Statistical Analysis Plan (SAP)

Protocol Title:	Randomized, Double-blind, Placebo-controlled, 2-way Crossover Trial to Evaluate the Effect of Nabiximols Oromucosal Spray on Clinical Measures in Patients with Multiple Sclerosis
Protocol Version No./Date:	V4.0 / 02-Sept-2021
CRF Version No./Date:	V4.1 / 28-April-2022
SAP Version No./Date:	Final / 06-June-2022

1.0 Approvals

Sponsor	
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Representative / Title:	[redacted] Contract Statistician
Signature / Date:	[redacted]
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PRA	
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Signature / Date:	[redacted]

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
1.0	Created as new
2.0	Added clarification to efficacy models as to model checking technique by reduction to using only unstructured/compound symmetry covariance structures.
Final	1) Updated to clarify tipping point instructions 2) eGFR to be presented as collected on eCRF and derivation removed 3) Section 12.3.1.2 MP dosing additional summaries added to titration phase and maximal presentation change to mode. 4) Overall combine (titration + maintenance) summary added

3.0 Table of Contents, List of Tables and Figures

Table of Contents

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4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under GW PHARMA LIMITED Protocol GWSP19066 V4.0 dated 2nd Sept 2021.

5.0 Scope

This plan supplements the study protocol for statistical analysis related aspects.

The SAP outlines the following:

- Study Objectives,
- Study Design,
- Endpoints to be Analyzed and the Analysis sets,
- Estimands,
- Applicable Study Definitions,
- Statistical Methods.

6.0 Introduction

This SAP should be read in conjunction with the study protocol V4.0 2nd Sept 2021 and case report form (CRF) V4.1 28th April 2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Final approval of the SAP by the GW and PRA statisticians will occur prior to database lock and unblinding of the study treatment.

6.1 Timings of Analyses

When at least 50% (24 patients) of the patients have completed both treatment periods and before database lock and unblinding, a blinded estimate of the pooled variability for the primary endpoint treatment difference will be conducted and sample size may be re-evaluated.

Analyses of efficacy, safety, and pharmacokinetics/pharmacodynamics will be performed after all patients complete or terminate early from the study following database lock and unblinding.

6.2 Changes from Protocol

Table 6.2-1 Change from protocol

Section of SAP Affected	Type of Change	Rationale
Section 9.6.2.3, Section 11.0, and Section 12.5	Change to the definition of the Full Analysis Set (FAS) that is detailed in protocol Section 13.3	The FAS includes all patients who have taken a dose of investigational medicinal product (IMP). Per our specified estimand, patients should continue Period 1 despite stopping IMP. Hence, if a patient withdraws from the study, they should be handled as a missing data problem and will be imputed per this analysis plan. Since IMP was taken, withdrawal may have been due to IMP and hence it may be important to include this patient in the analysis.
Section 7.3, Section 9.1, Section 10.15, and Section 12.5	Addition of an exploratory objective/ endpoint, the Lower Limb Muscle Tone-10 to those presented in Protocol Section 2 and Section 13.6.2	Since hip flexors and hip adductors are being collected the Lower Limb Muscle Tone-10 was added as exploratory endpoints

7.0 Study Objectives

7.1 Primary Objectives

To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone-6; LLMT-6) in patients with multiple sclerosis (MS) who have not achieved adequate relief from spasticity with other antispasticity medications.

7.2 Secondary Objectives

- To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone-4; LLMT-4) in patients with MS who have not achieved adequate relief from spasticity with other antispasticity medications.
- To evaluate the safety and tolerability of nabiximols after administration of multiple doses.
- To evaluate the pharmacokinetic (PK) profile of nabiximols after administration of multiple doses.

7.3 Exploratory Objectives

- To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone-10; LLMT-10) in patients with MS who have not achieved adequate relief from spasticity with other antispasticity medications.
- To evaluate the effect of nabiximols after administration of multiple doses on walking using the Timed 25-Foot Walk (T25FW) test.
- To evaluate the effect of nabiximols after administration of multiple doses on the following patient-reported outcomes:
  - The 11-point Numerical Rating Scale (NRS) spasticity score,
  - Daily spasm count,
  - The MS Spasticity Scale (MSSS-88) total and subdomain scores

8.0 Study Design

8.1 General Design

This multicenter, randomized, double-blind, placebo-controlled, 2-treatment, 2-period, Phase 3 crossover trial is being conducted to evaluate the effect of multiple doses of nabiximols as adjunctive therapy on clinical measures in the symptomatic treatment of patients with MS who have not achieved adequate relief from spasticity with other antispasticity medications.

Patients with MS who are naïve to treatment with nabiximols for spasticity will participate in a screening period of up to 28 days; no changes in the dose of the patients' current MS antispasticity medications will be made during this period.

As part of the baseline period of each treatment period, patients will keep an electronic diary (eDiary) to record 11-point NRS spasticity score, spasm count, and use of antispasticity medications once daily, around the same time each day, preferably in the evening before retiring to sleep, for at least 7 days prior to Visits 2 and 6. At Visit 2, in the morning of Day 1, eligible patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences, each composed of 2 treatment periods, with administration of multiple doses of nabiximols or placebo.

Patients randomized will complete 2 treatment periods with administration of IMP for 21 days per treatment period. Each treatment period will consist of a dose-titration phase of approximately 14 days, followed by a maintenance-dose phase of approximately 7 days, where the individually determined optimized dose level remains unchanged for the remainder of each treatment period after titration. Doses greater than 1 spray/day will be divided into a morning dose and an evening dose.

Throughout both treatment periods, patients will initiate IMP treatment as a single spray in the clinic in the morning of Visits 2 (Day 1) and 6 (Day 31) of each treatment period. Patients will gradually titrate their daily dose by 1 to 2 additional sprays/day to an optimized dose or to a maximum of 12 sprays/day over the first approximately 14 days of treatment with an approximately 15-minute interval between sprays. Patients should complete titration within approximately 14 days of their first dose of IMP in each treatment period and 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. Once a stable daily dose has been reached, patients should 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.

Table 8.1-1 Example Titration Schedule

Day	Number of Sprays in the Morning	Number of Sprays in the Evening	Total Number of Sprays/Day
1	1	0	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

The patient's first dose of IMP will be administered in the clinic.

On the days of scheduled Modified Ashworth Scale (MAS) assessments other than Visit 1 (i.e., Visits 2, 5, 6, and 9), patients will attend the trial site without having administered any IMP in the morning. On the day of MAS assessment, patients who are taking baclofen and/or tizanidine as part of their optimized antispasticity therapy should take their regular morning dose of either or both medication(s) at least 1 hour before the administration of IMP. Administration of the morning dose of IMP with a standardized snack containing at least 300 kcal (of which approximately 30 kcal is composed of fat) will occur at the trial site under the supervision of site staff; MAS assessments will occur at scheduled time points before (Visits 2 and 6 [pre-dose]) and after (Visits 2, 5, 6, and 9 [3 hours ± 15 minutes post-dose]) IMP administration

A washout period of at least 7 days will separate the 2 treatment periods. During the washout period, patients will continue to take their current MS antispasticity medications without any changes in dose.

Patients who complete the 2 treatment periods will complete an End of Treatment Visit (Visit 9). Patients who discontinue IMP early will be encouraged to remain in the study for the duration of the treatment period in which they discontinue IMP and will complete an End of Treatment Visit (Visit 9) at the end of that period. A Safety Follow-up Visit (Visit 10) will occur 7 (+3) days after the last dose of IMP or after the End-of-Treatment visit (Visit 9), whichever is later, for all patients.

The total daily dose should be administered as a morning dose and an evening dose, which may be comprised of a different number of sprays during titration. During the period of stable dosing following titration, patients should attempt to achieve a balance in the number of sprays administered as part of the morning and evening doses of IMP.

The study overview is specified in Figure 8.1-1.

The schedule of study events is specified in Table 8.1-1 and in Table 8.1-2.

Figure 8.1-1 Trial Design and Treatment Schematic

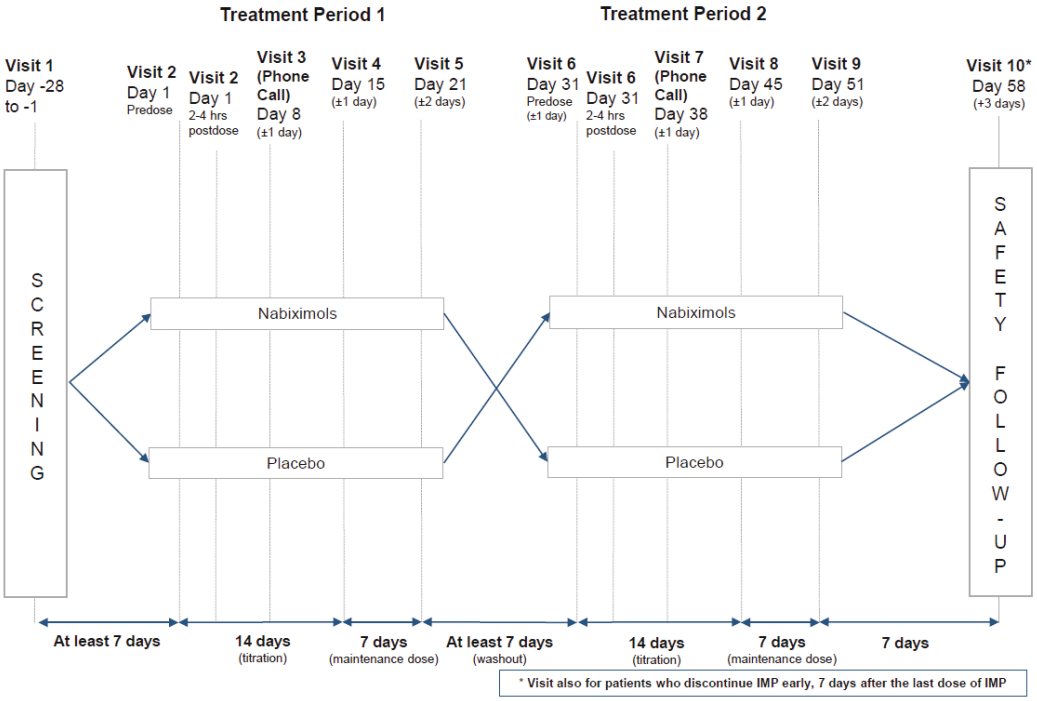

Table 8.1-1 Schedule of Assessments

Period	**Screening**	**Treatment Period 1**					**Treatment Period 2**					**Safety Follow-up**
Visit Number	**Visit 1**	**Visit 2**		**Visit 3 (Phone Call)**	**Visit 4**	**Visit 5[a]**	**Visit 6**		**Visit 7 (Phone Call)**	**Visit 8**	**Visit 9**	**Visit 10 (or 7 days after final IMP dose or ET visit)**
Day/Hour	**Days -28 to -1**	**Day 1 Pre-dose**	**Day 1 2-4 hrs Post-dose**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**D21 (±2 days)**	**Day 31 Pre-dose (±1 day)**	**Day 31 2-4 hrs Post-dose**	**Day 38 (±1 day)**	**Day 45 (±1 day)**	**Day 51 (±2 days) End of Treatment Visit**	**Day 58 (+3 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	Assessed at each visit											
AEs	Assessed at each visit											
Physical examination[b]	X					X					X	
Examination of oral mucosa	X	X			X	X	X			X	X	X
Body weight measurement	X	X					X					X
Vital signs	X	X	X		X	X	X	X		X	X	X

Period		Screening	Treatment Period 1					Treatment Period 2					Safety Follow-up
Visit Number		Visit 1	Visit 2		Visit 3 (Phone Call)	Visit 4	Visit 5[a]	Visit 6		Visit 7 (Phone Call)	Visit 8	Visit 9	Visit 10 (or 7 days after final IMP dose or ET visit)
Day/Hour		Days -28 to -1	Day 1 Pre-dose	Day 1 2-4 hrs Post-dose	Day 8 (±1 day)	Day 15 (±1 day)	D21 (±2 days)	Day 31 Pre-dose (±1 day)	Day 31 2-4 hrs Post-dose	Day 38 (±1 day)	Day 45 (±1 day)	Day 51 (±2 days) End of Treatment Visit	Day 58 (+3 days)
12-lead ECG		X					X					X	
Clinical laboratory blood sampling (hematology and biochemistry)		X					X					X	
Dipstick urinalysis		X											X
Urine drug screen (including THC)		X	X										
Serum/urine pregnancy test (if appropriate)[c]		X	X					X					X
Blood THC test		X											
PK blood sampling (IMP)[d]			X	X		X	X	X	X		X	X	
Electronic daily diary	11-Point NRS spasticity[e]	X	X			X	X	X			X	X	
	Daily spasm count[e]	X	X			X	X	X			X	X	
	Use of antispasticity medications[e]	X	X			X	X	X			X	X	

Period	Screening	Treatment Period 1					Treatment Period 2					Safety Follow-up
Visit Number	Visit 1	Visit 2		Visit 3 (Phone Call)	Visit 4	Visit 5[a]	Visit 6		Visit 7 (Phone Call)	Visit 8	Visit 9	Visit 10 (or 7 days after final IMP dose or ET visit)
Day/Hour	Days -28 to -1	Day 1 Pre-dose	Day 1 2-4 hrs Post-dose	Day 8 (±1 day)	Day 15 (±1 day)	D21 (±2 days)	Day 31 Pre-dose (±1 day)	Day 31 2-4 hrs Post-dose	Day 38 (±1 day)	Day 45 (±1 day)	Day 51 (±2 days) End of Treatment Visit	Day 58 (+3 days)
IMP dosing record[e]		X			X	X	X			X	X	
MAS[f]	X	X	X			X	X	X			X	
MSSS-88						X					X	
T25FW test[g]		X				X	X				X	
C-SSRS	X	X			X	X	X			X	X	X
IMP dosing training		X										
IMP dosing[h]		X				X	X				X	
IMP dispensing[i]		X			X		X			X		
IMP collection and compliance review					X	X				X	X	

AE = adverse events; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; IMP = investigational medicinal product; MAS = Modified Ashworth Scale; MS = multiple sclerosis; MSSS-88 = Multiple Sclerosis Spasticity Scale; NRS = Numerical Rating Scale; PK = pharmacokinetics; T25FW = Timed 25-Foot Walk; THC = Δ9-tetrahydrocannabinol.

[a] A washout period of at least 7 days will separate the 2 treatment periods. Following the final dose of IMP in Treatment Period 1, in the morning of Visit 5 (D21), patients will discontinue treatment with IMP for the 7 days prior to Visit 6 (Day 31). During the washout period, patients will continue to take their current MS antispasticity medications without any changes in dose.

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

[c] Serum pregnancy test at Visits 1 and 10; urine pregnancy test at Visits 2 and 6 (pre-dose).

[d] On the day before PK blood sampling at Visits 4, 5, 8, and 9, patients will be prompted to record whether they started their morning and evening doses of IMP within 30 minutes of a snack or meal. On the day of PK blood sampling, the exact time and date of PK blood sampling and the time

of the patient's snacks and meals should be recorded for the PK blood sampling schedule (see Table 8.1-2). Please note that more than one PK sample may be collected at distinct time points during a single visit.

[e] *Patients will record their 11-point NRS spasticity score, spasm count, and use of antispasticity medications in an electronic diary once daily, around the same time each day, preferably in the evening before retiring to sleep, for at least 7 days prior to Visits 2 and 6 and throughout the trial until Visit 9. Investigational medicinal product dosing will be recorded by the patient in an electronic diary from Visits 2 through 9.*

[f] *MAS assessments will occur at Visit 1 (Screening) and at scheduled time points before (Visits 2 and 6 [pre-dose]) and after (Visits 2, 5, 6, and 9 [3 hours ± 15 minutes post-dose]) IMP administration; for Visits in which the morning dose consists of more than 1 spray (Visits 5 and 9), post-dose assessments will occur 3 hours ± 15 minutes after the first spray of the morning dose.*

[g] *Non-ambulatory patients are not expected to perform the T25FW test.*

[h] *IMP administration of the morning dose will occur at the trial site within 30 minutes after a standardized snack containing at least 300 kcal (of which approximately 30 kcal is composed of fat) under the supervision of site staff. On the days of scheduled MAS assessments other than Visit 1, patients who are taking baclofen and/or tizanidine as part of their optimized antispasticity therapy should take their regular morning dose of either or both medication(s) at least 1 hour before administration of IMP. IMP will not be administered in the evening of Days 21 and 51.*

[i] *In cases where patients are not able to attend study visits due to the presence of an infectious disease or other transmissible condition, the investigator will discuss with the Sponsor potential mitigation approaches for IMP dispensing, secure delivery, and collection.*

Table 8.1-2 Pharmacokinetic Blood Sample Schedule

Visit/Day	Period /Day	Timepoints
Visit 2 / Day 1	Period 1 Day 1	Pre-dose and 0-2 and 2-4 hours post-dose
Visit 4 / Day 15	Period 1 Day 15	0-2 and 2-4 hours post-dose
Visit 5 / D21	Period 1 D21	Pre-dose and 0-1 and 2-3 hours post-dose
Visit 6 / Day 31	Period 2 Day 1	Pre-dose and 0-2 and 2-4 hours post-dose
Visit 8 / Day 45	Period 2 Day 15	0-2 and 2-4 hours post-dose
Visit 9 / Day 51	Period 2 D21	Pre-dose and 0-1 and 2-3 hours post-dose

8.2 Sample Size Considerations

Approximately 26 patients will be randomly assigned to each treatment sequence to ensure that at least 46 patients in total complete the 2 treatment periods. The primary comparison will be the estimate of the mean treatment difference between nabiximols and placebo in the mean change from baseline in LLMT-6.

Assuming a standard deviation of the paired differences between nabiximols and placebo of 0.71 and a treatment difference of −0.30, 46 patients will provide 80% power using a 5% significance level and a two-sided test. Adjusting for 10% dropout, a total of approximately N=52 patients are required. If more than 6 patients withdraw from the trial, additional patients will be enrolled to have 46 completers.

A blinded sample size re-estimation was conducted based on methodology in section 11.1 and the estimated standard deviation of the pooled treatment period differences (treatment period 2 – treatment period 1) in changes from baseline to D21 in MAS was larger than 0.71 (the assumed standard deviation of the treatment differences at design stage). Using this new standard deviation as the estimate of the standard deviation of the treatment differences (nabiximols – placebo) of the changes from baseline to D21 in MAS, the sample size was recalculated. In a blinded sample size re-estimation committee meeting dated 30th November 2021, the committee recommended increasing the sample size to 68 completers. This new sample size will result in at least 80% power for this study if the new observed blinded standard deviation were the true unblinded standard deviation, and greater than 90% power if the true unblinded standard deviation was exactly 0.71.

SAS software version 9.4 was used to perform the sample size calculations.

8.3 Randomization

At Visit 2, in the morning of Day 1, eligible patients will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences, each composed of 2 treatment periods, with administration of multiple doses of nabiximols or placebo following the randomization schedule generated and kept by Endpoint.

Enrolled patients will be allocated a unique patient number in a sequential order by trial site. Following randomization, GW Pharma Limited will provide all IMP in a packed and labelled state, and the Interactive Web Response Technology (IRT) will identify the pack number to be dispensed to the patient at each relevant visit according to the treatment sequence assigned in the randomization schedule.

9.0 Study Endpoints, Variables and Covariates

9.1 Overview

An overview of objectives and endpoints is shown in Table 9.1-1 and an overview of estimands is shown in Table 9.1-2.

Table 9.1-1 Objectives and Endpoints

Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
• To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in LLMT-6 in patients with MS who have not achieved adequate relief from spasticity with other antispasticity medications	• Change in LLMT-6; defined as the average of the 6 individual MAS transformed scores of knee flexors, knee extensors, and plantar flexors on both sides of the body, from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs in LLMT-4 in patients with multiple sclerosis (MS) who have not achieved adequate relief from spasticity with other antispasticity medications	• Change in LLMT-4; defined as the average of the 4 individual MAS transformed scores of knee flexors and knee extensors on both sides of the body, from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51

• To evaluate the safety and tolerability of nabiximols after administration of multiple doses	• Frequency of treatment-emergent adverse events (TEAEs)
	• Change from baseline to each assessment timepoint by treatment period for the following:
	  ○ Clinical laboratory parameters
	  ○ Vital signs
	  ○ Physical examination procedure
	  ○ 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)

• To evaluate the PK profile of nabiximols after administration of multiple doses	• Plasma concentrations for Δ^9-tetrahydrocannabinol (THC) and its relevant metabolites (11-hydroxy-Δ^9-tetrahydrocannabinol and 11-carboxy-Δ9-tetrahydrocannabinol) and cannabidiol (CBD) and its relevant metabolites (7-hydroxy-cannabidiol and 7-carboxy-cannabidiol) at distinct time points during each treatment period (Visits 2, 4, 5, 6, 8, and 9)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs in LLMT-10 in patients with multiple sclerosis (MS) who have not achieved adequate relief from spasticity with other antispasticity medications	• Difference between treatment arm in change in LLMT-10; defined as the average of the 10 individual MAS transformed scores of knee flexors, knee extensors; plantar flexors, hip flexors and hip adductors on both sides of the body, from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51
• To evaluate the effect of nabiximols after administration of multiple doses on walking using the T25FW test	• Difference between treatments in the change in T25FW test from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51

• To evaluate the effect of nabiximols after administration of multiple doses on the following patient-reported outcomes:
  ○ The 11-point Numerical Rating Scale (NRS) spasticity score
  ○ Daily spasm count
  ○ The MS Spasticity Scale (MSS-88) total and subdomain scores
	• Difference between treatments in average 11-point NRS spasticity score over the last 7 days of each double-blind treatment period
	• Difference between treatments in average daily spasm count over the last 7 days of each double-blind treatment period
	• Difference between treatments in total and subdomain scores of the MSSS-88 at the end of maintenance-dose phase of each double-blind treatment period

Table 9.1-2 Estimands

Estimands
Primary Estimand
The primary estimand for this study is defined by the following 4 components: • **Population:** Patients with MS, naïve to treatment with nabiximols who have not achieved adequate relief from spasticity with other antispasticity agents but have optimized treatment with at least 1 oral antispasticity drug. • **Treatment:** • **Endpoint:** Change in LLMT-6 from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51. • **Intercurrent events:** o *Treatment-policy*: Intercurrent events of non-adherence with IMP, use of prohibited medications, or other protocol deviations will be handled following a '*treatment-policy*' strategy. Study data will continue to be collected and analyzed following the occurrence of the intercurrent event, i.e., the measure of effect is regardless of non-compliance, use of prohibited medications, or other protocol deviations. For patients who discontinue IMP, only the period in which this intercurrent event occurs will follow a treatment-policy strategy. Data will continue to be collected and analyzed following the occurrence of the intercurrent event up to the end of the period. o Hypothetical strategy: For patients who discontinue IMP during Period 1, their Period 2 data will be assumed to follow a hypothetical strategy, i.e., patients will be assumed to follow a similar pattern of data in Period 2 to those patients in the same Period 2 treatment arm who did not experience this intercurrent event during Period 1. For these patients, Period 2 data will not be collected, and these data will be imputed according to Table 9.1-3. **Summary Measure:** Mean difference in 'change from period level baseline to 21 days of the period assigned to nabiximols' compared to 'change from period level baseline to 21 days of the period assigned to placebo' regardless of treatment compliance and change of other antispasticity medications; following a treatment policy and hypothetical strategy for handling intercurrent events (as described above).
Secondary Estimand
The secondary estimand for this study is defined by the following 4 components: • **Population:** Patients with MS, naïve to treatment with nabiximols who have not achieved adequate relief from spasticity with other antispasticity agents but have optimized treatment with at least 1 oral antispasticity drug. • **Treatment:** • **Endpoint:** Change in LLMT-4 from Day 1 pre-dose to D21 and from Day 31 pre-dose to Day 51. • **Intercurrent events:** o *Treatment-policy*: Intercurrent events of non-adherence with IMP, use of prohibited medications, or other protocol deviations will be handled following a '*treatment-policy*' strategy. Study data will continue to be collected and analyzed following the occurrence of the intercurrent event, i.e., the measure of effect is regardless of non-compliance, use of prohibited medications, or other protocol deviations. For patients who discontinue IMP, only the period in which this intercurrent event occurs will follow a treatment-policy strategy. Data will continue to be collected and analyzed following the occurrence of the intercurrent event up to the end of the period. o *Hypothetical strategy:* For patients who discontinue IMP during Period 1, their Period 2 data will be assumed to follow a hypothetical strategy, i.e., patients will be assumed to follow a similar pattern of data in Period 2 to those patients in the same Period 2 treatment arm who did not experience this intercurrent event during Period 1. For these patients, Period 2 data will not be collected, and these data will be imputed according to Table 9.1-4. **Summary Measure:** Mean difference in 'change from period level baseline to 21 days during period assigned to nabiximols' compared to 'change from period level baseline to 21 days during period assigned to placebo' regardless of treatment compliance and change of other antispasticity medications; following a treatment policy and hypothetical strategy for handling intercurrent events (as described above).

9.2 Predetermined Covariates and Prognostic Factors and other Analyzed Factors

The following factors will be adjusted for as covariates and used in the analysis models as fixed effect:

- Treatment sequence, which has two levels: nabiximols/placebo (coded as 1) and placebo/nabiximols (coded as 2),
- Treatment period, which has two levels: Period 1 (coded as 1) and Period 2 (coded as 2),
- Baseline / Period baseline (as continuous covariates)

9.3 Analysis Sets

9.3.1 Treatment Arm

The "as randomized" treatment arm called the "planned treatment arm" is defined as the treatment allocated at each treatment period according to the randomization scheme.

The "as treated" treatment arm also called "actual treatment arm" is defined as the treatment received for the longest period of time within each treatment period.

9.3.2 Definition of Analysis Sets

9.3.2.1 Screening Analysis Set

All patients who signed the inform consent and have performed Visit 1 (screening).

9.3.2.2 Randomized Analysis Set

All patients who signed the informed consent and were randomized by IRT will be included and analysed according to their randomized treatment arm / treatment sequence.

9.3.2.3 Full Analysis Set

All patients who signed the informed consent and are randomized and received at least 1 dose of IMP in the trial, will be included and analyzed according to their randomized treatment. The Full Analysis Set is the primary analysis set for all efficacy endpoints and patient reported outcome (PRO) assessment.

9.3.2.4 Safety Analysis Set

All patients from the Screening Analysis Set, who received at least 1 dose of IMP in the trial will be included in the Safety Analysis Set and analysed 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 using the actual treatment arm.

9.3.2.5 Study Completer Analysis Set

All patients from the FAS who have completed the trial (completed both treatment period 1 and treatment period 2), regardless whether they have permanently withdrawn from study drug. The analyses on the Study Completer Analysis Set will only be conducted on efficacy endpoints and patients analyzed according to their randomized treatment arm.

9.3.2.6 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set is defined as follows: a subset of the FAS that includes all patients who have completed the trial with no major important protocol deviations deemed to compromise the assessment of efficacy. Major important protocol deviations will be identified as a subset of the important protocol deviations and fully defined prior to unblinding of the trial. The PP analysis will only be conducted on efficacy endpoints and patients analyzed according to their randomized treatment arm.

9.3.2.7 Pharmacokinetic Analysis Set

All patients who have received at least 1 dose of IMP and provided sufficient bioanalytical data to calculate reliable (based on the judgement of the pharmacokineticist) estimates of the PK parameters of THC, CBD, and their metabolites will be included in the PK Analysis Set. This analysis set cannot be determined before unblinded analysis.

10.0 Conventions and Derivations

10.1 Study Period, Reference Day, Study Day, Analysis Day and Visit Window

10.1.1 Study Periods

For each patient, there will be a screening period, an evaluable period composed of a treatment period 1, a washout period, and a treatment period 2, and a safety follow-up period.

The Screening period starts on the day of the informed consent signature and ends on Day 1 (as defined on in Section 10.1.2) before 1st IMP intake.

The evaluable period starts on the day of randomization and ends the day of the safety follow-up visit.

- The **51-day efficacy period** which starts on the first day of IMP administration and ends at the end of treatment date.
  - This period will be composed of:
    - The **21-day on-treatment efficacy Period 1** which starts the day of first IMP intake during Period 1 and ends the earliest between end of Period 1 D21 date and permanent end of treatment date;
    - The on-treatment **wash-out period** which begins the day following the end of the 21-day on-treatment efficacy Period 1 and ends the day before the beginning of the 21-day on-treatment efficacy Period 2;
    - **The 21-days on-treatment efficacy Period 2** which starts the day of IRT call for Period 2 and ends on the end of treatment date. This period is only defined for patients exposed to IMP during Period 2.
  - It will be used for efficacy analyses using the Full Analysis Set.

- The **51-day safety period** which starts on the first day of IMP administration and ends at the end of treatment date (+ x days).
  - This period will be composed of:
    - The **21 day on-treatment Safety Period 1** which starts the day of first IMP intake during Period 1 and ends the earliest between end of the wash out period date, the day before the date of IRT call for Period 2, the day before Visit 6 date and permanent end of treatment date + x days.
    - **The 21 day on-treatment Safety Period 2** which starts the earliest between date of Visit 6, day of IRT on treatment safety period call for Period 2 date, and ends on the end of treatment day date + x days.
  - x will be equal to 14 days for Adverse events, 4 days for C-SSRS and 0 days otherwise.
  - it will be used for safety analyses using the Safety Analysis Set (unless otherwise specified).

- The **Follow-up period** which starts the day following the 51-day on-treatment safety period and ends on the end of study date.

10.1.2 Reference Day and Study Day

The reference day (Day 1) will be the day of the first dose of study drug administration.
For a patient who was randomized but not exposed, the reference day date will be imputed by the randomization date.

The reference day for Period 1 (Period 1 Day 1) will be the reference day.

The reference day for Period 2 (Period 2 Day 1) will be the first day of IMP administration during Period 2. For a patient who entered the second period but was not exposed during this period, this reference day date will be imputed by the date of Visit 6 IRT call, if any, or the Visit 6 date.

The study day is defined relative to the reference day date. For assessments that occur after this visit date, the study day is calculated as (assessment date – reference day date + 1). For assessments that occur prior to first dose date, study day will be calculated as (assessment date – reference day date).

For the analyses being done by treatment arm, an **analysis day** will need to be derived for each treatment period as described in Table 10.1-1. The analysis day is defined relative to the date of reference day of each study period.
For assessments that occur prior to reference day date, analysis day will be calculated as (assessment date – reference day date);
For assessments that occur on or after the Period 1 reference day date until the end of the wash-out period, analysis day will be calculated as (assessment date – Period 1 reference day date +1);
For assessments that occur on or after Period 2 reference day date the analysis day will be calculated as (assessment date – Period 2 reference day date +1);

Thus, there is no study day or analysis day referring to Day 0.

10.1.3 Target Days and Visit Window

Visit windows are summarized in Table 10.1-3 for efficacy data and urine drug screen collection and, in Table 10.1-2 for all other safety endpoints.

When there are multiple observations within a visit window, the value closest to the target day will be analyzed (as described in Table 10.1-1).

For safety assessments, on-treatment assessments will be preferred to off-treatment ones.
In case of ties between observations located on different sides of the target, the observation with the earliest date/time will be used. In case of ties between observations located on the same side of the target, (i.e., more than one value for the same day but at different time), the observation with the earliest date/time will be used. However, in case of non-respect of wash-out period, the one done at least 7 days after last Period 1 dosing date will be preferred.

For efficacy, PRO endpoints visit windowing will apply whether patient is on or off treatment.

Table 10.1-1 Longitudinal Assessment – Analysis Day and Target Day

Treatment Period	Visit / Day	Analysis visit	Target Day (defined by period)	Observation used for analysis, if more than one exists
Screening	Visit 1 / Day -28 to -1	Screening	Day -28 to -1	Latest value
Period 1	Visit 2 / Day 1	Day 1	Day 1*	Closest to Target Day But Day 1 H0 should be before 1st IMP intake and D1H3 should be post IMP intake
	Visit 3 / Day 8	Day 8	Day 8	Closest to Target Day
	Visit 4 / Day 15	Day 15	Day 15	Closest to Target Day
	Visit 5 / D21	D21	D21	Closest to Target Day
Period 2	Visit 6 / Day 31	Day 1	Day 1*	Closest to Target Day But Day 1 H0 should be before 1st IMP intake and

Treatment Period	Visit / Day	Analysis visit	Target Day (defined by period)	Observation used for analysis, if more than one exists
				D1H3 should be post IMP intake.
	Visit 7 / Day 38	Day 8	Day 8	Closest to Target Day
	Visit 8 / Day 45	Day 15	Day 15	Closest to Target Day
	Visit 9 / Day 51	D21	D21	Closest to Target Day
Follow-up	Visit 10 / Day 58	Day 28	Day 28**	Closest to Target Day

H = Hours; IMP = Investigational medical product.
** Day 1 is based on the date of IRT call within each period*
*** Day 28 relative to the period where IMP is permanently discontinued thus visit is expected between Day 25 and Day 31*

Table 10.1-2 Longitudinal Assessment – Target Day and Visit Window – Part 1

Treatment Period	Visit / Day	Target Day (defined by period)	Physical examination / 12-lead ECG / Clinical laboratory blood sampling	Examination of oral mucosa / C-SSRS	Body weight / Serum urine pregnancy test	Vital signs	Dipstick urine
Screening	Visit 1 / Day -28 to -01	Day -28 to -01	Day-28 – D1H0	Day -28 to -01	Day -28 to -01	Day -28 to -01	Day-28 – D1H0 (before 1st IMP dosing)
Period 1	Visit 2 / Day 1H0	Day 1*		Day 1H0 *	Day 1 H0 (before P1 IMP intake)	Day 1 H0 (before P1 IMP intake)	
	Visit 2 / Day 1	Day 1 H2-H4*				Day 1 post dose (the day of 1st P1 IMP intake)	
	Visit 4 / Day 15	Day 15		Day 1 post dose to Day 18		Day 2 (day following IMP intake) – Day 18	
	Visit 5 / D21	D21	Day 1 post dose to LP1V	Day 19 to LP1V		Day 19 to LP1V	
Wash-out							
Period 2	Visit 6 / Day -31	Day 1H0*		Day 1 – 4 days to D1H0 *	D1H0 (before P2 IMP intake)	Day 1 – 4 days to D1H0	
	Visit 6 / Day -31	Day 1H2-H4*				Day 1 post dose (the day of 1st P2 IMP intake)	
	Visit 8 / Day 45	Day 15		Day 1 post dose to Day 18		Day 2 (day following IMP intake) – Day 18	
	Visit 9 / Day 51	D21	Day 1 post dose to LP2V	Day 19 to LP2V		Day 19 to LP2V	
Follow-up	Visit 10 / Day 58	Day 28***		after last IMP dosing	After last IMP dosing		Day 1 post 1st IMP dosing to after last IMP dosing

H = Hour; P = Period; LP1V = Last visit during Period 1, LP2V = Last visit during Period 2, IMP = Investigational Medical Product; IRT = Interactive response technology; ECG = Electrocardiogram; C-SSRS = Columbia-Suicide Severity Rating Scale.

** Day 1 is based on the date of IRT call within each period.*

**** Day 28 relative to the period where IMP is permanently discontinued.*

Table 10.1-3 Longitudinal Assessment –Target Day and Visit Window – Part 2

Treatment Period	Visit / Day	Target Day (defined by period)	Urine drug screen	11-point NRS spasticity / Daily spasm count	MAS	MSSS-88	T25FW test
Screening	Visit 1 / Day -28 to -01	Day -28 to -01	Day -28 to -01	Day -28 to -01	Day -28 to -01		
Period 1	Visit 2 / Day 1H0	Day 1*	Day 1 H0 (before P1 IMP intake)	Day1H0 (before P1 IMP intake) *	Day1H0 (before P1 IMP intake)		Day 1H0 (before P1 IMP intake)
	Visit 2 / Day 1	Day 1 H2-H4**			Day1 post dose (the day of 1st P1 IMP intake)** up to Day 18		
	Visit 4 / Day 15	Day 15		Day 2 (day following IMP intake) – Day 18 (or the first day of maintenance phase)			
	Visit 5 / D21	D21***		Day 19 up to LP1V	Day 19 up to LP1V	Day 1 post dose of 1st IMP intake up to LP1V	Day 1 post dose of 1st IMP intake up to LVP1
Wash out period							
Period 2	Visit 6 / Day 31	Day 1H0*		Day 1 – 4 days to D1H0 *	Day 1H0 (before P2 IMP intake)		Day 1H0 (before P2 IMP intake)
	Visit 6 / Day 31	Day 1H2-H4**			Day 1 post dose (the day of 1st P2 IMP intake)** up to Day 18		
	Visit 8 / Day 45	Day 15		Day 2 (day following IMP intake) – Day 18 (or the first day of maintenance phase)			
	Visit 9 / Day 51	D21***		Day 19 to LP2V	Day 19 to LP2V	Day 1 post dose of Period 2 1st IMP intake up to LP2V	Day 1 post dose of Period 2 1st IMP intake up to LVP2
Follow-up	Visit 10 / Day 58	Day 28****		After last IMP dosing			

H = Hours, P = Period; LP1V = Last visit during Period 1, LP2V = Last visit during Period 2, IMP = Investigational Medicinal Product, NRS = Numerical Rating Scale; IRT = Interactive Response System; MAS = Modified Ashworth Scale,.MSSS-88 = Multiple Sclerosis Spasticity Scale; T25FW = Timed 25-Foot Walk.

* *Day 1 is based on the date of IRT call within each period.*

** *D1H2-H4 for sensitivity analysis purpose only assessments collected between at H3 (+/- 15 min) post first IMP morning spray will be considered. Should be collected during the titration phase*

*** *D21 should be collected during the maintenance phase (including off-treatment days).*

**** *Day 28 relative to the period where IMP is permanently discontinued.*

For patient electronic diary-based endpoints (NRS-spasticity and spasm count), baseline is defined as the weekly average of daily electronic diary entries over the last 7 days prior to randomization (Visit 2, Period 1 Day 1H0).

In case of missing assessments within the 7 days preceding Period1 Day1 H0

- For 11-point NRS spasticity scale, the weekly average will be set to missing if scores are missing for 4 days in total or for 3 consecutive days within the 7-days period.
- For daily spasm count, the weekly average will be derived as detailed in Section 10.19) and will be set to missing if spasm count is not collected during 4 days out of 7 or for 3 consecutive days during the last 7 days preceding Day 1H0.

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

However, if deemed necessary the baseline will be defined for each period as described in Section 10.1.2 as:

- the reference day for Period 1,
- the reference day for Period 2,

For clinic-safety based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP or if deemed necessary as the reference day as described in Section 10.1.2.

10.3 Change from Baseline

Change from baseline (CFB) will be calculated as:

(post-baseline – baseline).

CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

10.4 Percentage Change from Baseline

Percent CFB will be calculated, where applicable, as:

(CFB/baseline)*100.

If a baseline value has not been recorded for a parameter, then percent CFB will be missing for that parameter.

If baseline and post baseline are rates the following formula will be used:

$$\left(\left(\frac{Post\ baseline\ score/count * baseline\ duration}{Baseline\ score/count * post\ baseline\ duration} - 1\right) \times 100\right)$$

10.5 Time Conversion

Time conversion will follow the rules described below:

- 1 week = 7 days,
- 1 Month = 30.4375 days,
- 1 year = 365.25 days.

10.6 Patient Disposition

The time to treatment discontinuation expressed in day is defined as:

- the date of last administration – the date of 1st IMP spray intake +1 day.

The time to study discontinuation expressed in day is defined as:

- End of study day – date of randomization + 1 day.

Where the date of the 1st IMP spray intake (e.g., IMP start date) will be retrieved from the eCRF "PK sample collection form" and, if missing, from the eDiary first spray date for Period 1 whereas, the end of treatment date will be the latest date between the end of treatment date coming from eCRF "End of treatment Period 1" form and "End of treatment Period 2" form.

Censoring rules for time to event analysis are defined in Section 12.1.

10.7 Duration of Treatment

The duration of study drug exposure expressed in days will be defined for each study drug as:

- the date of last administration – the first day of administration +1 day.

The mean duration of study drug exposure expressed in patient-time will be defined as follows:

- The mean duration (patient-year) = $(\sum_{i=1}^{i=n} Di\ )\ /365.25$
- The mean duration (patient-week) = $(\sum_{i=1}^{i=n} Di\ )\ /7$

With n being the number of patients within the Safety Analysis Set and i=1,2, 3,…,n, and, with Di being the duration of treatment (in days) for patient i.

The IMP start date will be retrieved from the eCRF "PK sample collection form" for each treatment period whereas the end of treatment date for each period will respectively be coming from eCRF "End of treatment Period 1" form and "End of treatment Period 2" form. However, if the information is missing on the eCRF "PK sample collection", the first IMP spray date will be retrieved from the eDiary first spray date of each treatment period.

10.8.1 Study Phases Start and Stop Dates used to summarize IMP Dosing

The titration phase

- Start of the titration phase during Period 1 is defined as:
  Min(randomization date, 1st IMP dosing date)
- Start of the titration phase during Period 2 is defined as:
  Min(the date of IRT call for Period 2, Visit 6 date)
- End of the titration phase during Period 1 is defined as:
  Min(the day preceding Visit 4 date, the last dose date during Period)
- End of the titration phase during Period 2 is defined as:
  Min(the day preceding Visit 8 date, the last dose date during Period 2)

The maintenance phase

- Start of the of the maintenance phase during Period 1 is defined as:
  the date of Visit 4,
- Start of the of the maintenance phase during Period 2 is defined as:
  the date of Visit 8,
- End date of the maintenance phase during Period 1 is defined as:
  Min(Visit 5 date, the date of the last dose of study drug)

- End date of the maintenance phase during Period 2 is defined as:
  the date of the last dose of study drug

10.8.2 Number of Sprays Summary

For each parameter presented in this section,

- **The start and stop date** of each studied period is defined in Section 10.8.1. These studied periods are defined for Period 1 and Period 2 to allow summaries by treatment arm.
- **The duration of each studied period** will then be derived using the appropriate treatment phase (titration, maintenance) for each treatment period as: Date of stop – date of start + 1 day
- eDiary information will be used to retrieve the total daily number of sprays taken by a given patient
- A **non-missing diary day** is defined as any day where the eDiary is filled but IMP dosing information are fully included or partial (missing morning or evening dose) or totally missing.
- **A missing diary da**y is defined as any day where the eDiary is not filled
- **Imputation rule:** for a non-missing diary day where IMP dosing information is partial or missing the number of sprays taken on that missing morning or evening administration will be imputed to “0” to derive the total daily number of spray taken.

The mean number of sprays is defined for each treatment arm as the total number of sprays taken during the studied period divided by the number of patients within the studied period regardless intermittent IMP discontinuation.

The patient mean number of daily sprays a patient has taken on a daily basis is calculated for each studied period as the total number of sprays taken divided by the number of non-missing diary days for each patient.

Based on the above the patient mean number of daily sprays (also called mean use of IMP) will also be categorized as follows:

- ≤ 6 sprays,
- > 6 sprays and ≤ 12 sprays,
- > 12 sprays.

The total number of daily sprays is referring to the total number of sprays a patient has taken on a daily basis for a studied period.

The patient median number of daily sprays refers to is referring to the median number of sprays a patient has taken on a daily basis for a studied period.

The patient mode number of daily sprays refers to more frequently occurring number of sprays a patient has taken on a daily basis for a studied period. If a patient has more than one mode or no mode determined then the patient has a ‘missing’ mode.

The patient maximal number of daily sprays refers to the maximal number of sprays a patient has taken on a daily basis for a studied period.

The patient percentage of imputed diary days is derived for each patients as the number of non-missing diary days where morning and/or evening number of sprays are imputed to ‘0’ to calculate the total daily dose divided by the number of non-missing diary days for a studied period and multiply by 100.

10.9 Compliance

Compliance will be derived, for each patient, during the maintenance phase, based on optimized and amended doses information as reported in the "Dose amendment" eCRF form and the total daily number of sprays derived from the eDiary as the sum of morning and evening number sprays applying missing data rule imputation on non-missing diary days as described in Section 10.8.2.

A compliant day, is defined for each patient as a day when the total number of sprays taken is

- Within +/- 1 (and between 1 and 12) of the patients' optimized dose range as defined in Table 10.9-1 when sprays are taken outside of an amended dose period,
- Equal to the amended dose +/- 1 spray (and between 1 and 12) when sprays are taken between start and stop date of an amended dose period as collected in the eCRF.

The compliance will then be defined as

$$100*\left(\frac{\text{number of compliant days}}{\text{number of days with non-missing total daily dose information within the study period}}\right)$$

Table 10.9-1 Optimized Daily Dose and Allowed Optimized Dose Range

Optimized dose	Maximal allowed dose	Minimal Allowed dose
1	2	1
2	3	1
3	4	2
4	5	3
5	6	4
6	7	5
7	8	6
8	9	7
9	10	8
10	11	9
11	12	10
12	12	11

The rate of "0" total daily spray is defined at patient level as

$$100*\left(\frac{\text{number of days with total daily dose}= 0}{\text{study period duration}*}\right)$$

The rate of "> 12" total daily spray is defined at patient level as

$$100*\left(\frac{\text{number of days with total daily dose is} >12}{\text{study period duration}*}\right)$$

The rate of missing diary day IMP information is defined for each patient as:

$$100*\left(\frac{\text{number of days with missing diary dosing information}}{\text{study period duration}*}\right)$$

Using missing morning and/or evening number of sprays information from either missing diary day and non-missing diary day (as defined in Section 10.8.2)

* The study period duration refers to either the titration phase duration or the maintenance phase duration for period.

10.10 Age

The age at consent will be determined as follows:

- If age is recorded in the eCRF then this will be the one used for analysis
- If only year of birth is known, Date of Birth is imputed to the 15 June of the year of birth and age is derived as:

Age at Informed Consent (years) = (Date of Informed Consent – Date of Birth + 1)/365.25

However, if derived age is resolved to 17-year-old and inclusion criteria 6.1.1 is met then age will be set to 18 years.

Based on the above age will also be categorized as ≤18, > 18 to ≤ 45, > 45 to ≤ 65 and > 65 years old and labelled ≤18, > 18 to ≤ 45, ≥ 46 to ≤ 65 and > 65 years, respectively.

10.11 Body Mass Index

At each weight measurement, the Body Mass Index (BMI) will be derived using height collected at screening.

It is calculated using the following formula:

BMI (kg/m²) = Weight (kg) / [Height (cm)]) x0.01]^2

Based on the above value BMI will also be categorized as follows:

- < 18.5 as underweight;
- ≥ 18.5 and < 25.0 as normal or healthy weight;
- ≥ 25.0 and < 30.0 as overweight;
- ≥ 30.0 as obese.

10.12 Disease History

As part of Disease history description, the following parameters will be derived:

- **Time since diagnosis of MS (years)**
  (Date of Informed consent – Date of MS diagnosis + 1) / 365.25;
- **Age at diagnosis of MS (years)**
  (year of MS diagnosis – year of Birth + 1)
- **Time since onset of spasticity due to MS (years)**
  (Date of Informed consent – Date of onset of spasticity due to MS + 1) / 365.25;
- **Age at onset of spasticity due to MS (years)**
  (year of onset of spasticity due to MS – year of Birth + 1);
- **Time between MS diagnosis and onset of spasticity due to MS (years)**
  (Date of onset of spasticity due to MS - Date of MS diagnosis + 1) / 365.25;
- **Time between MS diagnosis and onset of spasticity due to MS (months)**
  (Date of onset of spasticity due to MS - Date of MS diagnosis + 1) / 30.4375.

The following conversion will be applied as appropriate:

- Time since last relapse (months) = Time since last relapse (years) * 12,
- Time since last relapse (months) = Time since last relapse (days) / 30.4375.

Age at diagnosis of MS and age at onset of spasticity due to MS are only using year because only year of birth is planned to be collected.

If date of MS diagnosis and/or date of onset of spasticity due to MS are unknown or partial, they will be imputed as follow:

- if only day is missing, it will be imputed to the 15th of the month,
- If day and month are missing, they will be imputed to the 30 June of the year,
- However, if any of these dates fall after the informed consent date, they will be set to the informed consent date. If the date of onset of spasticity due to MS before the date of MS diagnosis due to imputation rule, it will be set to the date of MS diagnosis.

10.13 Renal Function Formula

Estimated Glomerular filtration rate (eGFR)

For the purpose of summary, the eGFR collected by central laboratory will be used.

eGFR will also be categorized as follows:

- ≥ 90 as normal,
- >= 60 and < 90 as mild reduction,
- >= 30 and < 60 as moderate reduction,
- >= 15 and < 30 as severe reduction,
- <15 as end stage kidney failure.

10.14 Prior and Concomitant Medication Start/Stop Date Imputation Rule

Table 10.14-1 Imputation Rules for Partial Medication Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for concomitant meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month but should fall on or after first study drug intake or if impossible after informed consent date
	M and D	Y same as Y of first dose of study drug intake during Period 1 and 2	Date of first dose of study drug
		Y after Y of first dose of study intake during period 1 but same Y as 1st study drug intake during Period 2	Date of first drug intake during period 2
		Y after Y of last study drug intake	The earliest date between date of last study drug intake and end of study date
	M, D, and Y	Not allowed by the system	Not applicable
Stop date for concomitant meds	D only	M and Y same as M and Y of last dose of study drug	The earliest date between date of last dose of study drug and end of study date
		M and/or Y not same as date of last dose of study drug	The earliest date between last day of month and end of study date
	M and D	Not allowed by the system	Not applicable
	M, D, and Y	Not allowed by the system	Not applicable

Meds = Medications.
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

10.15 Mobile Health Data handling

Data downloaded from the Mobile Health platform (MHP) such has number of morning and evening sprays administered, NRS scales, number of spasm counts, C-SSRS questionnaire, MSSS-88 questionnaire have specific information to link the date MHP data were submitted to the date the data are referring to which have to be reported in SDTM and ADAM as detailed in Table . In practice, any time the variable XGRID contains the term “Late” the date to be used refers to the day before the one coming from MHP.

Table 10.15-1 MHP data - Date Handling

XPGRID	Explanation
Initial on time Diary	Served from 6:00pm to 11:59 pm to the day a participant is moved to screening
Initial late Diary	Served from 12:00 am to 03:05 pm the next morning when the initial On Time Diary was NOT completed the previous day
On time diary	Served from 6:00pm to 11:59 pm when the Initial On Time, On time, or Missed On Time Diary was completed the previous day
Late diary	Served from 12:00 am to 03:05 pm when On Time Diary was NOT completed the previous day
Missed on time	Served from 6:00pm to 11:59 pm when an Initial Late, or Missed Late Diary was served on the same day
Missed late	Served from 12:00 am to 03:05 pm when the Missed On Time Diary was Not completed the previous day

10.16 Modified Ashworth Scale (MAS) Transformed Score

The MAS will be conducted and scored on 10 lower limb muscle groups (hip flexors and adductors, knee flexors and extensors, and plantar flexors) on the left and the right side of the body at Screening, Day 1 H0, D1H3 and D21 each treatment period.

For the purpose of the analysis, the result of each of the 10 MAS scores will be transformed using the following algorithm: MAS untransformed [to MAS transformed] scores; 0[0], 1[1], 1+[2], 2[3], 3[4] and 4[5].

Each MAS transformed score is ranging from ‘0’ (No increase in muscle tone) to ‘5’ (Affected part rigid in flexion or extension).

These scores will then be used to derive 3 mean Lower Limb Muscle Tone (LLMT) measures at D1H0, D1H3 and D21 of each treatment period.

- The LLMT-6: defined as the average of the 6 individual MAS transformed scores of knee flexors, knee extensors, and plantar flexors on both sides of the body. For any given patient, at a given visit, the LLMT-6 will be set to missing if individual MAS transformed scores are missing for 3 or more of the 6 specified muscle groups (as described in Table 10.16-1),
- The LLMT-10: defined as the average of the 10 individual MAS transformed scores of knee flexors, knee extensors, plantar flexors, hip flexors and hip adductors on both sides of the body. For any given patient, at a given visit, the LLMT-10 will be set to missing if individual MAS transformed scores are missing for 5 or more of the 10 specified muscle groups (as described in Table 10.16-1),
- The LLMT-4 defined as the average of the 4 individual MAS transformed scores of knee flexors, knee extensors on both sides of the body. For any given patient, at a given visit, the LLMT-4 will be set to missing if individual MAS transformed scores are missing for 2 or more of the 4 specified muscle groups (as described in Table 10.16-1).

In addition, LLMT-6/LLMT-4/LLMT-10 scores derived with individual MAS transformed score missing in at least one muscle group will be identified.

Table 10.16-1 Lower Limb Muscle Tone - Missing Data Handling

Parameter	Number of items (muscle groups) included in score derivation	Minimum number of muscle group scores required for score derivation (at least 50%)
LLMT-4	4	3
LLMT-6	6	4
LLMT-10	10	6

LLMT-4 = Lower Limb Muscle Tone-4; LLMT-6 = Lower Limb Muscle Tone-6; LLMT-10 = Lower Limb Muscle Tone-10.

The change and percentage change from baseline will then be calculated (as respectively described in Section 10.3 and in Section 10.4) for each LLMT score.

The percentage change from baseline values will also be categorized as ≤- 20%, ≤ -30%, ≤ -40% and ≤ -50% to assess an improvement of respectively ≥20%, ≥30%, ≥40% and ≥50%
Although unlikely to occur as per inclusion criteria 6.1.5, if a baseline LLMT score is equal to 0, the percentage change from baseline will be imputed using the following formula:

- Percentage change from baseline =(x+1)*100, where x is the post baseline value .

Missing LLMT scores will be considered as not having met any of the improvement criteria (imputed as failure).

10.17 Timed 25-Foot Walk

The T25FW is the time needed for a patient to walk 25-feet and will be performed at Day 1 H0 and D21 of each treatment period. The test consists of two trials separated by a 5-minute rest period. The maximum duration of each trial is set to 3 minutes (180 seconds).

The average T25FW (expressed in seconds) will be derived for each patient as the average of the two trials..

If a patient only performs 1 of the 2 trials at a given analysis day, the unperformed trial will be imputed using the highest T25FW (180 seconds) to perform the main analysis. An exploratory analysis will also be conducted without imputing unperformed trial as missing thus, leading to a missing average T25FW.

If a patient is not using the same device or is introducing a device within a given treatment period, the average T25FW will be set to missing.

The change and percentage change from baseline will then be calculated (as respectively described in Section 10.3 and in Section 10.4).

The percentage change from baseline will be categorized as ≤ = -20% and > -20% to assess respectively ≥ 20% improvement (as response) and < 20% improvement (as non–response) using imputed T25FW (as described above).

Missing average T25FW will be considered as not having met the improvement criteria (imputed as failure).

10.18 11-point Numerical Rating Scale Score (NRS-Spasticity Score)

The 7-day average 11-point NRS spasticity score will be derived for each patient as the mean NRS-spasticity score recorded in the eDiary during the last 7 days preceding Period 1 Day 1 H0 (Baseline), and Day 15 and D21 of each treatment period as follows:

$$\frac{Sum\ of\ the\ NRS\ spasticity\ scores\ \ during\ the\ 7-day\ period}{Number\ of\ days\ in\ which\ \ the\ \text{daily diary}\ \ was\ completed\ during\ the\ 7-day\ period}$$

For each assessment timepoint, the 7-day average 11-point NRS-spasticity score will be set to missing if scores are missing for 4 days or more in total or for 3 consecutive days within each 7-day period.

In case of the diary data are available but the visit does not take place the target visit date will be used.

On-treatment / off-treatment assessment

A 7-day average 11-point NRS spasticity score will be considered on-treatment if derived using only post baseline daily scores collected on or before the date of IMP discontinuation and will be considered off-treatment otherwise.

In case of IMP discontinuation, if possible with regards to missing data rule specified just above, the 7-day average 11-point NRS spasticity score considered on-treatment will also be derived using only post-baseline scores collected on or before the date of IMP discontinuation.

The change from baseline will then be calculated (as respectively described in Section 10.3).

10.19 Daily Spasm Count

The 7-day average daily spasm count will be derived for each patient using the number of spasms recorded in the eDiary during the last 7 days preceding Period 1 Day 1 H0 (Baseline), and Day 15 and D21 of each treatment period as follow:

$$\frac{Total\ spasm\ count\ during\ the\ 7-day\ period}{Number\ of\ days\ in\ which\ the\ daily\ diary\ was\ completed\ during\ the\ 7-day\ period}$$

For each analysis timepoint, the 7-day average daily spasm count will be set to missing if spasm counts are not collected during 4 days or more in total or for 3 consecutive days during the 7-day period.

In case of the diary data are available but the visit does not take place the target visit date will be used.

On-treatment / off-treatment assessment

A 7-days average daily spasm count will be considered on-treatment if derived using only post-baseline daily records collected on or before the date of IMP discontinuation and will be considered off-treatment otherwise.

In case of IMP discontinuation, if possible with regards to missing data rule specified just above, the 7-day average daily spasm count considered on-treatment will also be derived using only post- baseline spasm counts collected on or before the date of IMP discontinuation.

Missing daily spasm count information

If for a given day, the spasm count is missing whereas the eDiary has been filled by the patient, the number of spasms will be imputed to “0” to derive the 7-days average daily spasm count.

The change from baseline will then be calculated (as respectively described in Section 10.3).

10.20 Multiple Sclerosis Spasticity Scale (MSSS-88)

The MSSS-88 will be completed at D21 of each period, and 8 sub-scales representing 8 domains along with a total score will be derived by summing each of the constitutive items provided that at least 50% of the items are answered. Missing responses will be replaced by the mean score of the items completed.

The questions will be grouped as follows:

- 3 spasticity specific symptoms
  - Muscle Stiffness: sum of questions 1 to 12,
  - Pain and Discomfort: sum of questions 13 to 21,
  - Muscle Spasms: sum of questions 22 to 35,
- 3 areas of physical functioning
  - Activity of Daily living (ADL): sum of questions 36 to 46,

- Ability to Walk: sum of questions 47 to 56,
- Body Movement: sum of questions 57 to 67,

- 2 area of psychosocial impact
  - Emotional health: sum of questions 68 to 80,
  - Social Functioning: sum of questions 81 to 88,
- Total score
  - Sum of the 8 non-missing sub-scales after missing data rule has been applied for each subscale, otherwise set to missing if any of the sub-scales is missing.

Table 10.20-1 Multiple Sclerosis Spasticity Scale - Missing Data Handling

Subscale and total score	Number of questions included in subscale and total score	Minimum number of questions required for score derivation (at least 50%)
Muscle Stiffness	12	6
Pain and Discomfort	9	5
Muscle Spasms	14	7
Activity of Daily living	11	6
Ability to Walk	10	5
Body Movement	11	6
Emotional health	13	7
Social Functioning	8	4

10.21 Adverse Events

10.21.1 Start and Stop Date Imputation

Table 10.21-1 Imputation Rules for Partial Adverse Events Start/Stop Dates

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month but should fall after 1st study drug intake or if impossible after informed consent date
	D and M	Y same as Y of first dose of study drug intake during period 1 and 2	Date of first dose of study drug
		Y after Y of first dose of study intake during Period 1 but same Y as 1st study drug intake during Period 2	Date of first drug intake during period 2
		Y prior to Y of first dose of study drug but same as Y of informed consent date	Date of informed consent
		Y after Y of last study drug intake	The earliest date between date of last study drug intake + 14 days and end of study date
	D, M, Y	Not allowed by the system	Not applicable
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	The earliest date between date of last dose of study drug and end of study date
		M and/or Y not same as date of last dose of study drug	The earliest date between last day of month and end of study date
	D and M	Not allowed by the system	Not applicable
	D, M, Y	Not allowed by the system	Not applicable

AE = Adverse events; D = day; M = month; Y = year
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

10.21.2 COVID-19 AE

A confirmed or suspected COVID-19 AE will be any adverse event for which the AE term or the preferred term include the character “COVID-19” but should not be “COVID-19 ELISA test negative”.

For instance, confirmed COVID-19 TEAE will be reported as:

- COVID-19 infection,
- COVID-19 disease,
- COVID-19 pneumonia,
- COVID-19 respiratory infection,
- Asymptomatic COVID-19,

whereas suspected COVID-19 AE will be coded as Suspected COVID-19.

10.21.3 Time to First Onset of AE

The time to first onset of AE will be defined by study period as:

- AE start date – IMP start date in the studied period

For AEs with an onset date occurring during the 21-days on-treatment safety Period 1 (as defined in Section 10.1.1) the IMP start date refers to the date of 1st IMP spray intake during Period 1.

For AEs with onset date occurring during the 21-days on-treatment safety Period 2 (as defined in Section 10.1.1), the IMP start date refers to Period 2 start date provided that the patient is exposed during Period 2.

Based on the above value time to first onset of AE will be categorized as:

- 1-7 days,
- 8 to 14 days,
- 15 to 21 days,
- > 21 days.

If onset time is shorter as 1 day, it will be included in the 1-7 days category.

For the purpose of time-to-event analysis, censoring rules are defined in Section 12.7.2.3.

10.21.4 AE Duration

The AE duration (expressed in days) will be defined as:

- AE stop date – AE start date + 1 day.

The duration will not be derived in case of partial or missing start or stop date.

Based on the above value the AE duration will also be categorized as follows:

- 1-7 days,
- 8 to 14 days,
- 15 to 28 days,
- 28 to 42 days,
- 43 to 61 days,
- > 61 days,
- Ongoing,
- Indeterminate.

If AE stop date is missing and the outcome of the AE is “Not recovered, Not resolved”, the AE will be categorized as “Ongoing”.

If the AE start date is partial or missing and the AE is not considered as “Ongoing”, the AE will be classified as “Indeterminate”.

If AE duration is less than 1 day, the AE will be counted in the 1-7 days category.

10.22 Laboratory data

Strip-sign handling

In cases a hematology or chemistry value is recorded as ‘>x’ or ‘<x’, the value will be imputed as “x” to perform summary statistics but the strip sign will be presented in individual data listings.

10.23 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS scale is composed of 11 items answered Yes or No. Ten of them are ordered in categories as described below to determine the studied endpoints.

5 subtypes of suicidal ideation:

- Category 1 – Wish to be Dead,
- Category 2 – Non-specific Active Suicidal Thoughts,
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act,
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan,
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent.

5 subtypes of suicidal behavior:

- Category 6 – Preparatory Acts or Behavior,
- Category 7 – Aborted Attempt,
- Category 8 – Interrupted Attempt,
- Category 9 – Actual Attempt (non-fatal),
- Category 10 – Completed Suicide.

Last item:

- Self-injurious behavior without suicidal intent.

The C-SSRS also includes a suicidal ideation intensity rating from 1 (least severe) to 5 (most severe).

The following composite endpoints will be assessed based on the categories described above:

- Suicidal ideation (Yes/No): is Yes if one of the categories from 1 to 5 is answered Yes,
- Suicidal behavior (Yes/No): is Yes if one of the categories from 6 to 10 is answered Yes,
- Suicidal ideation or behavior (Yes/ No): is Yes if one of the categories from 1 to 10 is answered Yes,
- Self-injurious behavior without suicidal intent (Yes /No): is Yes if this question is answered Yes.

The following scores will be derived as follows:

- Suicidal ideation score is rating from 1 to 5 the most severe suicidal ideation category answered Yes and is assigned to 0 if categories 1 to 5 are answered No,

- Suicidal ideation intensity rating score (0 to 25) will be defined as the sum of the 5 features described below (ranging from 0 to 5, 0 being the least severe and 5 being the most severe) rated with respect to the most severe type of ideation category,
  - Frequency,
  - Duration,
  - Controllability,
  - Deterrents,
  - Reason for ideation.

Comparative endpoints will also be defined as described below:

Treatment emergent outcomes will include any events that first emerge of worsen, whereas emergent outcomes will refer to outcomes that first emerge.

- Treatment-emergent suicidal ideation compared to recent history (not using C-SSRS taken during screening):
  - Increase from baseline in suicidal ideation score,
  - Increase from last on-treatment visit to follow-up (FU) visit,

- Treatment-emergent serious suicidal ideation compared to recent history (not using C-SSRS taken during screening):
  - Increase in suicidal ideation score from a baseline (0-3) to (4-5),
  - Increase in suicidal ideation score from last on-treatment visit (0-3) to FU visit (4-5),

- Emergence of a serious suicidal ideation compared to recent history (not using C-SSRS taken during screening):
  - Increase in suicidal ideation score from baseline (0) to (4-5),
  - Increase in suicidal ideation score from last on-treatment visit (0) to FU visit (4-5),

- Emergence of suicidal behavior compared to all prior (using C-SSRS taken at and post screening assessments):
  - Occurrence of suicidal behavior (categories 6-10) post baseline with no screening or baseline suicidal behavior,

No imputation should be done with regards to missing data.

11.0 Interim Analyses

No interim analysis will be conducted.

However, a blinded assessment of the estimate of the variability of the treatment difference will be conducted during the study and the sample size recalculated using this blinded estimate. The study will still be ongoing at time of these blinded analyses and the decision whether or not to increase the sample size will be based on the Sponsor judgment.

This blinded review of the data will take place once, using the first 50% of the patients, from FAS, having completed both treatment periods, and for whom all MAS assessment data are cleaned (no open queries), coded and reconciled.

11.1 Blinded Sample Size Reassessment

The sample size estimate as described in Section 8.2 was assuming mean treatment difference of -0.30 and a standard deviation of paired difference of 0.71.

Let d_i denote the difference between Period 2 and Period 1 for Patient i (i = 1 to n) when n is the number of patients, at the interim analysis, having completed Period 1 and Period 2 on-treatment and for whom LLMT-6 score (as described in Section 10.16) can be derived for both treatment periods.

Let $\bar{d}$ is the overall mean of all d_i

When the n patients complete the assessment on the primary endpoint, the variability is estimated by pooling all the patients as follows

$$\hat{\sigma}^2_{diff} = \frac{1}{(n-1)}\sum_{i}^{n}(d_i - \bar{d})^2$$

The re-calculated sample size is given by

$$\hat{N} = \frac{\left(t_{1-\alpha} + t_{1-\beta}\right)^2}{\delta^2}\hat{\sigma}^2_{diff}$$

That is,

$$\hat{N} = \frac{\left(t_{1-\alpha} + t_{1-\beta}\right)^2}{\delta^2}\frac{1}{(n-1)}\sum_{i}^{n}(d_i - \bar{d})^2$$

where δ is the target treatment effect size. This re-calculated sample size will be provided to the sponsor to aid decision-making; however the sponsor has the final decision as to whether to increase the sample size and to what number.

11.2 Other Analyses

Baseline efficacy endpoints will be summarised and no other additional analyses are planned during the blinded sample size reassessment.

12.0 Statistical Methods

All analyses will use SAS® version 9.4 or higher. However, pharmacokinetic analyses may be performed using a dedicated software as mentioned in Section 12.6.

Standard Summary Statistics for Continuous and Discrete Variables.

Summaries will be tabulated either per treatment arm or per treatment sequence, and overall (when deemed appropriate), unless otherwise specified.

Unless otherwise noted, **categorical variables** will be summarized using non-missing counts and percentages. Percentage will be using the number of patients (or the number of patients at risk) in the treatment arm/treatment sequence and as appropriate in the analyzed categories as denominator. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.
Odd ratios (ORs) will be provided as appropriate. Odd ratios will be presented with 2 decimal places

Continuous data will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile 3 (Q3), minimum (Min), and maximum (Max). Minimum and maximum, will be rounded to the precision of the original value. Mean, median, Q1 and Q3 will be rounded to 1 decimal place greater than the precision of the original value. The SD will be rounded to 2 decimal places greater than the precision of the original value. Confidence intervals (CIs), LS means, standard error (SE), geometric mean, geometric SD and coefficient of variation (CV) (%) will be provided as appropriate. Confidence intervals, LS means and geometric mean will be presented with the same precision as the mean value whereas SE and geometric SD will be presented with the same precision as SD and the CV (%) will be presented with 1 decimal place.

Inferential Statistics

P-values will be rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999."

Statistical hypothesis testing will be 2-tailed and carried out at the 5% level of significance. Testing will be performed on the primary endpoint and secondary endpoint as appropriate.

To control for Type 1 error at a 2-sided alpha of 0.05, the primary endpoint and key secondary endpoint will be tested hierarchically, starting with the primary endpoint and followed by the secondary endpoint. No additional adjustments for multiplicity will be made for the other secondary endpoints and for exploratory endpoints although nominal p-values will be presented.

Individual Data Listings

All the listings will be displayed sorted by treatment sequence, patient identifier and date of assessment. They will present age, sex, race and country.
For those listings presenting on-treatment assessment post randomization, treatment arm along with the treatment period will also be displayed. A flag informing whether or not the data are impacted by COVID-19 may also be added.

12.1 Patient Disposition

The number and percentage of patients screened, re-screened, randomized and not randomized along with reason of screen failure will be presented using the Screening Analysis Set.

The number of patients randomized, randomized and treated, randomized and not treated, and the number of patients in each analysis set will be summarized per treatment sequence for the Randomized Analysis set.

The number and percentage of patients will also be summarized for the following patient disposition categories:

1. Completed study drug treatment per protocol
2. Discontinued study drug early and the reason for discontinuation
3. Completed the study including follow-up period
4. Discontinued from the study early and the reason for discontinuation

The table will be presented by treatment sequence, per period and overall using the Randomized Analysis Set and will be repeated for the different subgroups presented in Table 12.1-1.

Table 12.1-1 Subgroups Applied to Patient Disposition

Group Variables	Subgroup	Comments
Sex	Male Female	
Age group	• <= 18 years • > 18 and ≤ 45 • ≥ 46 to ≤ 65 • > 65	According to patient 's distribution within age, age group may be differently defined Detailed derivation is given in Section 10.10
Race	White Black or African American Asian American India or Alaska Native Native Hawaiian or Other Pacific Islander Other	According to patient's distribution within race some races may be grouped together
Prior cannabis use	Yes No	

Number of current antispasticity medication	0 1 2 ≥ 3	

A cumulative incidence plot of permanent IMP discontinuation due to any reason will be provided by treatment sequence on the Safety Analysis Set. The Time to treatment discontinuation (in days) is defined as the number of days from 1st IMP intake until permanent treatment discontinuation (as detailed in Section 10.6). Patients who will not permanently withdraw from study drug will be censored to the earliest of last contact date and their date of completion of Period 2,whereas patients lost to follow-up will be censored at their last contact date.

A cumulative incidence plot of study discontinuation due to any reason will be provided by treatment sequence on the Randomized Analysis Set. The Time to study discontinuation (in days) is defined as the number of days from randomization until study discontinuation (as detailed in Section 10.6). Patients who will not permanently withdrawn from study drug, or lost to follow-up will be censored at their last contact date.

Each cumulative incidence plot will only be provided if more than 5 patients are presenting an event in each treatment sequence (i.e., premature end of treatment, premature study discontinuation).

A tabulation based on the Randomized Analysis Set of the number and percentage of patients randomized at country and center will be presented per randomization sequence and overall.

All patient's disposition data will be listed by treatment sequences.

12.2 Demographic and Baseline Characteristics

For all demographic and baseline characteristics assessments presented below the baseline is defined as the last available assessment collected before the first administration of study drug. Further details are given in Section 10.2.

Demographic and baseline characteristics will be summarized by treatment sequence and overall using appropriate summary statistics as described in Section 12.0 in the FAS and the Randomized Analysis Set if different from FAS.

If deemed appropriate (i.e., more than 20 % of the randomized patients experiencing at least one major protocol deviation, as defined in Appendix 1), demographic and selected baseline characteristics will also be summarized using the PP Analysis Set, and may also be summarized on the Study Completer Analysis Set.

All summaries for continuous parameters will be based on non-missing observation. For categorical variables, the percentage will be based on the total number of patients, within the studied dataset, overall and per treatment sequence (i.e., each denominator includes the number of patients with missing/unknown value for this parameter).

Demographic, baseline characteristics, and disease history data will also be listed with a flag identifying those belonging to the FAS, the PP Analysis Set, the Study Completer Analysis Set, and the Safety Analysis Set.

All baseline safety and efficacy parameters (apart those presented below) are presented along with summary statistics in the safety and the efficacy sections, respectively (Section 12.7 and Section 12.5).

12.2.1 Demographics Characteristics

As defined in Section 10.10, the following demographic and baseline characteristics will be summarized:

- Age (years),
- Age groups (≤ 18,> 18 to ≤ 45; ≥ 46 to ≤ 65; > 65 years old),
- Sex (Male, Female),

- Race (White, Black or African American, Asian, American India or Alaska Native, Native Hawaiian or Other Pacific Islander, other) (per legal data protection law),
- Country (Poland, Czech Republic),

12.2.2 Baseline Physical Examination

As defined in Section 10.11. the following baseline physical examination will be summarized.

- Baseline height (cm),
- Baseline weight (kg),
- Baseline BMI (kg/m²),
- Baseline BMI category (< 18.5 as underweight; ≥ 18.5 and < 25.0 as normal or Healthy Weight; ≥ 25.0 and < 30.0 as overweight; ≥ 30 as obese),

12.2.3 Baseline Vital Signs

The following baseline vital signs including postural drop assessment will be summarized.

- Baseline Supine Systolic blood pressure (SBP) (mmHg),
- Baseline Orthostatic SBP (mmHg)
  Orthostatic SBP being defined as supine SBP- Standing SBP,
- Baseline Orthostatic SBP ≥ - 20 mm Hg,
- Baseline Supine Diastolic blood pressure (DBP) (mmHg),
- Baseline Orthostatic DBP (mmHg)
  Orthostatic DBP being defined as supine DBP- Standing DBP,
- Baseline Orthostatic DBP ≥ - 10 mm Hg,
- Baseline Supine Heart Rate (HR) (Beats/min),
- Baseline Orthostatic HR (Beats/min)
  Orthostatic HR being defined as supine HR- Standing HR,
- Proportion of patients who meet criteria for orthostatic hypotension.
  defined as either drop in SBP of 20 mmHg or greater or drop in DBP of 10 mmHg or greater.

12.2.4 Medical History

Previous and current medical conditions (medical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and will be summarized by system organ class (SOC) and preferred term (PT) per treatment sequence and overall in the FAS.

12.2.5 Disease Characteristics

The following disease characteristics will be summarized.

Multiple sclerosis diagnosis

As defined in Section 10.12:

- MS subtype (primary progressive, secondary progressive, relapsing-remitting),
- Time since diagnosis of MS (years),
- Age at diagnosis of MS (years),
- Time since onset of spasticity due to MS (expressed in months or years as appropriate),
- Age at onset of spasticity due to MS (years),
- Time between MS diagnosis and onset of spasticity due to MS (months or years as appropriate),

  - also presenting the number and percentage of patients experiencing spasticity before MS diagnosis,
- Time between MS diagnosis and onset of spasticity due to MS (years),
- Number of relapses in the past 12 months,
- Time since last relapse (months or years as appropriate),

Current MS medications

As defined in Section 12.3.2, the following summaries relative to current MS medications will be provided:

- At least 1 MS medication
  - At least 1 antispasticity medication
    - Baclofen,
    - Tizanidine,
    - Dantrolene,
    - Benzodiazepine,
    - Muscle relaxants,
    - Botulinum toxin,
    - Gabapentin,
    - Pregabalin,
    - Other.
  - Number of antispasticity medications used
    - 0,
    - 1,
    - 2,
    - >= 3.
  - At least 1 MS disease modifying drug (DMD),
  - At least 1 medication to treat other MS Symptoms,
    - Dalfampridine,
    - Fampridine.

Current MS medications are those taken at time of randomization/1st IMP dosing as described in Section 12.3.2). They will be determined based on information retrieved from eCRF concomitant medication form; further determination criteria being given in Appendix 10.

Prior use of cannabis or cannabinoid

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

Prior use of cannabis or cannabinoid will be summarized for the following

- Prior use of cannabis or cannabinoid
  - Medicinal use,
  - Recreational use.

12.2.6 Baseline Efficacy Endpoints

The following endpoints derived from MAS transformed scores (as defined in Section 10.16) will be summarized:

- Baseline Lower Limb Muscle Tone-6,

- Baseline Lower Limb Muscle Tone-4,
- Baseline Lower Limb Muscle Tone-10,
- Other Baseline Efficacy Endpoints

The following other endpoint will be summarized:

Baseline 7-day average NRS Spasticity Score

12.2.7 Baseline Safety Endpoints

The following baseline safety endpoints linked to renal function and C-SSRS will be summarized

- Renal function (as defined in Section 10.13)
  - Baseline eGFR (ml/min/1.73m²),
  - Baseline eGFR category (ml/min/1.73m²): ≥ 90 as normal, ≥ 60 and < 90 as mild reduction, ≥ 30 and < 60 as moderate reduction, ≥ 15 and < 30 as severe reduction, <15 as end-stage kidney failure.

- C-SSRS (as defined in Section 10.23)
  - Baseline Suicidal Ideation Score,
  - Baseline Suicidal Behavior.

12.3 Treatments

12.3.1 Extent of Exposure

Exposure to study drug, IMP dosing, treatment compliance and drug accountability will be presented using the Safety Analysis set.

12.3.1.1 Duration of Therapy

The extent of exposure will be for each study drug (e.g., nabiximols or placebo) the total number of days of administration of IMP, ignoring temporary drug discontinuation, within the designated treatment period.

The duration of exposure (as defined in Section 10.7) will be summarized descriptively as quantitative variable (number, mean, SD, median, Q1, Q3, minimum and maximum) but also presenting the total number of days and the mean number of days (expressed in patient-week) as defined in Section 10.7.

The number and percentage of patients with an extent of exposure within a predefined study day range will also be presented for each of the following categories and the cumulative distribution according to these categories:

- Day 1 to 7,
- Day 8 to 14,
- Day 15 to 21,
- > D21.

Extend to exposure will also be summarized per treatment arm by subgroups of interest as presented in Table 12.1-1.

12.3.1.2 IMP Dosing

Patients are expected to record, daily, the number of morning and evening spray(s) they have taken in their eDiary. This information will be integrated in the eCRF.

At Day 15 of each treatment period (at the end of the titration phase), the daily number of sprays to be taken by each patient defined as the optimized dose will be reported in the eCRF “Dose adjustment” form.

Whenever a patient has taken an amended dose, this will also be reported in the eCRF "Dose adjustment" form along with start and stop date of each amended dose and the reason why the optimized dose was amended (e.g., adverse event, insufficient therapeutic effect, other).

During the Titration Phase (up to Day 14)

The number of sprays taken will be summarized by day as quantitative variable (n, mean, SD, median, Q1, Q3, min and max) but also presenting per day, the number of sprays administered as a categorical variable.

Additionally,

- the rate of missing diary day information (%),
- the patient percentage of imputed diary days (%),
- the patient total number of daily sprays,
- the patient mean number of daily sprays,
- the patient mode number of daily sprays,
- the patient median number of daily sprays,
- the rate of "0" total daily sprays (%),
- the rate of ">12" total daily sprays (%),

as defined in Section 10.8.2 and Section 10.9, will be summarized per treatment arm as quantitative variable (n, mean, SD, median, Q1, Q3, min and max).

During the Maintenance Phase (Day 15 to D21)

As defined in Section 10.8.2,

- the patient total number of daily sprays,
- the patient mean number of daily sprays,
- the patient mode number of daily sprays,
- the patient median number of daily sprays

Combined: During the Titration Phase (up to Day 14) + Maintenance Phase (Day 15 to D21)

- the rate of "0" total daily sprays (%),
- the patient maximal number of daily sprays

will be summarized as quantitative variable (n, mean, SD, median, Q1, Q3, min and max).

In addition, the patient mean number of daily sprays used by patient will be categorized as ≤ 6 sprays; > 6 to ≤ 12 sprays and >12 sprays and summarized.

As defined in Section 10.9,

- the rate of missing diary day information (%),
- the patient percentage of imputed diary days (%),
- the rate of "0" total daily sprays (%),
- the rate of >12 total daily sprays (%)

will be summarized per treatment arm as quantitative variable (n, mean, SD, Median, Q1, Q3 min and max). These four parameters are also part of compliance assessment (as presented in Section 12.3.1.3).

Graphical Representations

The mean (± SD) number of sprays will also be presented by day using a line plot by treatment arm.

The patient mean number of daily sprays during the titration phase, during the maintenance phase and overall will also be presented by treatment arm using a cumulative distribution function.

12.3.1.3 Compliance

Compliance

Based on the total daily number of sprays taken recorded by the patient on the eDiary and on the optimized dose defined at Day 15 of each treatment period and collected on the eCRF "Dose adjustment" form the compliance to study drug will be assessed, during the maintenance phase of each treatment period, by the means of the 4 below parameters:

- The compliance (%),
- The rate of "0 total daily spray (%),
- The rate of "> 12" total daily sprays (%),
- The rate of missing diary day IMP information (%),

which will be summarized by treatment arm.

Detailed calculation along with missing data handling is described in Section 10.9.

Furthermore, the percentage of patients meeting study drug compliance will be presented in the following categories of days in the allowed dose range (coded as yes/no): < 80%, ≥ 80% to < 90%, ≥ 90% to < 100 % and = 100%.

Additionally, the **patient percentage of imputed diary days** (as defined in Section 10.8.2) which represents the percentage of days where missing morning and/or evening number of sprays taken have been imputed to '0' to derive the total daily IMP dose and thus compliance is based on imputed total number of sprays taken that day will be described by treatment arm.

Optimized Dose

The optimized dose will be summarized as quantitative and categorical variable per treatment arm. The need of optimized dose adjustment will also be described along with reason for dose adjustment.

12.3.1.4 Drug Accountability

Study drug accountability including volume dispensed (mm), residual volume (mm), volume used (mm), number of sprays taken and eDiary sprays accountability (%) will be listed.

12.3.2 Prior, Concomitant and Prohibited Therapies

For any medications / non-drug therapies initiated or ongoing since Visit 1 (Screening), the start and stop date, dose, unit, frequency, route of administration, and indication will be recorded respectively in the 'Concomitant Medication' eCRF page and in the 'Concomitant Physiotherapy' eCRF page.

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 MS antispasticity medication. Optimized oral MS antispasticity medications will include at least baclofen, tizanidine, and/or dantrolene (monotherapy or combination therapy). Their MS antispasticity medication must have been stable for at least 30 days prior to Screening (Visit 1) and the medication is expected to remain stable throughout the duration of the trial.

All medications will be categorized by medication anatomic and therapeutic class (ATC) according to the most current version of World Health Organization-Drug Dictionary (WHO-DD) global March 2021 Dictionary Version B3 or higher according to the version in used at time of database lock.

Medication used for MS will also be categorized according to information recorded in the CRF as:

- Disease modifying drug,
- Antispasticity drug (baclofen, tizadinidine, dentrolene, benzodiazepine, muscle relaxants, botulinum toxin, gabapentin, pregabalin),
- Other MS symptoms.

Whereas physiotherapy used will be categorized according to the reason as recorded in CRF as:

- Spasticity,
- Adverse events (other than spasticity),
- Other MS symptoms,
- Other symptoms not associated with MS.

Patients should stop taking any prohibited therapy prior to Screening (Visit 1) and, within 30 days of Visit 1 regarding use of cannabis for medical or recreational purposes or any cannabinoid-based medication. These medications are prohibited for the duration of the trial.

Prohibited medications are categorized as:

- Nabiximols, cannabis or cannabinoid-based derived products,
- Botulinum toxin injections,
- Antipsychotic medications,
- Benzodiazepines (if not following protocol requirements),
- Medications that are solely metabolized by UGT1A9 (see Appendix 8),
- Medications that are solely metabolized by UGT2B7 (see Appendix 8),
- Strong CYP3A4 inducers (e.g., rifampicine, carbamazepine, phenytoin, phenobarbital, St John's Wort) (see Appendix 8).

In order to flag prohibited medications taken in the study, each medication taken will be compared against a pre-specified list of all prohibited medications as presented in Appendix 7, Appendix 8 and Appendix 9 along with their determination criteria.

All medications / non-drug therapies (e.g., physiotherapies) will be classified as follows:

- Prior medications are those the patient used prior to the first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during the treatment periods (and wash-out period).
- Current medications are those the patient used at time of randomization and at the same time as study drug intake. This classification will mainly be used to summarize MS medications.

- Concomitant medications are any medications / non-drug therapies that are ongoing at the time of each study medication (e.g., nabiximols, placebo) intake; these medications can be initiated
  - Before first intake of study medication.
  - At the same time of study medication.

  Medications concomitant the Period 1 study medication are those:
  - Initiated before first intake of study medication,
  - Initiated and /or taken at the same time of Period 1 study medication,
  - Initiated and /or taken during the wash-out period.

  Medications concomitant the Period 2 study medication are those:
  - Initiated before first intake of Period 2 study medication,
  - Initiated and /or taken at the same time of Period 2 study medication,

- Post treatment medications (FU medications) are any medications / non-drug therapies initiated following last IMP intake.

To classify each therapy in case of missing / partial start and /or stop date, imputation rules as described in Section 10.14 will be applied.

All medications / non-drug therapies (including physiotherapies) taken during the trial will be summarized in the Safety Analysis Set. If it appears that the randomized treatment arm is different from the actual treatment arm (for summary by treatment arm) and/or if patients belonging to the Safety Analysis Set are different from those belonging to the FAS, medication summaries will be presented using both study populations.

The number and percentage of patients using each medication along with the number and percentage of patients using at least one medication within each medication group will be summarized. For each summary by treatment arm, a patient can be counted in both treatment arms for instance if:

- A patient stops one medication on or before the wash-out period and initiates a new one belonging to the same ATC class
- A patient is taking a medication concomitant to both Period 1 and Period 2.

All medications and all physiotherapy will be separately listed.

12.3.2.1 Non-MS Medications

Prior medications: The number and percentage of patient taking each non-MS prior medication will be summarized by treatment sequence and overall according to the first digit of the ATC class (anatomic category), first 3 digits of the ATC class (pharmacological category) and standard medication name.

Concomitant medications: The number and percentage of patient taking each non-MS concomitant medication will be summarized by treatment arm according to the first digit of the ATC class (anatomic category), first 3 digits of the ATC class (pharmacological category) and standard medication name.

Post-treatment medications: The number and percentage of patient taking each non-MS post-treatment medication will be summarized by treatment sequence according to the first digit of the ATC class (anatomic category) and first 3 digits of the ATC class (pharmacological category) and standard medication name.

Tables for non-MS prior and post-treatment medications will be sorted by decreasing frequency of anatomic class followed by pharmacological class, followed by standard medication name based on overall incidence. In case of equal frequency, the alphabetic order will be used.

Tables for non-MS concomitant medications will be sorted by decreasing frequency of anatomic class followed by pharmacological class, followed by standard medication name based on the incidence in the nabiximols treatment arm. In case of equal frequency, based on decreasing frequency in the placebo arm then in case of equal frequency the alphabetic order will be used.

12.3.2.2 Medications Used for MS

Prior medications: The number and percentage of patient taking each MS prior medication will be summarized by treatment sequence and overall according to the predefined categories and standard medication name.

Concomitant medications: The number and percentage of patient taking each MS concomitant medication will be summarized by treatment arm according to the predefined categories and standard medication name.

Post-treatment medications: The number and percentage of patient taking each MS post-treatment medication will be summarized by treatment sequence according to the predefined categories and standard medication name.

Tables for MS prior and post-MS medications will be sorted by decreasing frequency of standard medication name within each predefined category based on overall incidence. In case of equal frequency, the alphabetic order will be used.

Tables for MS concomitant medications will be sorted by decreasing frequency of standard medication name based on the incidence within each predefined category in the nabiximols treatment arm. In case of equal frequency, based on decreasing frequency in the placebo arm then in case of equal frequency the alphabetic order will be used.

12.3.2.3 Non-Antispasticity Medications and Antispasticity Medications

Prior medications: The number and percentage of patient taking either antispasticity medications or non-antispasticity medications will be separately summarized by treatment sequence and overall according to the first 2 digits of the ATC class (therapeutic category) and standard medication name.

Concomitant medications: The number and percentage of patient taking either antispasticity medications or non-antispasticity medications will be separately summarized by treatment arm according to the first 2 digits of the ATC class (therapeutic category) and standard medication name.

Post-treatment medications: The number and percentage of patient taking either antispasticity medications or non-antispasticity medications will be separately summarized by treatment sequence according to the two first digits of the ATC class (therapeutic category) and standard medication name.

Tables for prior and post-treatment antispasticity or non-antispasticity medications will be sorted by decreasing frequency in by therapeutic class, followed by standard medication name based on overall incidence. In case of equal frequency, the alphabetic order will be used.

Tables for concomitant medications antispasticity or non-antispasticity medications will be sorted by decreasing frequency of therapeutic class, followed by standard medication name based on the incidence in the nabiximols treatment arm. In case of equal frequency, based on decreasing frequency in the placebo arm then in case of equal frequency the alphabetic order will be used.

12.3.2.4 Prohibited Medication

Prior medications: The number and percentage of patient taking prohibited prior medications will be summarized by treatment sequence and overall according to the predefined categories and standard medication name.

Concomitant medications: The number and percentage of patient taking prohibited concomitant medications will be summarized by treatment arm according to the predefined categories and standard medication name.

Tables for prohibited prior medications will be sorted by decreasing frequency of standard medication name within each predefined category based on overall incidence. In case of equal frequency, the alphabetic order will be used.

Tables for prohibited concomitant medications will be sorted by decreasing frequency of standard medication name based on the incidence within each predefined category in the nabiximols treatment arm. In case of equal frequency, based on decreasing frequency in the placebo arm then in case of equal frequency, the alphabetic order will be used.

12.3.2.5 Physiotherapy

Summary of use of Physiotherapy will be summarized for each predefined category using the same approach as the one used for MS medication.

12.4 Important Protocol Deviations

All important protocol deviations (IPDs) are defined in a study specific protocol deviation guidance and classified as presented in Appendix 1. The IPDs that are determined to affect the primary efficacy results

will be classified as major IPDs as reported in Appendix 1**Error! Reference source not found.**. The occurrence of major IPDs will identify which patients maybe excluded from PP Analysis Set.

IPDs linked to COVID-19 will be identified. Patients for which at least one IPD has been identified, will be listed along with their deviation reason; demographics and treatment sequence for inclusion in the clinical study report (CSR) based on the deviation data will be entered into the clinical trial management system (CTMS).

The study team and the Sponsor will conduct ongoing reviews of the deviation data from both an internal system of record named Predictive Study Operations (PSO) and any other additional major IPDs that were missed and now identified through SAS programming of the blinded ADaM datasets, and the resulting set of evaluable patients throughout the study, adjusting the deviation criteria as seems appropriate. The PP Analysis Set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock and unblinding. However, in case a patient is receiving a treatment kit he/she is not allocated to, this will be considered as a major IPD before unblinding but the impact on the PP Analysis Set will only be determined following unblinding. This particular case will clearly be identified prior to database lock.

Based on the Randomized Analysis Set, the number and percentage of patients with important protocol deviations by category, as well as the number and percentage of patient with IPDs linked to COVID-19, by category, will be summarized by treatment sequence and overall.

Based on the FAS, the number and percentage of patients with at least one major IPD and the number and percentage of patients with major IPDs linked to COVID-19 will also be summarized by treatment sequence and overall.

Using the Randomized Analysis Set and the Safety Analysis Set (if deemed necessary to account for any patients exposed out of randomization) IPDs will be listed by treatment sequence and patient identifier and flagged for belonging to FAS and Safety Analysis Set. In this listing major IPDs, and IPDs linked to COVID-19 will be identified.

Furthermore, a COVID-19 deviation listing identifying COVID-19-related IPDs will be issued including date of the deviation and duration of the impact.

12.5 Efficacy Analysis

All efficacy analyses, unless otherwise specified will be performed on the FAS during the 51-day randomized efficacy period (as defined in Section 10.1) regardless of treatment compliance and permanent treatment discontinuation.

To assess robustness of the results with regard to intercurrent events some efficacy analyses may be repeated, for instance:

- During the 51-day on-treatment efficacy period (as defined in Section 10.1) using only on-treatment assessments (assessments obtained post treatment being set to missing);
- During the 51-days randomized period (as defined in Section 10.1) using the PP analysis set, If more than 20% of patients from FAS are excluded from the PP Analysis Set;
- During the 51-days randomized period using the Study Completer Analysis Set.
- During the 51-days randomized period excluding patients having at least one efficacy assessment impacted by COVID-19.

12.5.1 Hypothesis Testing Strategy and Multiplicity

To control for Type 1 error at a 2-sided alpha of 0.05, the primary endpoint and key secondary efficacy endpoint will be tested hierarchically, starting with the primary endpoint and followed by the key secondary endpoint. No adjustments for multiplicity will be made for other secondary or exploratory endpoints.

12.5.2 Primary Endpoint

The primary endpoint is the estimated mean treatment difference between nabiximols and placebo on the estimated change from baseline to D21 on LLMT-6 score (as defined in Section 10.16), where MAS scores

are collected during the 51-day randomized efficacy period, for all randomized patients belonging to the FAS.

The comparison between nabiximols and placebo treatment arm will be performed at a type I error level of 0.05 (two-sided).

12.5.2.1 Primary Efficacy Analysis

The primary analysis on the primary estimand (see Section 9.1), the change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) in LLMT-6 (as defined in Section 10.16) will be analyzed using a linear mixed-effects (LME) model for crossover data (as detailed in Section 12.5.2.1.8) performed following a multiple imputation strategy applied to missing data (as presented in Section 12.5.2.1.6 and summarized in Table 12.5-1) during the 51-day randomized efficacy period using FAS.

12.5.2.1.1 Missing Data Handling

As stated in Section 9.1, under the hypothetical strategy for handling intercurrent events, Period 2 data will not be collected when patients discontinue IMP during Period 1. In addition, missing data within a single period only may arise if patients decide to withdraw from the study or are lost to follow-up.

For patients who discontinue study before entering Period 2,

- Not collected Period 1 data will be imputed under the missing at random (MAR) assumption if the patient withdraws from the study due to a reason relative to COVID-19 or if the patient is randomized to the placebo/nabiximols treatment sequence and will be imputed under the control-based missing not at random (MNAR) assumption otherwise (i.e., patient lost to follow up or prematurely withdraws from the study and randomized to nabiximols/placebo treatment sequence),
- Not collected Period 2 data will be imputed under the MAR assumption whether or not missing data arise under the hypothetical strategy and whatever the treatment sequence the patient is randomized to.

For patients who discontinue study but enter in Period 2 not collected Period 2 data will be imputed,

- under the MAR assumption if the patient withdraws from study due to a reason relative to COVID-19 and/or is randomized to the placebo/nabiximols treatment sequence,
- under the control-based MNAR assumption otherwise.

Under this framework, for those patients having their missing scores assumed MNAR, their mean profile will be assumed to be the same as those patients in the placebo treatment arm for the period containing the missing data. Details regarding missing data handling are given in Table 12.5-1 below.

Table 12.5-1 Scenarios for Methods of Imputation when Data are not Collected

Scenario	Missing Data	Period 1 Imputation	Period 2 Imputation
1. Data not collected under the hypothetical strategy for handling intercurrent events	Period 2 data not collected due to patients who discontinue IMP or withdraw during Period 1/washout	N/A	Within treatment arm under MAR
2. Missing data arising due to reasons related to COVID-19, (and/or for patients assigned to placebo/nabiximols treatment sequence assignment)	Period 1 post baseline missing data but patient continues in study at least up to Period 2 baseline	Within treatment arm under MAR	Within treatment arm under MAR
	Period 1 withdrawal	Within treatment arm under MAR	Within treatment arm under MAR (Scenario 1)
	Period 2 post-baseline missing data/withdrawal	N/A	Within treatment arm under MAR

3. Missing data arising due to reasons not related to COVID-19, and not from the placebo/nabiximols treatment sequence assignment	Period 1 post-baseline missing data but patient continues in study	Control-based imputation under MNAR	Control-based imputation under MNAR
	Period 1 withdrawal	Control-based imputation under MNAR	Within treatment arm under MAR (Scenario 1)
	Period 2 post-baseline missing data/withdrawal	N/A	Control-based imputation under MNAR

These scenarios will be applied to the monotone datasets as described in Section 12.5.2.1.6.

12.5.2.1.2 Indicator Variables

The following indicator variables will be used to allow inclusion of qualitative variables in the imputation models or to select the imputation strategy as described in Table 12.5-1.

- Treatment arm will be coded as:
  - DTRTP=1 for Nabiximols treatment arm,
  - DTRTP=0 for Placebo treatment arm.

- Treatment sequence will be coded as:
  - DTRTSEQP=1 for Nabiximols/Placebo treatment sequence,
  - DTRTSEQP=0 for Placebo/Nabiximols treatment sequence.

- Impact of COVID-19 on MAS score will be coded as:
  - COVID1=1 if at least score is impacted by the COVID-19 and/or at least one visit impacted by COVID-19 is missed or performed remotely during Period 1 or if the patient withdraws study during Period 1 due to COVID-19;
  - COVID1=0 if no scores are impacted by the COVID-19 and /or no visits are impacted by COVID-19 during Period 1, or if the patient withdraws study during Period 1 not due to COVID-19;
  - COVID2=1 if at least score is impacted by the COVID-19 or at least one visit impacted by COVID-19 is missed or performed remotely during Period 2 or if the patient withdraws study during Period 2 due to COVID-19;
  - COVID2=0 if no scores are impacted by the COVID-19 and /or no visits are impacted by COVID-19 during Period 2, or if the patient withdraws study during Period 2 not due to COVID-19.

12.5.2.1.3 Missing Data Description

Description of missing data patterns will present the number and percentage of patients within each missing data pattern by treatment sequence and overall for the LLMT-6 score and the 6 individual muscle group scores composing the LLMT-6 score (as defined in Section 10.16).

Description of LLMT-6 score monotone missing pattern will be performed by treatment arm and COVID-19 impact (using indicator variable for COVID-19 impact as defined in Section 12.5.2.1.2), presenting the number and percentage of patients within each of the following monotone missing data pattern.

- Pattern 1: Patient with no baseline nor post baseline LLMT-6 scores,
- Pattern 2: Patient with a baseline LLMT-6 score but no post baseline LLMT-6 scores,
- Pattern 3: Patient with a baseline LLMT-6 score and LLMT-6 scores up to Day 1H3 only,
- Pattern 4: Patient with a baseline LLMT-6 score and LLMT-6 scores up D21.

This summary will also provide Mean (SD) at Baseline, D1H3 and D21 of each treatment period for each monotone missing data pattern.

12.5.2.1.4 MI Models - General Consideration

Each imputation model will use a common random seed value of 20210714 and any imputed value > 5 will be set to 5 whereas any imputed value below 0 will be set to 0 to account for LLMT score ranging from 0 to 5.

Post Period 1 baseline missing LLMT-6 scores (see Section 10.16), will be imputed using the strategy described in Section 12.5.2.1.6.

12.5.2.1.5 Monotone data pattern

Prior to performing any imputation methods as described below, intermittent missing scores as well as missing period 2 baseline score will be imputed under a MAR model using a Markov Chain Monte Carlo (MCMC) method to generate monotone missing data patterns within each treatment period.

This will be performed using the MCMC method in conjunction with the IMPUTE = MONOTONE option of the SAS® MI procedure.

First, for patients with no missing Period 1 baseline score but missing Period 2 baseline score, missing Period 2 baseline score will be imputed using a REGRESSION method in conjunction with the MONOTONE statement of the SAS® MI procedure using a model with indicator variables representing treatment sequence, Period 1 baseline score and Period 2 baseline score to create 300 imputed datasets.

Second, for each of the 300 imputed datasets and separately for each treatment period, intermittent missing score (missing period D1H3 score) will be imputed using a MCMC method in conjunction with the IMPUTE = MONOTONE option of the SAS® MI procedure to create 300 monotone datasets. The model will include in the following indicator variable representing treatment sequence, and continuous variables for Period i baseline, Period i D1H3, and Period i D21 where i = 1,2.

Details regarding indicator variables are described in Section 12.5.2.1.2.

12.5.2.1.6 Pattern Mixture Model Placebo-based Multiple Imputation Method

The Pattern mixture placebo-based multiple imputation method which is a “copy to reference method” will be implemented using baseline to predict D1H3 and D21 values in a MNAR model with indicator variables for treatment period, treatment sequence, and treatment.

For each of the 300 monotone by treatment period datasets generated as described in Section 12.5.2.1.5, the remaining missing data will be imputed separately for each treatment period within each treatment arm using the REGRESSION method in conjunction with the MONOTONE statement and either MNAR or MAR statement (as described in Table 12.5-1) of the SAS® MI procedure.

- Step1, the imputation model will create 300 monotone by treatment period datasets, as described in Section 12.5.2.1.5.
- Step 2a applied to Period 1 scores,
  - For patients on placebo treatment arm (i.e. placebo/nabiximols treatment sequence) and/or due to COVID-19 with non-missing LLMT-6 baseline score, LLMT-6 scores will be imputed sequentially at each post period baseline assessment (D1H3, D21) using a MAR imputation based on all non-missing LLMT-6 scores. Therefore, the models used to generate each post period baseline LLMT-6 scores are:
    - placebo LLMT-6 Period 1 D1H3 = placebo LLMT-6 Period 1 baseline score.
    - placebo LLMT-6 Period 1 D21 = placebo LLMT-6 Period 1 baseline score and placebo Period 1 D1H3 LLMT-6 score.
  - For patients on nabiximols treatment arm (i.e. nabiximols/placebo treatment sequence) with non-missing LLMT-6 baseline score, LLMT-6 scores will be imputed sequentially at each post period baseline assessment (D1H3, D21) using a MNAR imputation based on all non-missing LLMT-6 scores. Therefore, the models used to generate each post period baseline LLMT-6 scores are:

    - nabiximols LLMT-6 Period 1 D1H3 = placebo LLMT-6 Period 1 baseline score.
    - nabiximols LLMT-6 Period 1 D21 = placebo LLMT-6 Period 1 baseline score and placebo Period 1 D1H3 LLMT-6 score.
- Step 2b applied to Period 2 scores,
    - For patients on nabiximols treatment arm (i.e. placebo/nabiximols treatment sequence) and/or due to COVID-19 with non-missing LLMT-6 baseline score, LLMT-6 scores will be imputed sequentially at each post period baseline assessment (D1H3, D21) using a MAR imputation based on all non-missing LLMT-6 scores. Therefore, the models used to generate each post period baseline LLMT-6 scores are:
    - For patients on placebo treatment arm (i.e. nabiximols/placebo treatment sequence) with non-missing LLMT-6 baseline score, LLMT-6 scores will be imputed sequentially at each post period baseline assessment (D1H3, D21) based on all non-missing LLMT-6 scores.
        - If data is missing due to Period 1 withdrawal the procedure will use a MAR imputation and the models used to generate each post period baseline LLMT-6 scores are:
            - placebo LLMT-6 Period 1 D1H3 = placebo LLMT-6 Period 1 baseline score.
            - placebo LLMT-6 Period 1 D21 = placebo LLMT-6 Period 1 baseline score and placebo Period 1 D1H3 LLMT-6 score.
        - If data is missing due to not due to Period 1 withdrawal the procedure will use a MNAR imputation and the models used to generate each post period baseline LLMT-6 scores are:
            - placebo LLMT-6 Period 1 D1H3 = placebo LLMT-6 Period 1 baseline score.
            - placebo LLMT-6 Period 1 D21 = placebo LLMT-6 Period 1 baseline score and placebo Period 1 D1H3 LLMT-6 score.
- Step 3, Each of the 300 LLMT-6 scores generated from the fit of 300 placebo-based imputation models for each missing LLMT-6 score generated in Step 2 will correspond to a unique imputation number, and combination of imputed and non-missing LLMT-6 scores for each result in 300 complete datasets.
- Step 4: Imputed values from each of the 300 imputation datasets selected from step 3 and non-missing LLMT-6 scores will be analyzed by a linear mixed-effects model for crossover data applied to D21 as described in Section 12.5.2.1.8.
- Step 5: Result from each linear mixed-effects model for crossover data will be combined as described in Section 12.5.2.1.7.

12.5.2.1.7 Combining multiple imputation results

The analysis models will be evaluated in each imputed dataset and, the point estimates and SEs will be combined using Rubin's rules to produce valid global estimates with corresponding CIs and p-values. SAS® MIANALYZE procedure will be used for this purpose (Rubin, 1976).

12.5.2.1.8 Linear Mixed-effects Model for Crossover Data

The primary analysis model will be selected before multiple imputation and all subsequential statistical analysis conducted on this final model. The final selected model (after convergency and residual diagnostics and outlier searches, see below) will be fitted to each of the 300 imputed datasets. The model selection process will NOT be reconducted for each imputed dataset.

The change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) in LLMT-6 (as defined in Section 10.16) will be analyzed with a LME model for crossover data using the SAS® GLIMMIX procedure with an identity link function and a normal distribution. The change from period level baseline to D21 in LLMT-6 score will be included as the dependent variable. Hence, each patient will contribute two measurements to the model, one for each period of the study.

The preferred model will include a period level LLMT-6 baseline (pre-dose measurement) covariate, period level treatment arm, treatment period, and treatment sequence as fixed effects). An unstructured (UN) covariance structure will be used for the repeated LLMT-6 measurements of the changes from baseline in each treatment period and the denominator degrees of freedom will be calculated according to the Kenward-Roger method (e.g., KR2, 2009 version)

In case of non-convergence of the preferred model or memory space issue, the compound symmetry covariance structure will be applied to the preferred model described above.

This model will provide the least squares mean estimates for each treatment arm, along with the SEs and 95% CIs as well as, the least squares mean (LS mean) estimate of the mean treatment difference between nabiximols and placebo in change from baseline in LLMT-6 along with SE of the difference, 95% CI and associated nominal p-values will be presented.

In addition, this model will present the LSmeans estimates along with 95% CIs for each treatment period and treatment sequence, as well as the difference between treatment periods and treatment sequences and associated nominal p-values.

12.5.2.1.9 Model Assumption Assessment

Potential Period and Sequence effects

To assess potential period and sequence effects, using the primary efficacy model the following outputs will be presented:

- The combined estimates, 95% confidence intervals, and corresponding p-values for each treatment period and each treatment sequence, as well as the difference between treatment periods and between treatment sequences (representing the period term and sequence term combined estimates).
- A plot of the LLMT-6 mean change from baseline at D21 of each treatment arm by treatment period.

  In addition, summaries of the pre-dose baseline values for each treatment period (e.g., period baseline values) and overall per treatment arm will be explored from the descriptive statistics table presented in Section 12.5.2.3.3.

Distribution of Residual and Outliers search

The distribution of residuals as well as the search for potential outliers will be based on the analysis of primary endpoint using a LME model for cross-over data (as described in Section 12.5.2.1.8) but using observed cases LLMT-6 scores (not following any missing data MI strategy).

Distribution of the residuals will be assessed, based on outcome of the primary efficacy endpoint as follows:

- The normality of the residuals will be graphically assessed presenting boxplot, histogram, QQ-plots and scatterplot of residual versus linear predictors, based on studentized residuals obtained from the primary efficacy model.
- The distribution of the residuals obtained from the primary efficacy model will also be assessed using boxplots with each category of the fixed effect (treatment arm, treatment sequence and treatment period)

If the residuals appear not to be normally distributed, alternative approaches such as transformation of the data and nonparametric analyses may be considered to express treatment effect.

Outliers search: Outliers will be identified based on diagnosis performed from primary outcome measure using boxplot, and scatterplot of residual versus linear predictors,
If outliers are present, additional sensitivity analyses may be conducted with outliers excluded to assess their impact on the results.

12.5.2.2 Sensitivity Analysis – Tipping Point

The primary efficacy analysis assumes data are either missing at random or missing not at random as per missing data handling strategy described in Section 12.5.2.1.6

To assess the robustness of the treatment effect with regard to missing data, a sensitivity analysis based on a tipping point analysis will be performed for the primary efficacy endpoint to assess the impact of missing data assumed MNAR on the primary estimand.

This analysis will impute missing nabiximols D21 data under a Missing Not at Random assumption, using the FAS, during the 51-day randomized efficacy period (see Section 10.1).

Thus, when no penalty is added the tipping point analysis is the equivalent to the primary efficacy analysis.

Tipping point analyses

Using monotone datasets generated as described in Section 12.5.2.1.5, the remaining missing data will be imputed separately for each treatment period and each treatment arm using the REGRESSION method in conjunction with the MONOTONE statement and either MNAR statements (for nabiximols treatment arm following imputation strategy described in Table 12.5-1) or MAR statement (for either placebo treatment arm or nabiximols treatment arm following imputation strategy described in Table 12.5-1) of the SAS® MI procedure.

- Step1, the imputation model will create 300 monotone datasets, as described in Section 12.5.2.1.5
- Step 2
  - Step2a for Period 1 - first model

    Imputed missing D21 LLMT-6 scores for patients on placebo treatment arm with non-missing baseline score and missing D21 LLMT-6 score as well as for patients on nabiximols treatment arm with non-missing baseline LLMT-6 score and missing D21 LLMT-6 scores due to COVID-19 will remain MAR (no delta addition) and MI will follow the same approach as the one described in Section 12.5.2.1.6 Step 2a

    The first imputation model (e.g., delta=0) to impute missing D21 LLMT-6 scores for patients on nabiximols treatment arm with non-missing baseline scores and missing LLMT-6 scores not due to COVID-19 will follow the same MNAR placebo-based MI approach as the one described in Section 12.5.2.1.6 Step 2a.
  - Step2b for Period 2 - first model

I Imputed missing D21 LLMT-6 scores for patients on placebo treatment arm with missing D21 LLMT-6 score as well as for patients on nabiximols treatment arm with either missing D21 LLMT-6 scores due to COVID-19 for those entered in Period 2 or due to study withdrawal during Period 2 will remain MAR (no delta addition) and MI will follow the same approach as the one described in Section 12.5.2.1.6 Step 2b;

    The first imputation model (e.g., delta=0) to impute missing D21 LLMT-6 scores for patients on nabiximols treatment arm entered in Period 2 with missing D21 LLMT-6 scores not due to COVID-19 will follow the same MNAR placebo-based MI approach as the one described in Section 12.5.2.1.6 Step 2b.
  - Step2c subsequent models

    Separately for each treatment period, missing D21 LLMT-6 scores imputed under MAR at Step 2a or Step 2b will remain MAR (no delta addition) whereas for D21 LLMT-6 scores imputed under MNAR at Step 2a or Step 2b, in subsequent models, a common (non-zero) delta value (where delta value represents LLMT-6 score ranging from 0.12 to 5) will be added following MNAR imputation to each imputed value. Delta addition will be obtained using the DELTA option of the MNAR statement of the SAS® MI procedure.
    For the first imputation model (delta=0) 300 imputed datasets will be generated at Step 2a and Step 2b. For the subsequent models (delta >0), the same monotone datasets as those used for first imputation model (delta=0) will be retrieved.

  - Step 3, the 300 imputation datasets generated from each delta values will be analyzed by a LME model for crossover data applied to D21 as described in Section 12.5.2.1.8.
  - Step 4, for each value of delta, results from each LME model for crossover data as described in Section 12.5.2.1.8 will be combined as described in Section 12.5.2.1.7.
- Step 5, the tipping point will correspond to the first instance where the primary inference changes (i.e., p>=0.05 for between treatment arm difference in LSmeans). Consequently, the testing (Step 2 to Step 4) will be repeated for a plausible $_{nabiximols}$ value using a grid search method. Firstly, larger changes in delta values (delta will range from 0 to 5 by increments of 5/6 where 5/6 represents the maximum effect of an individual MAS transformed score on LLMT-6) will be used. If the primary inference changes, then smaller changes in delta values (1/6 representing the change of 1 in LLMT-6) will be used to identify a more accurate tipping point between the last two delta values which were using larger changes (ie. last delta value with p<0.05 and first delta value with p>=0.05).
- Step 6, results corresponding to each delta values will be presented within a summary table including combined LS mean estimate and corresponding SE and 95% CI for each treatment arm along with the combined LS mean estimate of the difference versus placebo along with its corresponding SE and confidence interval. The tipping point will be identified.

12.5.2.3 Supplementary Analyses Based on LLMT-6

12.5.2.3.1 Subgroup Analysis for Primary Endpoint

The treatment effect across the different subgroups indicated in Table 12.5-2 will be explored on the primary efficacy endpoint: LLMT-6.

Table 12.5-2 Subgroup Analyses of Primary Efficacy Endpoint

Group variables	Subgroup	Comments
Sex	Male Female	
Prior cannabis use	Yes No	
Baseline LLMT-6 category (cut off=2)	Period 1 baseline LLMT-6<=2 Period 1 baseline LLMT-6 >2	Baseline LLMT-6 categories refers to period 1 baseline score
Baseline LLMT-6 category (cut off=3)*	Period 1 baseline LLMT-6<=3 Period 1 baseline LLMT-6 >3	

If the value of a group variable cannot be determined, the patient will be excluded from the corresponding subgroup analysis.

The treatment arm-by-subgroup interaction will be assessed for the primary efficacy endpoint using the 300 imputation datasets derived to perform the primary efficacy analysis as described in Section 12.5.2.1.6. Each imputed dataset will be analysed using linear mixed-effects model for crossover data as described in Section 12.5.2.1.8 with subgroup and subgroup-by-period level treatment arm interaction, as 2 additional fixed effects. Result from each linear mixed-effects model for crossover data will then be combined as described in Section 12.5.2.1.7.

For each subgroup analyses, the following estimates will be presented. Within each subgroup; (i) the combined adjusted LS mean (SEs and 95% CIs) of the change from period baseline to D21 for nabiximols and placebo will be presented, (ii) the combined difference in LS means (nabiximols–placebo) together with SEs and 95% CIs as well as the nominal p-value will be presented. The subgroup-by-treatment arm interaction nominal p-value will be presented. In addition, frequency count and descriptive statistics for each subgroup will be presented in a separate table. Forest plots will be used to present subgroup analyses results. The forest plot created from subgroup analyses will display number of patients, all combined estimates (i, ii),including combined 95% CI for (ii) and interaction p-values.

If, in each treatment arm by subgroup, the number of patients is less than 5, only summary statistics will be displayed and no subgroup analyses will be conducted.

As the study is not stratified by site it is not planned to explore the impact of site on the treatment effect. However, if deemed necessary the impact of MAS assessors on LLMT-6 will be looked at.

12.5.2.3.2 Response Analyses Based on LLMT-6

The reduction from baseline to D21 of respectively >=20%, >=30%, >=40%, >=50% (as described in Section 10.16) will be analyzed using a logistic regression applied to crossover design using a generalized estimating equation (GEE). The models will be analyzed using the SAS® GLIMMIX procedure with a logit link function and a binary distribution. The marginal log likelihood will be approximated with an adaptive Gauss-Hermite quadrature (obtained using the EMPIRICAL option of the SAS® GLIMMIX procedure) using a likelihood-based sandwich estimator.

The preferred model will include a period level LLMT6 baseline covariate, treatment arm, treatment period, and treatment sequence as fixed effect.

An unstructured covariance will be used to model the residual errors between LLMT-6 scores within the same patient across period. The denominator degrees of freedom will be calculated according to the Kenward-Roger method (e.g. KR2, 2009 version).

This model will provide, for each response analysis, at D21, the estimate of the odds ratios (OR) representing the odds in nabiximols treatment arm versus placebo treatment arm and corresponding 95% CI and nominal p-value. These parameters will be summarized by treatment arm along with number of responders and associated crude response rates.

If less than 5 patients in either treatment arm are considered as responders, only descriptive statistics will be conducted presenting the number and percentage of responders by treatment arm.

In case of non-convergence, appropriate model will be applied.

12.5.2.3.3 Summary Descriptions and Listings

LLMT-6 values, change from baseline and percentage change from baseline in LLMT-6 will be summarized by treatment arm, per treatment period and overall, over time.

Mean ± SD LLMT-6 values and change from baseline by visit and treatment arm will be plotted.

Scatterplots of the change from baseline to D21 and percentage change from baseline to D21 in LLMT-6 against the baseline LLMT-6 will also be produced.

Spaghetti plots presenting baseline, D1H3 and D21 LLMT-6 sores from both treatment periods will be plotted for each patient by treatment arm. Paneled by treatment period and the treatment received in that period differentiated by line pattern.

Cumulative distribution functions on change from baseline and relative change from baseline to D21 in LLMT-6 will be plotted by treatment arm.

A by-patient listing will be provided for LLMT-6 observed, change and relative change from baseline along with responder status (as defined in Section 12.5.2.3.2).

12.5.3 Secondary Endpoint

12.5.3.1 Secondary Efficacy Endpoint

For comparison of nabiximols treatment arm versus placebo treatment arm, if primary endpoint is significant, the statistical test will be performed on the secondary endpoint. The Type I error rate for comparing nabiximols treatment arm to placebo treatment arm for the secondary endpoint will be controlled at 0.05 level (2-sided) and inference will be provided. Otherwise, if primary endpoint does not reach the statistical significance at the nominal Type I error rate, nominal p-value for the secondary endpoint will be calculated but no claim could be made based on that p-value as per testing strategy described above.

The secondary endpoint change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) in LLMT-4 (as defined in Section 10.16) will be analyzed in a similar way to the primary efficacy endpoint (see Section 12.5.2.1), during the 51-day randomized efficacy period using FAS . The comparison between nabiximols treatment arm and placebo treatment arm will be performed following the testing procedure outline just above and is assessing the secondary estimand (as defined in Section 9.1).

12.5.3.2 Sensitivity Analysis: Tipping Point

The primary efficacy analysis on secondary endpoint assumes data are either missing at random or missing not at random as per missing data handling strategy described in Section 12.5.2.1.3.

To assess the robustness of the treatment effect with regard to missing data, sensitivity analyses based on a tipping point analysis will be performed for the secondary efficacy endpoint to assess the impact of the missing data assumed MNAR on the secondary estimand.

This analysis will impute missing nabiximols D21 data under a Missing Not at Random approach, using the FAS during the 51-day randomized efficacy period (see Section 10.1).

Thus, when no penalty is added the tipping point analysis is equivalent to the primary analysis of the secondary endpoint.

This analysis will be conducted using the same approach as the one described for primary efficacy endpoint (see Section 12.5.2.2). However, as LLMT-4 score is based on 4 muscle groups (and not 6 muscle groups as LLMT-6)as described in Section 12.5.2.2,the Step 5 (Step 2 to Step 4 will be repeated for a plausible $_{\text{nabiximols}}$ value using a grid search method. Firstly larger changes in delta values (delta will range from 0 to 5 by increments of 5/4 where 5/4 represents the maximum effect of an individual MAS transformed score on LLMT-4) will be used. If the inference changes, then smaller changes in delta values (1/4 representing the change of 1 of LLMT-4 score) will be used to identify a more accurate tipping point between the last two delta values which were using larger changes (ie. last delta value with $p<0.05$ and first delta value with $p>=0.05$).

The same tables, figures and listing as those performed for LLMT-6 (as described in Section 12.5.2.3.3) will be provided for LLMT-4.

12.5.4 Other Analyses based on MAS

12.5.4.1 Analysis based on LLMT-10

The **exploratory efficacy** analysis **associated with the** LLMT-10 endpoint is defined as the estimated mean treatment difference between nabiximols and placebo on the estimated change from baseline to D21 on the LLMT-10 score (as defined in Section 10.16) where MAS scores are collected during the 51-day randomized efficacy period, for all randomized patients belonging to the FAS. The comparison between nabiximols and placebo will be performed at a type I error level of 0.05 (two-sided) and nominal p-values will be provided. No adjustments for multiplicity will be made on that endpoint and no claim could be made based on that p-value as per testing procedure outline in Section 12.5.1.

The same analyses as those conducted for LLMT-4 will be performed (see Section 12.5.3.1) apart from the tipping point analysis.

12.5.4.2 MI followed by Linear mixed-effect model with repeated measures for crossover data

Model Selection Before Multiple Imputations (MI)

The model will be selected before MI and all subsequent statistical analyses conducted on this model. The model selection process will NOT be reconducted for each imputed dataset.

The change from baseline to D21 of each treatment period (as defined in Sections 10.2 and 10.3) in LLMT-6, LLMT-4 and LLMT-10 scores (as defined in Section 10.16) will be analyzed using a linear mixed-effects model with repeated measures for crossover data using the SAS® GLIMMIX procedure with an identity link function and a normal distribution performed on each multiple imputed dataset. This model is an extension of the primary efficacy analysis by including the D1H3 post-dose timepoint.

The model will include period level LLMT-X* baseline covariate, period level treatment arm, treatment sequence, treatment period, visit, visit-by-period level LLMT-X* baseline covariate interaction and visit-by-period level treatment arm interaction as fixed effects. An unstructured covariance structure will be used to model the residual errors between LLMT-X* scores within the same patient across visit and period and the denominator degrees of freedom will be calculated according to the Kenward-Roger method (e.g. KR2, 2009 version). In case of non-convergence of the preferred model or memory space issues the compound symmetry (CS) covariance structure will be used. The final selected model from this process will be fitted to each of the 300 imputed datasets. Note: The model selection process will NOT be reconducted for each imputed dataset.

Pattern Mixture Model Placebo-based Multiple Imputation

Using the 300 imputed datasets obtained while performing primary analysis of LLMT-X* scores (see methodology in Section 12.5.2.1.6), each imputed dataset will be analyzed using a LME repeated measures for crossover data (described in Section 12.5.4.2). The result of each of these models will then be combined as described in Section 12.5.2.1.7 to produce for each post-dose assessment (D1H3, D21), valid combined estimates for each treatment arm with corresponding SEs and 95% CIs as well as combined valid estimates of treatment difference in change from baseline in LLMT-X* with corresponding SEs, 95% CIs and nominal p-value for treatment arm comparison at D1H3 and D21.

Combined LS means change from period baseline and 95% CI will be plotted by timepoint per treatment arm.

Linear Mixed-effect Model with Repeated Measure for Crossover Data

The model fitted to the data will be the one selected in the 'Model Selection Before Multiple Imputations (MI) section above.

12.5.4.3 Impact of Intercurrent Events

12.5.4.3.1 Impact of Missing individual transformed MAS muscle score

To assess the robustness of LLMT-6, LLMT-4 and LLMT-10 scores to missing individual muscle scores, the change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) for LLMT-6, LLMT-4 and LLMT-10 scores will be analyzed using the same approach as the one described respectively in Section 12.5.2.1 in Section 12.5.3.1**Error! Reference source not found.** and in Section 12.5.4.1 (LME model for crossover data applied to MI imputed datasets). The analyses will be conducted on FAS during the 51-days randomized period but only using LLMT-6, LLMT-4 and LLMT-10 scores derived without any missing individual MAS transformed muscle score.

12.5.4.3.2 Impact of Study/Treatment Discontinuation

To assess the robustness of the MAS scores results with regard to permanent premature treatment discontinuation and/or study withdrawal, the change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) for LLMT-6, LLMT-4 and LLMT-10 scores will be analyzed by means of a linear mixed-effects model for crossover data applied on MI datasets using the approach described respectively in Section 12.5.2.1, Section 12.5.3.1 and in Section 12.5.4.1 but conducted:

- during the 51-day on-treatment efficacy period (as defined in Section 10.1) using only on-treatment assessments (assessments obtained post treatment discontinuation are excluded from the analysis),

- during the 51-day randomized period using the Study Completer Analysis Set.

12.5.4.3.3 Impact of Major Important Protocol Deviations and Deviations from Predefined Time Windows

If more than 20% of patients from FAS are excluded in the PP Analysis Set; the robustness of the MAS scores results with regard to major IPDs will be assessed as described just above.

The change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) in LLMT-6, LLMT-4 and LLMT-10 scores will be analyzed with a linear mixed-effects model for crossover data applied to MI datasets using the approach described in respectively Section 12.5.2.1, Section 12.5.3.1 and in Section 12.5.4.1 during the 51-day randomized period using the PP Analysis Set.

Furthermore, to also assess the impact on deviation from predefined time window at D1H3, the change from baseline to D21 of each treatment period (as defined in Section 10.2 and Section 10.3) in LLMT-6 score will be analyzed by means of a linear mixed-effects model with repeated measures for crossover data applied to MI dataset using the approach described in Section 12.5.4.2, but during the 51-day on-treatment efficacy period. For this analysis any D1H3 MAS assessment not having taken place within 3 hours (± 15 minutes) post first morning dosing spray will be excluded from the analysis.

If more than 20% patients from FAS are excluded in the PP analysis set this analysis will be conducted on the PP analysis set, otherwise the FAS will be used.

12.5.4.3.4 Impact of COVID-19

If at least 5 patients have at least one visit where MAS scores are impacted by COVID-19, as assessed by the investigator, the impact of COVID-19 on the treatment effect will be assessed on MAS scores as described just below.

The change from baseline to D21 of each treatment period (as defined in Sections 10.2 and 10.3) in LLMT-6, LLMT-4 and LLMT-10 scores will be analyzed by the mean of a linear mixed-effects model for crossover data applied on MI datasets using the approach described respectively in Section 12.5.2.1, Section 12.5.3.1 and in Section 12.5.4.1 but removing the patients having at least one MAS assessment impacted by COVID-19.

12.5.4.4 Other Summaries and Listings based on MAS

An histogram presenting combined LS mean change from baseline to D21 estimates in LLMT-6, LLMT-4 and LLMT-10 along with their corresponding 95% CIs will be provided by treatment arm using combined LS means and 95% CIs coming from the linear mixed-effects model for crossover data applied to MI datasets used to analyze these 3 efficacy endpoints (as respectively described in Section 12.5.2.1, Section 12.5.3.1 and Section 12.5.4.1).

Descriptive statistics will be provided for each of the 10 individual muscle group MAS scores, presenting observed values along with change from baseline and percentage change from baseline score per treatment arm by treatment period and overall.

A by-patient listing will be provided for observed and derived variables presenting each of the 10 individual MAS scores along with LLMT-4, LLMT-6 and LLMT-10 scores.

12.5.5 Exploratory Efficacy Analysis

All exploratory efficacy analyses will be conducted among the full analysis set during the 51-day efficacy randomized period.

If more than 20% of patients from FAS are excluded in the PP Analysis Set; the analyses may be repeated using the PP analysis set as described in Section 12.5.

The exploratory efficacy analyses based on LLMT-10 are described in Section 12.5.5.

If at least 5 patients have at least one visit where the studied endpoint is impacted by the COVID-19, as assessed by the investigator, the analysis of that endpoint will be repeated excluding the concerned patients as described below:

- For the average 25-foot walk time (as described in Section 10.2 and in Section 10.17) if during Period 1 and/or Period 2, D21 visit, T25FW trials are impacted by COVID-19,
- For the 7-day average NRS spasticity score (as described in Section 10.2 and in Section 10.18) if during Period 1 and/or Period 2, Day 15 or D21 visits are impacted by COVID-19 and patient is infected*,
- For the 7-days average daily spasm counts (as described in Section 10.2 and in Section 10.19) if during Period 1 and/or Period 2, Day 15 or D21 visits are impacted by COVID-19 and patient is infected*,
- For MSSS-88 total and sub-scales scores (as described in Section 10.20) if during Period 1 and/or Period 2 at D21 Visit MSSS-88 scoring is impacted by COVID-19.

* For eDiary endpoints, impact on COVID-19 is assessed based on information collected on the “Visit COVID-19 Impact” eCRF form. Thus if reason is due to “Caregiver or family member infected with COVID-19” but not to “Patient infected by COVID-19” the assessment will not be discarded.

12.5.5.1 Timed 25-Foot Walk (T25FW)

A decrease in average time to complete the two trials will show an improvement.

The difference between treatment arms in the change from baseline to D21 in average 25-foot walk time (as defined in Section 10.17) will be analyzed using the same LME model for crossover data as the one used for the primary analysis of the primary efficacy endpoint (as described in Section 12.5.2.1.8).
As a sensitivity analysis, the same analysis will be repeated using non-imputed average 25-foot walk times (as defined in Section 10.17).

If model diagnostics suggests that the residuals are not normality distributed a non-parametric analysis will be conducted.

A >=20% reduction from baseline to D21 of in average time (as described in Section 10.17) will be analyzed using a logistic regression applied to crossover design using a GEE (as described in Section 12.5.2.3.2).

A histogram presenting LS means change from baseline estimates along with their corresponding 95% CI will be provided by treatment arm.

Descriptive statistics for the average T25FW values change from baseline and percentage change from baseline by treatment arm will be provided; as well as a by-patient listing presenting observed and derived variables.

12.5.5.2 11-point Numerical Rating Scale Score (NRS-spasticity score)

The 11-point NRS spasticity scale is composed of 11 items ranging from 0 (no spasticity) to 10 (maximal spasticity) to assess the overall spasticity in patients with MS during the last 24 hours.

The difference between treatment arms in the 7-day average NRS spasticity score over the last 7 day preceding D21 of each period (as defined in Section 10.18) will be analyzed using a linear mixed model for crossover data using the SAS® GLIMMIX procedure with an identity link function and a normal distribution. The 7-day average NRS spasticity D21 score will be included as the dependent variable. Hence, each patient will contribute two measurements to the model, one for each period of the study.

The preferred model will include period level treatment arm, treatment period, and treatment sequence as fixed effects. Unstructured (UN) covariance structure will be used to model the repeated 7-day average NRS spasticity scores. The denominator degrees of freedom will be calculated according to Kenward-Roger method (e.g., KR2, 2009 version).

In case of non-convergence of the preferred model or memory space issue the, the compound symmetry covariance structure will be applied to the preferred model described above.

This model will provide the LS mean estimates for each treatment arm, along with the SEs and 95% CIs as well as, the LS mean treatment difference between nabiximols and placebo in NRS spasticity score along with the SE , 95% CI and the nominal p-value for treatment arm comparison.

In addition, this model will present the LSmeans estimates along with 95% CIs for each treatment period and treatment sequence, as well as the difference between treatment periods and treatment sequences and nominal p-values for treatment sequence and treatment period comparison.

The 7-day average NRS spasticity scores will be summarized at baseline, Day 15 and D21 per treatment arm and, per treatment period and overall.

Mean ± SD 7-day average NRS spasticity score will be plotted per treatment arm by 7-day period.

Furthermore, a histogram presenting LS means estimates and corresponding 95% CIs will be plotted per treatment arm.

A by-patient listing presenting 7-day average NRS spasticity score along with the corresponding score per day will be provided.

12.5.5.3 Daily Spasm Count

The 7-day average daily spasm count is derived from spasm counts recorded daily by the patients in the eDiary.

The difference between treatment arms in the average daily spasm count over the last 7 day preceding D21 of each period (as defined in Section 10.19) will be analyzed using the same approach as the one used to analyze 7-day average NRS-spasticity score (as described in Section 12.5.5.2).

The 7-day average daily spasm count will be summarized at baseline, Day 15 and D21 per treatment arm and, per treatment period and overall.

Mean ± SD 7-days average daily spasm will be plotted per treatment arm by 7-day period.

Furthermore, a histogram presenting LS means estimates along with their corresponding 95% CIs will be provided by treatment arm.

A by-patient listing presenting 7-day average daily spasm count along with the corresponding count per day will be provided.

12.5.5.4 The MS Spasticity Scale

The MSSS-88 is a patient self-report measure of the impact of spasticity (muscle stiffness and spasms) in MS. It is composed of 88 items ranging from 1 (not at all bothered) to 4 (extremely bothered).

These items are grouped to derive 8 subscales (as defined in Section 10.20) within 3 different categories which are composed of: 3 spasticity symptoms (i.e., muscle stiffness, pain and discomfort, muscles spasms), 3 areas of physical functioning (i.e., effects on daily activities, ability to walk, body movement) and 2 areas of psychosocial impact (i.e., emotional health, social functioning).

Difference between treatment arms in total and subdomain scores of the MSSS-88 at the end of the maintenance-dose phase (D21) of each double-blind treatment period will be analyzed using the same approach as the one used to analyze the 7-day average NRS-spasticity score (as described in Section 12.5.5.2).

A histogram presenting LS means estimates along with their corresponding 95% CIs will be provided for respectively for the 8 subscale scores and for the total score.

The 88 items as well as subscales and total sores will be summarized by treatment arm.

A by-patient listing presenting the total score along with the 8 subscales scores will be provided

12.6 Pharmacokinetics

Plasma concentrations will be obtained for THC and its relevant metabolites (11-hydroxy-Δ9-tetrahydrocannabinol and 11-carboxy-Δ9-tetrahydrocannabinol) and CBD and its relevant metabolites (7-hydroxy-cannabidiol and 7-carboxy-cannabidiol) at distinct time points (as described in Table 8.1-2) on Day 1, Day 15 and D21 of each treatment period.

Concentration data will be summarized per treatment arm, treatment period and overall, by analysis day (as defined in Table 10.1-1) and hours (see Table 8.1-2) since last dose for post-baseline samples of THC and its relevant metabolites and of CBD and its relevant metabolites. Concentrations that are below the limit of quantitation (BLQ) will be excluded from the computation of descriptive statistics but the number of patients presenting a concentration below the limit of quantification will be presented at each time point. The number of observations, mean, standard deviation, geometric mean, geometric standard deviation, coefficient of variation (%), median, minimum, maximum values will be displayed

Individual data will be presented in listing.

If concentration data show that sufficient systemic exposure for THC or one or more of the metabolites is available, relevant PK parameters may be calculated using a population PK model. In that case, PK results will be presented in a stand-alone report. This report might also include a post hoc PK/PD analysis on the basis of PK and pharmacodynamics (PD) data collected in the study.

12.7 Safety Analyses

The safety analyses will be conducted during the 51-day on-treatment safety period (as described in Section 10.1) by actual treatment arm. As appropriate, the safety analyses will also be conducted during the follow-up period (as described in Section 10.1) by treatment sequence. All the safety analyses will be conducted using the Safety Analysis Set.

Some analyses of adverse events and laboratory parameters will assess the potential impact of the study drug among the subgroups presented in Table 12.7-1.

Table 12.7-1 Subgroups applied to Safety Analysis

Group Variables	Subgroup	Comments
Sex	Male Female	
Age group	≤18, > 18 and ≤ 45 ≥ 46 to ≤ 65 > 65	According to patient ‘s distribution within age, age group may be differently defined Detailed derivation is given in Section 10.10
Race	White Black or African American Asian American India or Alaska Native Native Hawaiian or Other Pacific Islander Other	According to patient’s distribution within race some races may be grouped together
Prior cannabis use	Yes No	If it appears that one patient has missing prior cannabis use information, the missing category will be added for AE summary
Number of current antispasticity medication	0 1 2 ≥ 3	

Patient mean number of daily sprays	≤ 6 sprays, > 6 sprays and ≤ 12 sprays, > 12 sprays.	This is referring to "Patient means number of daily spray" taken during the maintenance phase (derivation as described in Section 10.8.2)

12.7.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA 24.0 or higher according to the version in use at time of database lock. All safety analyses of AEs will be performed by actual treatment arm and reported using the Safety Analysis Set. An AE will be considered a TEAE if it first occurs or worsens in severity or seriousness after the first dose of IMP intake and before the last dose date + 15 days.

All AEs will be classified during the pre-treatment period, the 51-day safety on-treatment period or during the follow-up period as follows:

- Events that occurred before first IMP intake without worsening or becoming serious after the first IMP dose are classified as **pre-treatment AEs**;
- Events that occurred or worsens between first IMP dose and 14 days after IMP last dose are classified as on-treatment AE and are defined as **treatment-emergent AEs** (TEAEs);
  - TEAE occurring during 21-day on-treatment safety Period 1 will be considered emergent to actual treatment received during Period 1 (as defined in Section 10.1.1).
  - TEAE occurring during 21-day on-treatment safety Period 2 will be considered emergent to actual treatment received during Period 2 (as defined in Section 10.1.1).
- Events occurring more than 15 days after last dose are classified as f**ollow-up AEs**.

Consequently, TEAEs will be summarized by treatment arm using the actual treatment received at each given period. Any adverse event occurring during the wash-out period will be linked to the actual treatment arm defined for Period 1, whereas any AEs occurring after last IMP dose will be linked to the actual arm defined at time of permanent study drug discontinuation.

The following events will not be identified as AEs in this study:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, etc.). The condition (the "triggering event") that leads to the procedure are adverse events and will be reported as such.
- Pre-existing conditions present or detected prior to the first dose of study drug that do not worsen during the study.

Counting rules

For incidence reporting, if a patient reported more than one AE that was coded to the same preferred term/system organ class within a given treatment arm, the patient will be counted only once for that specific preferred term/system organ class by treatment arm and the rules defined below will be applied.

For TEAEs presented by action taken on study drug, the worst action taken among the events with same SOC/PT emergent to the same treatment arm will be selected for each patient. If action taken is missing for a TEAE, the action taken "drug withdrawn" will be assigned considering the AE leads to permanent IMP discontinuation. The imputed values for action taken will be used for incidence summaries, while the actual values will be used in data listings.

For TEAEs presented by severity, the worst severity among the events with same SOC/PT emergent to the same treatment arm will be selected for each patient. If the severity is missing for a TEAE, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

For TEAEs presented by relationship to study drug, the relationship to study drug, as assigned by the investigator, for each event during the clinical trial will be presented for each patient. If the relationship to

investigational product is missing for a TEAE, a causality of "Related" will be assigned. The imputed values for relationship assessment will be used for incidence summaries, while the actual values will be presented in data listings.

For TEAEs presented by categories for time of first onset of AE, if the AE start date is missing ,it will be imputed as specified in Table 10.21-1 for AE analysis or summary but actual values will be presented in data listing.

Summary of Adverse Events

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as specified in Table 10.21-1. No duration will be calculated for adverse events with incomplete start-or stop dates, or for ongoing adverse events.

For summary by SOC and PT the denominator to derive the percentage will be the number of patients at risk in the treatment arm.

For subgroup analysis by SOC and PT the denominator to calculate the percentage will be the number of patients at risk in the treatment arm and in the category of the analyzed subgroup.

For summary by SOC and PT and category of time to first onset of AE the denominator to derive the percentage will be the number of patients at risk in the treatment arm in each time interval category.

For summary by SOC and PT and category of duration of AE the denominator to derive the percentage will be the number of patients in the corresponding treatment arm having experienced a TEAE corresponding to the SOC or PT being summarized.

The number of patients at risk in the treatment arm is defined as the number of patients having taken at least 1 spray of respectively nabiximols or placebo in the actual treatment arm (as defined in Section 9.3.1) linked to either the 21-day safety period 1 or the 21-day safety period 2 (as defined in Section 10.1.1).

All summary by SOC and PT will be sorted by descending frequency of nabiximols for SOC and by descending frequency of nabiximols for PT within SOC.

Listing of Adverse Events

All AEs, SAEs, AEs leading to study drug discontinuation, AE with outcome of death; AE of special interest will be listed.

The listings will include Subject ID, actual treatment received, SOC, preferred term, investigator term, start and stop date of the AE, whether or not the AE was treatment emergent, duration, frequency, severity, relatedness, action taken, outcome, and seriousness of the AE. Imputed start or stop dates will not be displayed in listings of AEs. These listings will be sorted by treatment sequence, subject ID and onset of adverse events.

12.7.1.1 Overall Adverse Event Summary

An overall adverse event summary will provide, by treatment arm, the number and percentage of patients with at least:

- One TEAE,
- One TEAE related to IMP,
- One confirmed or suspected COVID-19 TEAE (as defined in Section 10.21.2),
- One TEAE leading to permanent IMP discontinuation,
- One TEAE related to IMP leading to permanent IMP discontinuation,
- One serious TEAE,

- One serious TEAE related to IMP,
- One TEAE with outcome of death,
- One AE with outcome of death related to IMP,
- One TEAE of special interest.

This table will also present the number of TEAEs and the number of TEAE of special interest by treatment arm.

12.7.1.2 All-causality Treatment-emergent Adverse Event Summary

Descriptive presentations of TEAEs will be given by PT and SOC for the Safety Analysis Set. The number and percentage of patients reporting at least one TEAE within a given treatment arm will be provided as described below

- *All TEAEs by SOC and PT,
- *All TEAEs by SOC, PT and subgroups (as described in Table 12.7-1),
- Most common TEAEs (incidence ≥ 5% in either treatment arm) by SOC and PT,
- Most common TEAEs (incidence ≥ 2 patients in either treatment arm) by SOC and PT,
- Most common TEAEs (incidence ≥ 2 patients in either treatment arm) by SOC, and PT and subgroups (as described in Table 12.7-1),
- All TEAEs by SOC, PT and maximum severity,
- All TEAEs by SOC, PT and worst action taken on study drug,
- All TEAEs by SOC, PT and time of first onset of AE categorized as:
  1-7 day, 8 to 14 days, 15 to 21 days and > 21 days (as described in Section 10.21.3),
- All TEAEs by SOC, PT and AE duration, categorized as:
  1-7 day, 8 to 14 days, 15 to 28 days, 29 to 42 days ,43 to 61 days ,> 61 days, ongoing, indeterminate (as described in Section 10.21.4),
- All TEAEs by SOC, PT and relationship to IMP,
- All treatment-related TEAEs by SOC and PT and maximum severity,
- *All treatment-related TEAEs by SOC and PT and subgroups (as described in Table 12.7-1),
- *All treatment-related TEAEs leading to permanent IMP discontinuation by SOC and PT,
- *All TEAEs leading to permanent IMP discontinuation by SOC and PT,
- *All TEAEs leading to permanent IMP discontinuation by SOC and PT and subgroups (as described in Table 12.7-1),
- All treatment-related TEAEs leading to permanent IMP discontinuation by SOC and PT and maximum severity,
- All non-serious TEAEs by SOC and PT,
- All most common non-serious TEAEs (incidence ≥ 5% in either treatment arm) by SOC and PT.

**These tables will also present the total number of AEs by treatment arm and as appropriate by category of subgroup.*

12.7.2 Death, Serious Adverse Events and Other Significant Adverse Events

12.7.2.1 Death

All deaths recorded in the EDC as adverse events, as the result of an adverse event or as fatal outcome of an adverse event will be listed and summarized as described in Section 12.7.1 and described in depth as narrative.

Descriptive presentations of fatal TEAEs will be given by PT and SOC for the Safety Analysis Set. The number and percentage of patients reporting at least one fatal TEAE within a given treatment arm will be provided as described below:

- All TEAEs leading to death by SOC and PT (if at least 2 patients experienced a fatal issue TEAE),
- All treatment-related TEAEs leading to death by SOC and PT (if at least 2 patients experienced a fatal issue TEAE related to study drug).

These tables will also present the total number of AEs by treatment arm.

12.7.2.2 Serious Adverse Events

Descriptive presentations of serious TEAEs will be given by **PT and SOC** for the Safety Analysis Set. The number and percentage of patients reporting at least one serious TEAE within a given treatment arm will be provided as described below:

- All serious TEAEs by SOC and PT,
- All serious TEAEs by SOC, PT and subgroups (as described in Table 12.7-1),
- All serious TEAEs leading to permanent IMP discontinuation by SOC and PT,
- All serious treatment-related TEAEs by SOC and PT,
- All serious treatment-related TEAEs by SOC and PT leading to permanent IMP discontinuation by SOC and PT,

These tables will also present the total number of AEs by treatment arm and as appropriate by category of subgroup.

12.7.2.3 Adverse Events of Special Interest

An adverse events of special interest (AESI) is any adverse event of scientific or medical interest to the study medication. The types of AESIs which will be analyzed are presented in **Descriptive presentations of AESIs** will be given for each AESI category on the safety analysis set presenting:

- The number and percentage of patients with at least one treatment-emergent AESI,
- The number and percentage of patients with at least one treatment-emergent AESI by SOC and PT,
- The number and percentage of patients with at least one severe treatment-emergent AESI,
- The number and percentage of patient with at least one serious treatment-emergent AESI,
- The number of and percentage of patients with at least one treatment-emergent AESI leading to permanent IMP discontinuation,
- The number of treatment-emergent AESI,
- The number of severe treatment-emergent AESI,
- The number of serious treatment-emergent AESI,
- The number of treatment-emergent AESI leading to permanent IMP discontinuation,
- The number of unique* treatment-emergent AESI,
- The number of unique* severe treatment-emergent AESI,
- The number of unique* serious treatment-emergent AESI,
- The number of unique* treatment-emergent AESI leading to permanent IMP discontinuation,
- The time to first onset of treatment-emergent AESI categorized as :1-7 day, 8 to 14 days, 15 to 21 days, 21 to 28 days and > 28 days (as described in Section 10.21.3),

**Unique AESI is defined as any AESI coded with the same PT and having the same date of onset.*
Analysis of time to first onset of AESIs will be conducted by actual treatment arm on the Safety Analysis SAS using the SAS® LIFEEST procedure.

Assuming no carry over effect, Kaplan-Meier plots (estimates) of cumulative incidence of first onset of AESI will be provided by actual treatment arm on the Safety analysis set. The time to AESI onset (in days) is defined as the number of days from 1st IMP intake of the treatment arm (e.g., nabiximols, placebo) the AESI is emergent to (as defined in Section 12.7.1) until the onset of the AESI (see detailed in Section 10.21.4).

For patients not known to have experienced an AESI during respectively Period 1 and Period 2:

- Period 1 censoring day is the date of 1st IMP intake during Period 2 minus 1 day for those patients continuing in Period 2 and, the end of study date for those patients who discontinued before Period 2,
- Period 2 censoring day is the end of study date in the period.

Additionally, for lost to follow-up patients:

- Period 1 censoring day is the earliest date between end of study date in the period and the planned Visit 6 day minus 1 day (Day 30),
- Period 2 censoring day is the earliest date between end of study date in the period and the planned Visit 10 day (Day 58).

To accompany the Kaplan-Meier (KM) plots, summary tables will display the KM estimates of cumulative probabilities (with 95% CI calculated based on the Greenwood method when applicable).

- of patients with on event at a specific time point such as 7, 14, 21, 28 (if applicable) days after 1st IMP intake in the studied period;
- time to first event based on the 10th, 20th, 30th, 40th, 50th (median) and 75th percentiles.

If the estimate of lower bound of the 95% CI is below '0' or the estimate of the upper bound of the 95% CI is over '1', then it will be respectively restricted to '0' and '1'.

The number of patients at risk along with the number and percentage of patients censored and with an event, using the number of patients at risk as denominator to calculate the percentage will also be displayed.

Each Kaplan-Meier plot (estimates) will only be provided if more than 5 patients are presenting an event in each treatment arm.

12.7.3 Laboratory Data

The clinical safety laboratory data (hematology and biochemistry) are planned to be collected at Screening and D21 of each treatment period. In case of premature end of treatment the latest assessment collected on-treatment will be used as described in Table 10.1-1.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. The investigator and medical monitor will be provided with a list of the normal ranges used by the central clinical laboratory for all variables assayed during the trial and a statement of accreditation (or similar) for the laboratory. However, AST, ALT, GGT, ALP and total bilirubin will be summarized using SI units.

Only scheduled laboratory parameters defined in Appendix 2 and those derived from them as eGFR (as defined in Section 10.13) will be included in summary tables and figures. However unscheduled laboratories values (coming from central or local laboratories) will be used in abnormality summary tables and will be presented in listings (using categories as defined in Appendix 6).

Baseline (Screening), D21 of each treatment period and the change from baseline to D21 (end of the treatment) will be summarized using the safety analysis set, by treatment arm, separately for red blood cells parameters and white blood cells parameters, hepatobiliary parameters, renal parameters, coagulation parameters and electrolytes and proteins (as described in Appendix 2). Furthermore, AST, ALT, GGT, ALP and total bilirubin will also be summarized as a multiple of the upper limit of normal (ULN).

Laboratory hematology and biochemistry (as described in Appendix 2) abnormalities will be evaluated, on patients from the Safety Analysis Set using shift tables at D21 according to baseline status with categories based on:

- reference ranges as either normal, below the lower limit of normal (LLN) as “Low” or above the ULN as “High”,
- based on CTCAE toxicity grade using version 5.0 or higher (as defined in Appendix 4 for hematology parameters and in Appendix 5 for biochemistry parameters),

presented by treatment arm.

Shift tables based on reference ranges will also be repeated for the subgroups presented in Table 12.7-1.

Furthermore, a summary of patients with laboratory values outside the reference ranges at baseline and during each 21-day on-treatment safety period (as defined in Section 10.1.1) will be presented for scheduled parameter including either scheduled visit only or scheduled and unscheduled visits, by treatment arm.

Scatterplot presenting baseline against last on-treatment value within each treatment period will be presented by treatment arm for scheduled biochemistry and hematological parameters of interest.

Regarding AST, ALT, GGT, ALP and total bilirubin these parameters will be summarized by treatment arm within the Safety Analysis Set for D21 of each treatment period using SI units and as a proportion of the population with no missing assessment if abnormal values with reference to ULN are presented using the All laboratory values will be listed and all test values outside the normal range will be flagged.

Urinalysis results will be summarized and listed.

12.7.3.1 Potential Drug-induced Liver Injury (DILI)

Liver function test data will also be provided in separate listings for:

- Patients who possibly met Hy’s Law criteria (i.e., had any elevated ALT or AST of > 3 x ULN, and increase in total bilirubin >= 2 x ULN, at the same visit)
- Patients who met any one or more of the following criteria at any post-baseline visit (list laboratory parameters ALT, AST, and total bilirubin only)
- 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)

A summary table will also be provided by treatment arm for number of patients who met any of the criteria specified above at any post-baseline visit. Any elevation during the wash-out period will be linked to the actual treatment arm received during Period 1 whereas any elevation observed permanent treatment discontinuation will be linked to the last treatment received.

A drug-induced serious hepatotoxicity (DISH) plot will display, for each patient during each 21-day on-treatment safety period (as defined in Section 10.1.1) the maximal total bilirubin value (expressed as a multiple of the ULN) against the maximal ALT value (expressed multiple of the ULN) to identify possible Hy’s Law range or Temple’s Corollary.

All post-baseline potential drug-induced liver injury laboratory data will be listed.

12.7.4 Vital Signs

Vital signs will include sitting SBP and DBP and pulse rate which are planned to be measured at Day 1 H0, D1H3, Day 15 and D21 of each treatment period as well as during the screening and the FU visit.

Vital signs parameters will be summarized on the Safety Analysis Set as described below.

Observed and change from baseline value in vital signs measures at each scheduled timepoint (D1H3, Day 15, D21) will we summarized by treatment arm.

The number and percentage of patients with any clinically significant abnormal value and change in vital signs (as defined in Appendix 6) within each treatment period will be summarized by treatment arm within the Safety Analysis Set.

Observed and change from baseline (Screening) to FU will also be summarized by treatment sequence.

All vital signs data will be listed.

12.7.5 Physical Examination, ECGs and other Observation Related to Safety

12.7.5.1 Physical Examination: Weight and BMI

Weight is planned to be measured at Screening, Day 1H0 of each period and at follow-up visit.

Based on the Safety Analysis Set, weight and BMI (as defined in Section 10.11), observed and change from baseline value at each scheduled timepoint (Period 2 Day 1 H0, D21) will we summarized by treatment arm.

Observed and change from Screening to FU will also be summarized by treatment sequence.

The number and percentage of patients meeting a clinically significant change in weight (as defined in Appendix 6 at any time during within each treatment period will be summarized by treatment arm. All measurements (scheduled or unscheduled) will be used to determine if any abnormality criteria is met(as determined in Appendix 6).

Weight and BMI will be listed.

12.7.5.2 Electrocardiogram Results

Based on the safety analysis set, 12-lead ECG parameters (Heart rate (beats/min), PR interval (msec), QRS duration (msec), QT Interval (ms), QTc B Interval (Bazett's formula) (msec), QTcF (Fridericia's formula) Interval (msec) will be summarized by treatment arm. All ECG results will be listed.

ECG results will be summarized for continuous variables and will be presented for the absolute result and change from baseline (Screening) to D21.

The number and percentage of patient with any abnormal QTcF (as detailed in Appendix 6) values or any other clinically significant ECG abnormality (as defined in Appendix 6) at baseline and within each treatment period will be summarized by treatment arm within the Safety Analysis Set.

12.7.5.3 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale is a patient questionnaire that evaluates suicidal ideation and behaviors. In this study, the C-SSRS is assessed at Screening using the "Baseline/Screening Version" and at subsequent timepoints using the "Since Last Visit" version. At the Screening visit, patient eligibility will be assessed with respect to suicidal ideation during the past month and suicidal behavior during the past 5 years.

The C-SSRS questionnaire is planned to be administered by the investigator (or designee) at Screening, Day 1 H0, Day 15 and D21 of each treatment period and at FU.

To analyze these questionnaires, events will be considered associated with:

- Nabiximols, if collected between first and last date of nabiximols intake.
- Placebo, if collected between first and last date of placebo intake.
- Any unscheduled C-SSRS questionnaire taken during the wash-out period will be linked to the actual treatment arm defined during Period 1.

- FU if collected after last IMP intake and only the latest one will be used for summary.

Derived parameters are presented in Section 10.23.

On treatment and by timepoints assessments

The number and percentage of patients who have answer "Yes" to each of the 5 suicidal ideation subtypes and each of the 5 suicidal behavior subtypes along with the number and percentage of patients presenting:

- A suicidal ideation,
- A suicidal behavior,
- A suicidal ideation or behavior,
- A self-injurious behaviour without suicidal intent.

will be summarized at baseline, for each scheduled on-treatment timepoint, for the 51-day safety on- treatment period, for last on-treatment assessment and for the Follow-up assessment by treatment arm. For this summary FU assessments will be linked to the last treatment received.

Shift table from baseline to maximal suicidal ideation score as well as a shift table for change in category (no suicidal ideation or behavior, suicidal ideation [without suicidal behavior], suicidal behavior) will also be summarized by treatment arm for patients having a baseline and at least 1 post baseline on-treatment assessment.

The number and percentage of patients presenting a suicide-related treatment-emergent event defined as:

- A treatment emergent suicidal ideation (without suicidal behavior) compared to recent history,
- A treatment emergent serious suicidal ideation compared to recent history,
- An emergence of serious suicidal ideation compared to recent history,
- An emergence of suicidal behavior compared to all prior history,

will be summarized by treatment arm.

Observed scores and changes from baseline in Suicidal ideation score and in Suicidal intensity rating score will be summarized at baseline and for each scheduled on-treatment timepoint, for the last on-treatment assessment and for the worst on-treatment score and for the follow-up assessment, by treatment arm using n, mean, median, SD, Q1, Q3, min and max.

Cumulative distribution function on change from baseline to last on-treatment value will be plotted by treatment arm. This will be displayed as an increasing CDF.

Withdrawal assessment from last on-treatment visit

The number and percentage of patients presenting:

- An emergence of suicidal ideation without suicidal behavior,
- An emergence of serious suicidal ideation,
- An emergence of suicidal behaviour.

From last on treatment assessment to FU will be summarized by treatment arm according to last treatment received.

Observed at last on-treatment assessment and FU along with change from last on-treatment assessment in Suicidal intensity rating score will be summarized by treatment group using n, mean, median, SD, Q1, Q3, min and max. A shift table of from last on-treatment to FU score will also be displayed.

For patients with any post-baseline suicidal ideation or suicidal behavior, listings will be prepared including all C-SSRS scores for these patients.

12.7.5.4 Drug of Abuse Screen

Drug of abuse screen is planned to be collected at Screening and Period 1 Day 1 H0.

A by-patient listing presenting all THC measures along with urinary drug screen results will also be provided.

12.7.5.5 Pregnancies

Any reported positive pregnancy results or reported pregnancies will be listed.

12.7.5.6 Examination of Oral Mucosa

Based on the Safety Analysis Set, results of oral mucosa examination (normal, abnormal NCS and Abnormal CS) planned to be performed at Screening, Day 1 H0, Day 15 and D21 of each period and during the follow-up visit will be described by treatment arm according to baseline status.

Each patient presenting at least one abnormal assessment will be listed.

12.7.5.7 Covid-19 Impact

The impact of COVID-19 on each visit will be summarized by treatment arm and a by-patient listing presenting patients impacted by COVID-19 during the conduct of the trial will be provided.

13.0 References

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
11-COOH-THC	11-carboxy-Δ^9-tetrahydrocannabinol
11-OH-THC	11-hydroxy-Δ^9-tetrahydrocannabinol
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy-cannabidiol
ADaM	Analysis dataset model
ADL	Activity of Daily Living
AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomic Therapeutic Class
ET visit	End of Treatment visit
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BLQ	Below Limit of Quantification
BDZ	Benzodiazepine
BMI	Body Mass Index
bpm	Beats per minutes
CBD	Cannabidiol
CDF	Cumulative distribution function
CFB	Change from baseline
CI	Confidence interval
CRF	Case report form
CS	Compound symmetry
CS	Clinically significant
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology criteria for adverse events
CTMS	Clinical Trial Management System
CV	Coefficient of variation
D	Day
DBP	Diastolic blood pressure
DILI	Drug-Induced Liver Injury
DISH	drug-induced serious hepatotoxicity

DMD	Disease Modifying Drug
DRESS	Drug reaction with eosinophilia and systemic systems
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
eGRF	Estimated Glomerular filtration rate
FAS	Full Analysis Set
FU	Follow-up
GEE	Generalized estimating equation
GGT	Gamma-glutamyl transferase
GW	GW Pharma Ltd / GW Pharma Limited
H	Hour
HLGT	High Level Group Term
HLT	High Level Term
HR	Heart rate
hrs	hours
ICF	Informed consent form
ICH	International Council for Harmonisation
IES	Intercurrent event(s) strategy
IMP	Investigational medicinal product
INR	International normalized ratio
IPD	Important protocol deviation
IRT	Interactive response technology
kcal	Kilo calories
KM	Kaplan-Meier
KR	Kenward-Roger
KR2	Kenward-Roger method (e.g., KR2, 2009 version)
LLMT	Lower Limb Muscle Tone
LLMT-4	Lower Limb Muscle Tone-4
LLMT-6	Lower Limb Muscle Tone-6
LLMT-10	Lower Limb Muscle Tone-10
LLN	Lower Limit of Normal
LME	Linear mixed-effects
LS mean	Least square mean

LSMD	Least square mean difference
M	Month
MAR	Missing at Random
MAS	Modified Ashworth Scale
Max	Maximum
MCMC	Markov Chain Monte Carlo
MDRD	Modification of Diet Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mobile Health Platform
MI	Multiple Imputation
Min	Minimum
MNAR	Missing Not At Random
MS	Multiple sclerosis
msec	millisecond
MSSS-88	Multiple Sclerosis Spasticity Scale
NC	Not Calculated
NCS	Not Clinically significant
NRS	Numerical Rating Scale
OR	Odds ratio
P	Period
PD	Pharmacodynamic
PK	Pharmacokinetic
PLS	Population-level summary
PP	Per Protocol
PRA	Pharmaceutical Research Associates
PRN	pro re nata (meaning as-needed)
PRO	Patient reported outcome
PSO	Predictive Study Operations
PT	Preferred term
Q1	First Quartile / Quartile 1
Q3	Third Quartile / Quartile 3
QTc B	QT corrected Bazett's formula
QTc F	QT corrected Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan

SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study data tabulation model
SE	Standard error
SI	Standard International
SOC	System organ class
T25FW	Timed 25-Foot Walk
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Δ^9-Tetrahydrocannabinol
UK	United Kingdom
ULN	Upper limit of normal
UN	Unstructured
WHO-DD	World Health Organization-Drug Dictionary
Y	Year

Appendix 1 Classification of Protocol Deviations

List of Important Protocol Deviation Category

Number	IPD category
01	Inclusion criteria
02	Exclusion criteria
03	Study drug
04	Assessment safety
05	Efficacy/pharmacodynamic endpoint
06	Visit window
07	Prohibited co-medication
08	Others

List of Major Important Protocol Deviations

Number	Major IPD category	Major IPD criteria
01	Inclusion criteria	Patient was not diagnosed with any disease subtype of MS, by revised 2017 McDonald criteria, for at least 12 months prior to Visit 1.
02	Inclusion criteria	Does not have a MAS untransformed score of at least 2 in 2 or more of six muscle groups (right knee flexors, left knee flexors, right knee extensors, left knee extensors, right plantar flexors, or left plantar flexors) at Visit 1.
03	Inclusion criteria	Subject was not receiving optimized treatment with at least 1 oral antispasticity drug (baclofen, tizanidine, and/or dantrolene) that has been stable for at least 30 days prior to Visit 1.
04	Exclusion criteria	Has taken nabiximols, cannabis, or a cannabis-derived product for medicinal or recreational purposes in the 30 days prior to Visit 1 and unable to abstain for the duration of the trial.
05	Exclusion criteria	Did not respond adequately to treatment with nabiximols or another cannabis-based medication if exposed at any time before the 30-day period prior to Visit 1.
06	Exclusion criteria	Any concomitant disease or disorder that has spasticity-like symptoms or that may influence the patient's level of spasticity.
07	Exclusion criteria	Has had a relapse of MS within the 60 days prior to Visit 1.
08	Exclusion criteria	Clinically suspected to have a contracture in one of the muscle groups of the lower limbs, preventing assessment with the MAS.
09	Exclusion criteria*	Has any other clinically significant disease or disorder (including seizure disorder) that, in the opinion of the investigator, may put the patient 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. *For certain disorders, determined with medical monitor*
10	Study drug	Subject taking more than 13 sprays per day at any time during each treatment phase.
11	Study drug	Patient randomized but not exposed to study drug.
12	Study drug	Subject not receiving at least 1 spray in the morning on the last day during maintenance phase.
13	Study drug	Subject receiving IMP during the washout period.
14	Study drug	Subject not exposed to IMP during at least 1 day during titration or the maintenance phase.
15	Study drug	Subject not exposed to IMP during at least 1 day in either treatment period.
16	Study drug	Patient receiving a kit number not allocated by IXRS which is not the treatment he/she was allocated to by IXRS during this period.
17	Efficacy endpoint	Missing evaluable MAS LLMT-6 pre-dose assessment.
18	Efficacy endpoint	Missing evaluable MAS LLMT-4 pre-dose assessment.
19	Efficacy endpoint	Missing evaluable MAS LLMT-6 at endpoint. (D21 or Day 51)
20	Efficacy endpoint	Missing evaluable MAS LLMT-4 at endpoint. (D21 or Day 51)
21	Visit window	Wash-out duration of less than 7 days.
22	Visit window	During maintenance phase: Visit 4 occurred +/- 2 days out of window

Number	Major IPD category	Major IPD criteria
		Visit 5 occurred +/- 3 days out of window Visit 6 occurred +/- 2 days out of window Visit 8 occurred +/- 2 days out of window Visit 9 occurred +/- 3 days out of window
23	Prohibited co-medication	Patient taking antipsychotic medication at any time during the trial.
24	Prohibited co-medication	Patient taking benzodiazepine on an as needed (PRN) basis during the trial.
25	Prohibited co-medication	Patient taking commercial cannabis or any cannabinoid medication during the trial.
26	Prohibited co-medication	Patient taking botulinum injection during the trial.
27	Prohibited co-medication	Initiation or changes in the dose of MS disease modifying therapy any time after randomization at Visit 2
28	Prohibited co-medication	Patient taking drugs solely metabolized by UGT1A9 and UGT2B7 during the trial
29	Prohibited co-medication	Patient taking strong CYP3A4 inducer during the trial
30	Prohibited co-medication	Initiation of a new course of physiotherapy any time after randomization at Visit 2
31	Prohibited co-medication	Patient changing dose or introducing antispasticity medication (baclofen, tizanidine, dantrolene)
32	Prohibited co-medication	Patient changing dose or introducing dalfampridine or fampridine

MS = Multiple sclerosis; MAS = Modified Ashworth Scale, IMP = Investigational Medicinal Product; IXRS = Interactive x Response System; LLMT-6 = Lower Limb Muscle Tone-6, LLMT-4 = Lower Limb Muscle Tone-6, PRN = pro re nata meaning as needed.

** Refers to important protocol which may or not be considered as major important deviation*

Appendix 2 Clinical laboratory parameters

Biochemistry (Serum[1])		**Hematology (Whole Blood[1])**		**Urinalysis (Urine[2])**
Category	**Parameters**	**Category**	**Parameters**	**Parameters**
Hepatobiliary	Alanine aminotransferase	Red blood cells	Hematocrit	Blood
Hepatobiliary	Albumin	Red blood cells	Hemoglobin	Glucose
Hepatobiliary	Alkaline phosphatase	Red blood cells	Mean cell volume	Nitrites
Hepatobiliary	Aspartate aminotransferase	Red blood cells	Mean corpuscular hemoglobin	pH
Electrolytes and proteins	Calcium	Coagulation parameter	Platelets	Protein
Renal	Creatinine	Red blood cells	Red blood cell count	White blood cells
Hepatobiliary	Gamma-glutamyl transferase	White blood cells parameters	White blood cell count with automated differential	Specific gravity
Electrolytes and proteins	Potassium			Ketones
Electrolytes and proteins	Sodium			Urobilinogen
Hepatobiliary	Total bilirubin			Bilirubin
Electrolytes and proteins	Total protein			
Renal	Urea (blood urea nitrogen)			
Coagulation parameters	Prothrombin time (plasma4)			

[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. Patients will undergo a separate blood THC test at Visit 1 only.
[4]Analyzed at Screening (Visit 1) only.

Appendix 3 Unscheduled Clinical laboratory parameters

Biochemistry (Serum[1])		Hematology (Whole Blood[1])		Urinalysis (Urine[2])
Category	**Parameters**	**Category**	**Parameters**	**Parameters**
Hepatobiliary	Alanine aminotransferase	Red blood cells	Hematocrit	Blood
Hepatobiliary	Albumin	Red blood cells	Hemoglobin	Glucose
Hepatobiliary	Alkaline phosphatase	Red blood cells	Mean cell volume	Nitrites
Hepatobiliary	Aspartate aminotransferase	Red blood cells	Mean corpuscular hemoglobin	pH
Electrolytes, proteins and creatinine kinase	Calcium	Coagulation parameter	Platelet count	Protein
Renal	Creatinine	Red blood cells	Red blood cell count	White blood cells
Hepatobiliary	Gamma-glutamyl transferase	White blood cells parameters	White blood cell count	Specific gravity
Electrolytes, proteins and creatinine kinase	Potassium	White blood cells parameters	Total neutrophil count	Ketones
Electrolytes, proteins and creatinine kinase	Sodium	White blood cells parameters	Monocyte count	Urobilinogen
Hepatobiliary	Total bilirubin	White blood cells parameters	Lymphocyte count	Bilirubin
Electrolytes, proteins and creatinine kinase	Total protein	White blood cells parameters	Basophil count	Squamous epithelial cells
Renal	Urea (blood urea nitrogen)	White blood cells parameters	Eosinophil count	Mucus
Coagulation parameters	Prothrombin time (plasma4)			Microscopy
Hepatobiliary	Amylase			Leucocyte esterase
Electrolytes, proteins and creatinine kinase	chloride			Color
Electrolytes, proteins and creatinine kinase	Bicarbonate			Appearance
Lipids	HDL-Cholesterol			Bacteria

Biochemistry (Serum[1])		**Hematology (Whole Blood[1])**		**Urinalysis (Urine[2])**
Lipids	LDL-Cholesterol			
Lipids	Total Cholesterol			
Lipids	Triglycerides			
Hepatobiliary	Lipase			
Electrolytes and proteins	Magnesium			
Electrolytes, proteins and creatinine kinase	Phosphorus			
Renal	Creatinine clearance			
Endocrinology	Insulin-like growth factor-1			
Endocrinology	Prolactin			
Renal	Estimate glomerular filtration rate			
Coagulation	INR			
Endocrinology	Glucose			
Electrolytes, proteins and creatinine kinase	Creatinine Kinase			
Immunology	HBaAg			
Immunology	HCV			
Immunology	HIV			

Appendix 4 Toxicity Criteria for Laboratory Hematology and coagulation Parameters based on CTCAE version 5.0

Laboratory Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Anemia (Hemoglobin Decreased)	<LLN – 6.2 mmol/L <LLN - 100 g/L <LLN – 10.0 g/L	<6.2 – 4.9 mmol/L <100 - 80 g/L <10.0 to 80.0 g/dL	<4.9 mmol/L <80 g/L <8.0 g/dL	
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	
White Blood Cells Decreased	<LLN – 3000/mm3 <LLN – 3.0 x 109/L	<3000 - 2000/mm3 <3.0 – 2.0 x 109/L	<2000 - 1000/mm3 <2.0 – 1.0 x 109/L	<1000/mm3 <1.0 x 109/L
Neutrophils count Decreased	<LLN – 1500/mm3 <LLN – 1.5 x 109/L	<1500 - 1000/mm3 <1.5 – 1.0 x 109/L	<1000 - 500/mm3 <1.0 – 0.5 x 109/L	<500/mm3 <0.5 x 109/L
Lymphocytes count Decreased	<LLN – 800/mm3 <LLN – 0.8 x 109/L	<800 – 500/mm3 <0.8 – 0.5 x 109/L	<500 - 200/mm3 <0.5 – 0.2 x 109/L	<200/mm3 < 0.2 x 109/L
Lymphocyte count increased		>4000/mm3-20,000/mm3 >4 - 20 x 109/L	>20,000/mm3 > 20 x 109/L	
Platelets count Decreased	<LLN – 75,000/mm3 <LLN – 75.0 x 109/L	<75,000 – 50,000/mm3 <75.0 – 50.0 x 109/L	<50,000 – 25,000/mm3 <50.0 – 25.0 x 109/L	<25,000/mm3 <25.0 x 109/L
Activated partial thromboplastin time prolonged (aPTT)	>ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 ULN °	

Appendix 5 Toxicity Criteria for Laboratory Biochemistry Parameters based on CTCAE version 5.0

Laboratory Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry				
Sodium Increased (Hypernatremia)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Sodium Decreased (Hyponatremia)	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L
Potassium Increased (Hyperkaliemia)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L;
Potassium Decreased (Hypokaliemia)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Calcium Increased (Hypercalcemia)	>ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L	>12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L	>13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L
Calcium Decreased (Hypocalcemia)	<LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <ULN – 1.0 mmol/L	<8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L	<7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9-0.8 mmol/L	<6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L
Albumin Decreased (hypoalbuminemia)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
Alkaline Phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.50 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 – 5.0 x baseline if baseline abnormal	>5.0 - 20.0 x ULN if baseline normal >5.0 – 20.0 x baseline if baseline abnormal	>20.0 x ULN if baseline normal 20.0 x baseline if baseline abnormal
Alanine amino transferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	> 3.0 - 5.0 ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 – 20.0 x ULN if baseline normal >5.0 - 20.0 x baseline if baseline abnormal	>20.0 x ULN if baseline normal > 20.0 x baseline if baseline abnormal
Aspartate amino transferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	> 3.0 - 5.0 ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 – 20.0 x ULN if baseline normal >5.0 - 20.0 x baseline if baseline abnormal	>20.0 x ULN if baseline normal > 20.0 x baseline if baseline abnormal
Blood Bilirubin Increased	>ULN – 1.5 x ULN if baseline normal >1.0-1.50 x baseline if baseline abnormal	>1.5 – 3.0 x ULN if baseline normal >1.5-3.0 x baseline if baseline abnormal	>3.0 – 10.0 x ULN if baseline normal >3.0- 10.0 x baseline if baseline abnormal	>10.0 x ULN if baseline normal > 10.0 x baseline if baseline abnormal
Gamma Glutamyl Transferase Increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 - 20.0 x ULN if baseline normal >5.0 - 20.0 x baseline if baseline abnormal	>20.0 x ULN if baseline normal >20.0 x ULN if baseline abnormal
Creatinine Increased	>ULN – 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 baseline; >3.0 – 6.0 x ULN	>6.0 x ULN

Chronic Kidney Disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
Proteinuria	1+ proteinuria	2+ and 3+ proteinuria	4+ proteinuria	

Appendix 6 Abnormality Criteria

Hepatic abnormality criteria		
Hepatic laboratory Parameters	**Abnormality criteria**	
ALT	> 3 x ULN	
	>5 x ULN	
	> 8 x ULN	
	> 10 x ULN	
	> 20 x ULN	
AST	> 3 x ULN	
	>5 x ULN	
	> 8 x ULN	
	> 10 x ULN	
	> 20 x ULN	
ALP	> 1.5 x ULN	
	> 2 x ULN	
	> 3 x ULN	
Total bilirubin	> 1.5 x ULN	
	> 2 x ULN	
	> 3 x ULN	
	> 5 x ULN	
GGT	> 1 x ULN	
Blood pressures and pule rate abnormality criteria		
Blood pressures and pulse rate criteria	**Abnormality criterion value**	**Abnormality criterion on change from baseline**
SBP	> 180 mmHg	≥ 20 mmHg increase from baseline

	< 90 mmHg	≥ 20 mmHg decrease from baseline
DBP	> 105 mmHg	≥ 15 mmHg increase from baseline
	< 50 mmHg	≥ 15 mmHg decrease from baseline
Pulse rate	> 120 bpm	≥ 10 bpm increase from baseline
	< 50 bpm	≥ 10 bpm decrease from baseline
Weight Abnormality Criteria		
Weight criteria	**Abnormality criteria**	
Weight (kg)	≥ 7% increase from baseline	
	≥ 7% decrease from baseline	
ECG abnormality criteria		
ECG criteria	**Abnormality criteria**	
QTcF interval prolongation*	> 450 msec	
	> 480 msec	
	> 500 msec	
Change from baseline in QTcF interval*	> 30 msec increase from baseline	
	> 60 msec increase from baseline	
PR interval	< 120 msec	
	> 200 msec	
QRS complex	< 80 msec	
	> 120 msec	
HR	< 60 bpm	
	> 100 bpm	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT= gamma-glutamyl transferase; SBP = Systolic blood pressure; DBP = diastolic blood pressure; bpm=beats per minutes to be classified as potentially clinically significant, the measurement must satisfy both criteria: the criterion for the value and the criterion for the change relative to baseline.
**Abnormal QTcF interval categories as defined in ICH Guidelines E14*

Any patients fulfilling at least one ECG abnormality criteria (as described in Appendix 6) or having at least one abnormal ECG assessed as significant by the investigator will be listed presenting all his/her ECG information.

Appendix 7 Prohibited medication solely metabolized by UGT1A9 and UGT2B7 and determination criteria

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

Medications solely metabolized by UGT1A9		**Medications solely metabolized by UGT2B7**		
Medication name	**ATC code**	**Medication name**	**ATC code**	**Comments**
Flavopiridol		Benoxaprofen	M01AE06	
Propofol	N01AX10	Carbamazepine	N03AF01	
		Codeine	R05DA12 R05DA04 N02AJ01 N02AJ02 N02AJ03 N02AJ07 N02AJ08 N02AJ09 N02AA08 N02AA58 N02AA59 N02AA79	
		Cyclosporin A	L04AD01, S01XA18	
		Epirubicin	L01DB03	
		Indomethacin	C01EB03 M01AB01 M01AB51 M02AA23 S01BC01 S01CC02	S01CC02 also contains anti-infective medications
		Tacrolimus	D11AH01 L04AD02	
		Tiaprofenic acid	M01AE11	
		Zaltoprofen		Not popped up in ATC code list.
		Zomepirac	M01AB04	
		Zidovudine	J05AF01	

			J05AR01 J05AR04 J05AR05	Combination product Combination product Combination product

ATC = Anatomic Therapeutic Class

Appendix 8 Prohibited medications strong CYP3A4 inducers and determination criteria

Strong CYP3A4 inducers		
Medication name	**ATC code**	**Comments**
Rifampicin	J04AB02 J04AB03 J04AM02 J04AM05 J04AM06 J04AM07 A07AA13* D06AX15* S01AA16* S02AA12*	This is a list on rifampicin only but also on products which contain rifampicin * refers to rifamycin
carbamazepine	N03AF01	
phenytoin	N03AB02 N03AB04 N03AB05 N03AB52	
phenobarbital,	N03AA01 N03AA02	
Primidone	N03AA03	
St John's Wort (hypericum perforatum)		Not popped up in ATC code list.

ATC = Anatomic Therapeutic Class

Appendix 9 Other Prohibited medications and determination criteria

Other prohibited medication			
Medication name	**ATC code**	**Verbatim code**	**Comments**
Nabiximols, cannabis or cannabinoid-based derived product	N03AX24 N02BG10		N03AX24: group of other anti-epileptics and cannabidiol is one of them This is the greater group of analgesics, and N02BG10 is a cannabinoid
Botulinum toxin injections,	M03AX01	Contains: 'BO' and 'Tox' '"Dysport 'Xeomin	Muscle relaxant products
Antipsychotic medications,	N05A apart from N05AN (Lithium) Including N05AH02 (BDZ)		
Benzodiazepines (if not following protocol requirements)	N03AE N05BA N05CD M03BX07		N03AE: clonazepam N05BA: broader group of anxiolytics contain the main used BDZ N05CD broader group of hypnotics but also contains melatonin for instance. M03BX07: tetrazepam

BDZ=Benzodiazepines

Appendix 10 Medications used in MS and determination criteria

Any medication used for MS along with its category will be retrieved from the eCRF Concomitant medication form. However, the information in the table below will be used to define subcategory of interest.

MS medications type	WHO-DD Therapeutic class	Standardized Medication name	ATC code	Verbatim term	Comments
Antispasticity medication	Muscle relaxant (M03)	Baclofen	M03BX01	Contains: • ‘‘BACLOFEN”’	
		Tizanidine	M03BX02	Contains: • ‘‘TIZANIDINE”’	
		Dantrolene	M03CA	Contains: • ‘DANTROLENE’	
		Tetrazapam (BDZ)	M03BX07		Not considered as a BDZ in the coding of ATC, but as a centrally acting muscle relaxant.
		Botulinum toxin	M03AX01	Contains: • ‘BO’ and ‘Tox’ • Dysport’ • ‘Xeomin’	
		Others	M03B and M03C apart those mentioned above		Refers to the broader group of muscle relaxants
	Antiepileptic (N03)	Clonazepam	N03AE		N03AE is a BDZ
		Gabapentin	N03AX12		
		Pregabaline	N03AX16		
		Cannabinidiol	N03AX24		Not allowed per protocol
	Psychoanaleptic (N05)	Clozapine (BDZ)	N05AH02		
		Benzodiazepines	N05BA N05CD		N05BA and N05CD refers to a list of BDZ
Medication to treat other MS symptoms	Other system nervous system drug (N07)	Dalfampridine	N07XX007		
		Fampridine	N07XX007		

MS=Multiple sclerosis; ATC= Anatomic Therapeutic Class; BDZ=Benzodiazepines

Appendix 11 Adverse Drug Reaction of Special Interest – AE selections

Adverse drug of special interest type	AESI search
Falls and injuries	PT from either: SOC "Injury, Poisoning, and procedural complications" Accidents and injuries (SMQ) [20000135]
Drug reaction with eosinophilia and systemic systems (DRESS)	See Appendix 13
Disorientation and confusion	Confusion and disorientation High Level Term (HLT) [10010301]
Driving and road traffic accident	Impaired driving ability (PT) [10049564] Road traffic accident (PT) [10039203] Impaired ability to use machinery (PT) (10077474) Accident – for machinery (PT) (10000369)
Abuse liability	Drug abuse, dependence and withdrawal (SMQ) [20000100] Euphoric mood (PT) [10015535]
Abnormal liver adverse events	Drug related hepatic disorders – comprehensive search (SMQ) [20000006] Drug related hepatic disorders – severe events only (SMQ) [20000007]
Somnolence and sedation	Somnolence (PT) [10041349] Hypersomnia (PT) [10020765] Sedation (PT) [10039897]
Fatigue and lethargy	Fatigue (PT) [10016256] Lethargy (PT) [10024264]
Suicidal ideation and behavior	Suicide/self-injury (SMQ) [20000037] AEs will also be searched using the following search term string of suicidality-related terms (Bangs, 2008): accident, asphyxiation, burn, cut, drown, firearm, die, dying, gas, gun, hang, hung, immolat, injur, jump, attempt, kill, monoxide, mutilate, overdos, poison, self-damag, self-harm, self injur, shoot, slash, suffocation, and suic.
Significant cardiovascular (CVD) disease	Cardiac arrhythmias (SMQ) [20000049] Cardiac failure (SMQ) [20000004] Cardiomyopathy (SMQ) [20000150] Hypertension (SMQ) [20000147] Ischaemic heart disease (SMQ) [20000043] Pulmonary hypertension (SMQ) [20000130]
Cognitive function	Cognitive and attention disorders and disturbances High Level Group Term (HLGT) [10009841]
Depression and depressed mood	Depression (excl. suicide and self-injury) (SMQ) [20000167]
Psychosis and psychotic disorders	Psychosis and psychotic disorders (SMQ) [20000117] Disturbances in thinking and perception (HGLT) [1001351]
Seizures	Convulsions (SMQ) [20000079] (includes Seizure [PT]) [10039906]

Appendix 12 Category of Adverse Events of Special Interest

List number	Category of adverse events of special interest
01	Falls and injuries
02	Drug reaction with eosinophilia and systemic systems
03	Disorientation and confusion
04	Driving and road traffic accident
05	Abuse liability
06	Abnormal liver adverse events
07	Somnolence and sedation
08	Fatigue and lethargy
09	Suicidal ideation and behavior
10	Significant cardiovascular disease
11	Cognitive function
12	Depression and depressed mood
13	Psychiatric disorders
14	Seizures

Appendix 13 Modify registry of severe cutaneous adverse reaction criteria for Drug reaction with eosinophilia and systemic systems (DRESS)

Only patients meeting the criteria will be presented.

At least 3 of the following criteria should be present for hypersensitivity syndrome or DRESS:

- 1. Acute skin rash
- 2. Involvement of at least 1 internal organ
- 3. Enlarged lymph nodes of at least 2 sites
- 4. One of the following blood count abnormalities (limits provided by laboratory):
  - lymphocytes above or below the laboratory limits
  - eosinophils above the laboratory limits (in % or absolute count)
  - platelets below the laboratory limits
- 5. Fever above 38 degrees Celsius

The adverse events should occur within 30 days of each other (There should be temporal proximity for the onset of these AEs.). Some PTs may be mentioned in more than one SOC. (within 1 month of each other).

Appendix 13.1 Acute skin reaction

Search in ‘Skin and subcutaneous tissue disorders’ SOC the following preferred term:

- Dermatitis (any Preferred Term that includes the word “dermatitis”)
- Drug eruption
- Eczema
- Erythema multiforme
- Erythema nodosum

- Rash (any PT that includes the word “rash”)
- Skin lesion
- Skin reaction
- Skin exfoliation
- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis
- Toxic skin eruption
- Urticaria

Appendix 13.2 Involvement of at least 1 internal organ

Blood and lymphatic system disorders SOC	Cardiac disorders SOC:	Endocrine disorders SOC:
Agranulocytosis	Autoimmune myocarditis	Adrenalitis
Aplastic anemia	Cardiomyopathy	Autoimmune thyroiditis
Aplasia pure red cell	Endocarditis	Thyroiditis
Autoimmune lymphoproliferative syndrome	Eosinophilic myocarditis	
Autoimmune neutropenia	Myocarditis	
Autoimmune pancytopenia	Pericarditis	
Blood disorder	Pericardial effusion	
Bone marrow disorder	Pericardial disease	
Bone marrow failure	Pleuropericarditis	
Bone marrow toxicity		
Coagulopathy		
Disseminated intravascular coagulation		
Disseminated intravascular coagulation in newborn		
Drug reaction with eosinophilia and systemic symptoms		
Eosinophilia		
Febrile neutropenia		
Granulocytopenia		
Haemolytic anemia		
Hemolysis		
Hypereosinophilic syndrome		
Leukemoid reaction		
Leukopenia		
Lymphocytosis		
Lymphopenia		
Hypersensitivity vasculitis		
Lymphadenitis		
Lymphadenopathy		
Lymphoma		
Monocytosis		
Mononucleosis		
Neutropenia		
Pancytopenia		
Platelet disorder		
Platelet toxicity		
Splenitis		
Splenomegaly		
Splenosis		
Thrombocytopenia		

Eye disorders SOC	Gastrointestinal disorders SOC	Hepatobiliary disorders SOC
Eye allergy	Allergic colitis	Autoimmune hepatitis
Eye swelling	Colitis	Amylase increased
Iritis	Eosinophilic colitis	Blood trypsin increased
Iridocyclitis	Eosinophilic oesophagitis	Cholangitis
Optic neuritis	Gastritis	Cholecystitis
Retinitis	Gingival edema	Hepatic failure
Uveitis	Gingival swelling	Hepatic functional abnormal
Vitritis	Gingivitis	Hepatic encephalopathy
Scleritis	Glossitis	Hepatic infiltration eosinophilic
	Enteritis	Hepatitis
	Mouth ulceration	Hepatitis acute
	Mesenteritis	Hepatitis toxic
	Edema mouth	Hepatocellular injury
	Oropharyngeal swelling	Hepatomegaly
	Parotitis	Hepatosplenomegaly
	Pancreatitis	Hepatorenal failure
	Periodontitis	Hepatorenal syndrome
	Sialadenitis	Hepatotoxicity
	Stomatitis	Hyperbilirubinemia
	Swollen tongue	Hyperbilirubinemia neonatal
	Tongue oedema	Hyperlipidemia
	Vasculitis gastrointestinal	Jaundice
		Jaundice neonatal
		Liver disorder
		Lipase abnormal
		Lipase increased
		Edema due to hepatic disease
		Edematous pancreatitis
		Pancreatic enzymes increased
		Pancreatic hemorrhage
		Pancreatic necrosis
		Pancreatitis (any PT that includes the word “pancreatitis”)
		Pancreatorenal syndrome
		Peripancreatic fluid collection
		Swollen tongue

General disorders and administration site conditions SOC:	Immune system disorders SOC (Part 1)	Immune system disorders SOC (Part 2)
Influenza like illness	Allergic bronchitis	Eyelid edema
Malaise	Allergic cough	Eosinophilic fasciitis
Multi-organ failure	Allergic cystitis	Face edema
Neonatal multi-organ failure	Allergic keratitis	Hypersensitivity
	Allergic oedema	Immune thrombocytopenic purpura
	Allergic sinusitis	Glomerulonephritis
	Alveolitis allergic	Laryngeal edema
	Anaphylactic reaction	Lip edema
	Anaphylactic shock	Lip swelling
	Anaphylactoid reaction	Myasthenia Gravis
	Anaphylactoid shock	Myositis
	Asthma	Nephrogenic systemic fibrosis
	Angioedema	Edema mouth
	Antiphospholipid syndrome	Panniculitis
	Autoimmune disorder	Pemphigus
	Autoimmune hepatitis	Pemphigoid
	Biliary cirrhosis primary	Periorbital edema
	Biliary cirrhosis	Pruritus allergic
	Bronchospasm	Polymyositis
	Circumoral edema	Reaction to drug excipients
	Cholangitis sclerosing	Sarcoidosis
	Dermatomyositis	Serum sickness
	Drug hypersensitivity	Systemic lupus erythematosus
	Drug reaction with eosinophilia and systemic symptoms	Systemic sclerosis
	Encephalitis	Type IV hypersensitivity reaction
	Encephalopathy allergic	Vitiligo

Investigations SOC: Hematologic	Investigations SOC: Immunologic	Investigations SOC: others
Any PT that reflects increased, decreased or abnormal MedDRA Hematology investigations (incl blood groups) HLGT Any PT that reflects increase or abnormal under MedDRA Hepatobiliary investigations HLGT	Any PT that reflects a positive or abnormal result under MedDRA Immunology and allergy investigations HLGT, and Investigations, imaging and histopathology procedures NEC, HLGT	Alanine aminotransferase Amylase Aspartate aminotransferase Bilirubin conjugated Blood amylase Blood bilirubin Blood bilirubin unconjugated Gamma-glutamyltransferase increased Lipase Liver function test Transaminases Biopsy liver abnormal Lung Biopsy lung abnormal Renal Blood creatinine increased Blood creatinine abnormal Blood urea increased Blood urea abnormal Creatinine renal clearance decreased Glomerular filtration rate decreased Blood urine Cells in urine Eosinophils urine Protein urine Red blood cells urine Urinary casts Urinary casts present Biopsy kidney abnormal Skin Biopsy skin abnormal

Musculoskeletal and connective tissue disorders SOC:	**Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC**	**Nervous system disorders SOC**
Arthralgia Arthritis Arthroplasty Ankle arthroplasty Hip arthroplasty Joint arthroplasty Knee arthroplasty Shoulder arthroplasty Joint swelling Joint warmth Lupus-like syndrome Myopathy Myositis Polyarthritis Tendonitis Tenosynovitis Synovitis Any PT under the MedDRA Connective tissue disorders (excl congenital) HLGT.	Lymphoma (any PT that includes the word “lymphoma”) Pseudolymphoma	Acoustic neuritis Arachnoiditis CNS inflammation CNS ventriculitis Spinal cord infection Encephalitis (all PTs under Encephalitis NEC, HLT) Encephalopathy Leukoencephalopathy Leukoencephalomyelitis Meningitis (all PTs under Meningitis NEC, HLT) Myelitis Neuritis cranial Neuropathy peripheral Polyneuropathy Reye’s syndrome Toxic optic neuropathy Vasculitis cerebral

Renal and urinary disorders SOC:	Respiratory, thoracic and mediastinal disorders SOC:	Vascular disorders SOC:
Anuria Cardiorenal syndrome Dialysis Eosinophilic cystitis Hematuria Hemodialysis Hemolytic uremic syndrome Hepatorenal failure Hepatorenal syndrome Pancreatorenal syndrome Peritoneal dialysis Edema due to renal disease Renal disorder Renal failure Renal impairment Nephropathy toxic Any PT under MedDRA Nephropathies HLGT	Allergic bronchitis Acute interstitial pneumonitis Asthma Allergic granulomatous angiitis Alveolitis Alveolitis allergic Angiolymphoid hyperplasia with Eosinophilia Eosinophilic bronchitis Eosinophilia myalgia syndrome Eosinophilic pneumonia Interstitial lung disease Pleural effusion Pleurisy Pleurisy viral Pleuropericarditis Pneumonitis Pulmonary eosinophilia Pulmonary vasculitis Pulmonary toxicity	Arteritis (any PT that includes the word “arteritis”) Capillaritis Vasculitis (any PT that includes the word “vasculitis”)

Renal and urinary disorders SOC:	**Respiratory, thoracic and mediastinal disorders SOC:**	**Vascular disorders SOC:**
Anuria Cardiorenal syndrome Dialysis Eosinophilic cystitis Hematuria Hemodialysis Hemolytic uremic syndrome Hepatorenal failure Hepatorenal syndrome Pancreatorenal syndrome Peritoneal dialysis Edema due to renal disease Renal disorder Renal failure Renal impairment Nephropathy toxic Any PT under MedDRA Nephropathies HLGT	Allergic bronchitis Acute interstitial pneumonitis Asthma Allergic granulomatous angiitis Alveolitis Alveolitis allergic Angiolymphoid hyperplasia with Eosinophilia Eosinophilic bronchitis Eosinophilia myalgia syndrome Eosinophilic pneumonia Interstitial lung disease Pleural effusion Pleurisy Pleurisy viral Pleuropericarditis Pneumonitis Pulmonary eosinophilia Pulmonary vasculitis Pulmonary toxicity	Arteritis (any PT that includes the word “arteritis”) Capillaritis Vasculitis (any PT that includes the word “vasculitis”)

Appendix 13.3 Enlarged lymph nodes of at least 2 sites

Search for PT including the word “Lymphadenopathy” alone or as part of another PT

Such as some examples are given below:

- Lymphadenopathy Mediastinal
- Paratracheal Generalized
- Retroperitoneal
- Vaccination site

Search for other PT that could reflect lymphadenopathy

- Benign lymph node neoplasm
- Lymph node palpable
- Lymph node scan abnormal

Appendix 13.4 One of the following blood count abnormalities

The search will use laboratory blood sample values along with their corresponding reference ranges

- Lymphocytes above or below lab limits
- Eosinophils above the lab limits
- Platelets below lab limits

Appendix 13.5 Fever above 38 degrees Celsius

The following selection will be performed based on AE

- Hyperthermia
- Hyperpyrexia
- Pyrexia
- Febrile bone marrow aplasia (and all PTs that include the word “febrile”)
- Body temperature increased
- Body temperature abnormal

Appendix 14 Overview of primary, secondary and exploratory efficacy objectives

Objective Clinical Category	Statistical Category	Estimand/Variable
Primary Objective: To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone-6; LLMT-6) in patients with multiple sclerosis (MS) who have not achieved adequate relief from spasticity with other antispasticity medications.		
LLMT-6	P1, Primary	Variable: Change from period baseline in LLMT-6 at D21 Population: FAS Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SA1 (Sensitivity)	Variable: Change from period baseline in LLMT-6 at D21 Population: FAS Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with MI under MNAR assumption. Tipping point analysis
	P1, SUP1 (Supplementary , Subgroup)	Subgroup analyses based on same estimand as primary endpoint
	P1, SUP2 (response analyses)	Variable: proportion of patients with LLMT-6 score reduction criterion cut-offs defined by different percentages of >=20%, >=30%, >=40%, >=50% from period baseline in LLMT-6 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Odd ratio in nabiximols versus placebo Analysis: OR from logistic regression model for crossover data adjusted on period baseline LLMT-6. Single imputation: Missing D21 values are imputed a failure.

	P1, SUP 3 (Repeated measure analysis)	Variable: Change from period baseline in LLMT-6 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless deviation from time window at D1H3 Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model with repeated measure for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SUP4 (Supplementary without missing individual muscle group MAS score	Variable: Change from period baseline in LLMT-6 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact Excluding LLMT-6 score derived with missing individual muscle group MAS score PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SUP5 (Supplementary without premature study discontinuation	Variable: Change from period baseline in LLMT-6 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SUP6 (Supplementary on-treatment assessment)	Variable: Change from period baseline in LLMT-6 at D21 Population: FAS IES: Prior permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.

	P1, SUP7 (Supplementary without major IPD impact)	Variable: Change from period baseline in LLMT-6 at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Prior to major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SUP8 (Supplementary without major IPD impact and without deviation from time window)	Variable: Change from period baseline in LLMT-6 at D21 Population: PP analysis set IES: Prior permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Without deviation from time window at D1H3 Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model with repeated measure for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
	P1, SUP9 (Supplementary without COVID-19 impact)	Variable: Change from period baseline in LLMT-6 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-6 with placebo-based MI under MNAR assumption.
Secondary objective (efficacy): To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone 4; LLMT-4) in patients with multiple sclerosis who have not achieved adequate relief from spasticity with other antispasticity medications.		
LLMT-4	S1, Primary	Variable: Change from period baseline in LLMT-4 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.

	S1, SA1 (Sensitivity)	Variable: Change from period baseline in LLMT-4 at D21 Population: FAS Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with MI under MNAR assumption. Tipping point analysis
	S1, SUP1 (Repeated measure analysis)	Variable: Change from period baseline in LLMT-4 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless deviation from time window at D1H3 Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model with repeated measure for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.
	S1, SUP2 (Supplementary without missing individual muscle group MAS score	Variable: Change from period baseline in LLMT-4 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact Excluding LLMT-4 score derived with missing individual muscle group MAS score PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.
	S1, SUP3 (Supplementary without premature study discontinuation	Variable: Change from period baseline in LLMT-4 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.

	S1, SUP4 (Supplementary on-treatment assessment)	Variable: Change from period baseline in LLMT-4 at D21 Population: FAS IES: Prior permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.
	S1, SUP5 (Supplementary without major IPD impact)	Variable: Change from period baseline in LLMT-4 at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.
	S1, SUP6 (Supplementary without COVID-19 impact)	Variable: Change from period baseline in LLMT-4 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-4 with placebo-based MI under MNAR assumption.
Exploratory objective: To evaluate the effect of multiple doses of nabiximols as adjunctive therapy compared with placebo on a clinical measure of velocity-dependent muscle tone in the lower limbs (Lower Limb Muscle Tone-10; LLMT-10) in patients with multiple sclerosis who have not achieved adequate relief from spasticity with other antispasticity medications		
LLMT-10	*E1, Primary*	Variable: Change from period baseline in LLMT-10 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.

	E1, SUP1 Repeated measure analysis)	Variable: Change from period baseline in LLMT-10 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless deviation from time window at D1H3 Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model with repeated measure for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption
	E1, SUP2 (Supplementary without missing individual muscle group MAS score	Variable: Change from period baseline in LLMT-10 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact Excluding LLMT-10 score derived with missing individual muscle group MAS score PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.
	E1, SUP3 (Supplementary without premature study discontinuation	Variable: Change from period baseline in LLMT-10 at D21 Population: Study completer analysis set IES: Regardless permanent treatment discontinuation Without premature study discontinuation Regardless major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.
	E1, SUP4 (Supplementary on-treatment assessment)	Variable: Change from period baseline in LLMT-10 at D21 Population: FAS IES: Prior permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.

	E1, SUP5 (Supplementary without major IPD impact)	Variable: Change from period baseline in LLMT-10 at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Accounting for COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.
	E1, SUP6 (Supplementary without COVID-19 impact)	Variable: Change from period baseline in LLMT-10 at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline LLMT-10 with placebo-based MI under MNAR assumption.
Exploratory Objective: To evaluate the effect of nabiximols after administration of multiple doses on walking using the Timed 25-Foot Walk (T25FW) test.		
T25FW	*E2,Primary*	Variable: Change from period baseline in average 25-foot walk time at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline average T25FW. Single imputation at trial level: missing trial time are imputed to 180 seconds under MAR assumption

	E2, S1 (without missing trial time imputation)	Variable: Change from period baseline in average 25-foot walk time at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline average T25FW. No imputation under MAR assumption
	E2, SUP1 (response analysis)	Variable: proportion of patients with a 20% decrease from period baseline in average T25FW at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Odd ratio in nabiximols versus placebo Analysis: OR from logistic regression model for crossover data adjusted on period baseline average T25FW. Single imputation: Missing D21 values are imputed a failure.
	E2, SUP2 (Supplementary without major IPD impact)	Variable: Change from period baseline in average 25-foot walk time at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline average T25FW. No imputation under MAR assumption
	E2, SUP3 (Supplementary without COVID-19 impact)	Variable: Change from period baseline in average 25-foot walk time at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact. PLS: Mean difference between nabiximols and placebo Analysis: LSMD from CFB linear mixed-effect model for crossover data adjusted on period baseline average T25FW. No imputation under MAR assumption

Exploratory Objectives: To evaluate the effect of nabiximols after administration of multiple doses on the following patient-reported outcomes: the 11-point Numerical Rating Scale (NRS) spasticity score, Daily spasm count as well as the MS Spasticity Scale (MSSS-88) total and subdomain scores.		
11-point NRS-spasticity score	*E3,Primary*	Variable: 7-day average NSR spasticity score at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption
	E3, SUP1 (Supplementary without major IPD impact)	Variable: 7-day average NSR spasticity score at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for cross over data. No imputation under MAR assumption
	E3, SUP2 (Supplementary without COVID-19 impact)	Variable: 7-day average NSR spasticity score at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact. PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption
7-days average daily spasm count	*E4,Primary*	Variable: 7-days average daily spasm count at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption

	E4, SUP1 (Supplementary without major IPD impact)	Variable: 7-days average daily spasm count at D21 Population: PP analysis set IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption
	E4, SUP2 (Supplementary without COVID-19 impact)	Variable: 7-days average daily spasm count at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact. PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption
MSSS-88 total and sub scale scores	*E5,Primary*	Variable: Score at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption
	E5, SUP1 (Supplementary without major IPD impact)	Variable: Score at D21 Population: PP population IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Without major IPD Regardless COVID-19 impact PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption

	E5, SUP2 (Supplementary without COVID-19 impact)	Variable: Score at D21 Population: FAS IES: Regardless permanent treatment discontinuation Regardless premature study discontinuation Regardless major IPD Without COVID-19 impact. PLS: Mean difference between nabiximols and placebo Analysis: LSMD from observed value linear mixed-effect model for crossover data. No imputation under MAR assumption

P = Primary – S=Secondary - SA= Sensitivity analysis – SUP=Supplementary analysis
E=Exploratory analysis
FAS = Full analysis set – PP = Per Protocol
PLS = Population-level summary.
IES = Intercurrent event(s) strategy – IPD = Important protocol deviation;
CFB = Change from baselines analysis. - OR= odds ratio - LSMD = Least square mean difference.
MI = Multiple Imputation
MAR = Missing at Random – MNAR = Missing not a random.
MS = Multiple Sclerosis – NRS= Numerical rating scale
LLMT-6 = Lower Limb Muscle Tone-6 - LLMT-4 = Lower Limb Muscle Tone-4
LLMT-10 = Lower Limb Muscle Tone-10
T25FW = Timed 25-foot walk