X[2]	X				X	
Examination of oral mucosa	X	X	X	X	X	X	
Body weight measurement	X	X		X		X	

	Screening	**Treatment Period**					**Safety Follow-up Period**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day Number (Visit Window)	**Days -28**	**Day 1/Randomization[1] (+2)**	**Day 15 14 days from Day 1 (± 3 days)**	**Day 29 28 days from Day 1 (± 3 days)**	**Day 57 56 days from Day 1 (± 7 days)**	**End of Treatment /Early Withdrawal Day 85 84 days from Day 1 (± 7 days)**	**Day 99 14 days from Visit 6 (± 4 days)**
Vital signs	X	X	X	X	X	X	X
Postural changes in vital signs	X						
12-lead ECG	X	X		X		X	
Clinical laboratory blood sampling (hematology and biochemistry)	X	X		X		X	
Dipstick urinalysis	X					X	
Urine drug screen (including THC)[3]	X	X					
Serum/urine pregnancy test (if appropriate)[4]	X	X				X	
Blood THC test	X						
PK blood sampling (IMP)[5]		X	X	X	X	X	

		Screening	Treatment Period					Safety Follow-up Period
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day Number (Visit Window)		**Days -28**	**Day 1/Randomization[1] (+2)**	**Day 15 14 days from Day 1 (± 3 days)**	**Day 29 28 days from Day 1 (± 3 days)**	**Day 57 56 days from Day 1 (± 7 days)**	**End of Treatment /Early Withdrawal Day 85 84 days from Day 1 (± 7 days)**	**Day 99 14 days from Visit 6 (± 4 days)**
Electronic daily diary	Spasm count[6]	X	X	X	X	X	X	X[7]
	11-point NRS for spasm severity[6]	X	X	X	X	X	X	X[7]
	11-point NRS for spasticity[6]	X	X	X	X	X	X	X[7]
	Use of antispasticity medications[6]	X	X	X	X	X	X	X[7]
	IMP dosing record[6]		X	X	X	X	X	
Electronic Clinical Outcome Assessments	MSSS-88		X			X	X	
	C-SSRS[8]	X	X	X	X	X	X	
	SF-36		X				X	
	MUS						X	

	Screening	**Treatment Period**					**Safety Follow-up Period**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day Number (Visit Window)	**Days -28**	**Day 1/Randomization[1] (+2)**	**Day 15 14 days from Day 1 (± 3 days)**	**Day 29 28 days from Day 1 (± 3 days)**	**Day 57 56 days from Day 1 (± 7 days)**	**End of Treatment /Early Withdrawal Day 85 84 days from Day 1 (± 7 days)**	**Day 99 14 days from Visit 6 (± 4 days)**
Spasm count training	X	X	X	X	X	X	X
T25FW		X				X	
IMP dosing training		X					
IMP collection and compliance review			X	X	X	X	
IMP dispensing[9]		X	X	X	X		

C-SSRS = Columbia-Suicide Severity Rating Scale; COVID-19 = coronavirus disease 2019; ECG = 12-lead electrocardiogram; FSH = follicle stimulating hormone; IMP = investigational medicinal product; MSSS-88 = Multiple Sclerosis Spasticity Scale; MUS = Medication Use Survey; NRS = Numerical Rating Scale; PK = pharmacokinetics; SF-36 = 36-Item Short Form Health Survey; T25FW = Timed 25-Foot Walk; THC = Δ^9-tetrahydrocannabinol.

[1] Visit 2 will occur 28 days after Visit 1. A visit window of +2 days is permitted but it is preferred that the visit is performed on the scheduled visit day, where possible.

[2] A comprehensive physical examination, including an assessment of height, will be completed at Screening (Visit 1) only, subsequent physical examinations will be symptom-directed.

[3] A positive urine drug screen at Visit 1or pre dose at Visit 2 for illicit drugs may be repeated locally at the investigator's discretion. Urine drug tests must not be performed once the patient has received IMP

[4] Serum pregnancy test at Visits 1 and 6; urine pregnancy test before randomization at Visit 2. Note that pregnancy testing is not required for females postmenopausal for ≥ 12 consecutive months with a FSH ≥ 30 mIU/mL.

[5] On the day before PK blood sampling, patients will be prompted to record whether they started their morning and evening doses of IMP within 30 minutes of a meal. During the visits, the exact time of PK blood sampling and the time of the patient's snacks and meals should be recorded. There will be 2 options for the collections of PK samples:
Option 1: For patients choosing the sparse PK sampling option, blood samples will be taken as follows: Visit 2 – 1 sample predose; Visits 3, 4, 5, and 6 – 1 sample collected at any time during the visit. **Option 2:** For patients choosing the semi-intensive PK sampling option, blood samples will be taken as follows: Visit 2 – 1 sample predose; At 1 visit (either Visit 3, 4, or 5), – 1 sample predose (i.e., prior to administration of IMP at the investigational site), 1 sample between 2 and 3 hours postdose, 1 sample between 4 and 6 hours postdose, and 1 sample between 6 and 8 hours postdose. There must be a minimum period of at least 2 hours between each of the 4 blood-sampling time-points. The predose sample will be taken prior to the morning IMP dose. On the day of the semi-intensive PK sampling, the patient must bring their study medication with them to the visit and not take their morning IMP dose until instructed to do so by the site staff.

[6] Patients will record their spasm count, 11-point NRS spasm severity score, 11-point NRS spasticity score, and use of antispasticity medications in an electronic diary once daily, around the same time of day, preferably in the evening before retiring to sleep, during the baseline period prior to Visit 2 and throughout the trial until Visit 7. Patients are to be instructed to start completing their electronic diary in the evening of their screening visit. IMP dosing will be recorded by the patient in the electronic diary from Visits 2 through 6.

[7] Data for the day of Visit 7 should not be entered in the electronic diary. Site staff will confirm that data that relates to the day prior to attending the site for Visit 7 has been entered in the electronic diary prior to completion of the trial.

[8] C-SSRS: 'Baseline' version should be used at Visit 1, and 'Since last visit' version should be used at all subsequent visits.

[9] In cases where patients are not able to attend study visits due to the presence of an infectious disease or other transmissible condition (such as COVID-19/other pandemic restrictions), the investigator will discuss with the Sponsor potential mitigation approaches for IMP dispensing and collection.

Appendix 2 TRIAL PERSONNEL

Appendix 2.1 Investigator Details

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

Appendix 2.2 Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:	**Email:** [redacted] **Fax:** [redacted] **USA Toll-free Fax:** [redacted] Tel: [redacted]
Sponsor:	GW Pharma Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1223 266 800 Fax: +44 (0) 1223 235 667
Medical Advisor & Clinical Project Manager:	Please refer to the Sponsor and Related Contact Details form in the trial site file.
Clinical Trial Supplies:	GW Tel: +44 (0) 1795 435 029 Fax: +44 (0) 1795 475 439

Appendix 2.3 Contract Research Organizations

At the time of protocol production, the CROs and the central 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).

Appendix 3 QUESTIONNAIRES/ASSESSMENTS

At the time of protocol finalization, questionnaire/assessment licensing has not yet been obtained. Copies of the questionnaires/assessments will be made available to all investigators.

Appendix 4 PROHIBITED MEDICATIONS SOLELY METABOLIZED BY UGT1A9 AND UGT2B7

Examples of medications that are solely metabolized by UGT1A9 and UGT2B7 and prohibited for the duration of the trial are provided in the sections below.

Appendix 4.1 Prohibited Medications Metabolized by UGT1A9

- Flavopiridol
- Propofol

Appendix 4.2 Prohibited Medications Metabolized Solely by UGT2B7

- Benoxaprofen
- Carbamazepine
- Codeine
- Cyclosporin A
- Epirubicin
- Indomethacin
- Tacrolimus
- Tiaprofenic acid
- Zaltoprofen
- Zomepirac
- Zidovudine