



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, 2-way Crossover Trial to Evaluate the Effect of Nabiximols Oromucosal Spray on Clinical Measures of Spasticity in Patients with Multiple Sclerosis

Summary

EudraCT number	2019-002625-29
Trial protocol	PL GB CZ
Global end of trial date	10 May 2022

Results information

Result version number	v1 (current)
This version publication date	12 May 2023
First version publication date	12 May 2023

Trial information

Trial identification

Sponsor protocol code	GWSP19066
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04657666
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GW Pharma Ltd
Sponsor organisation address	Sovereign House, Vision Park, Histon, Cambridge, United Kingdom,
Public contact	Clinical Trial Disclosure & Transparency, GW Pharma Limited, +1 215-832-3750, ClinicalTrialDisclosure@JazzPharma.com
Scientific contact	Clinical Trial Disclosure & Transparency, GW Pharma Limited, +1 215-832-3750, ClinicalTrialDisclosure@JazzPharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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) in patients with MS who have not achieved adequate relief from spasticity with other antispasticity medications

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, the ICH Tripartite Guideline for GCP Topic E6(R2), the EU Clinical Trials Directive, the EU GCP Directive, and the clinical study regulations adopting European Commission Directives into national legislation. The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents were submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study was initiated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Czechia: 1
Worldwide total number of subjects	68
EEA total number of subjects	68

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	66
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 68 participants who met all inclusion and no exclusion criteria were randomized to treatment at 9 clinic centers in Poland and 1 center in Czech Republic.

Pre-assignment

Screening details:

Randomized participants completed two 21-day treatment periods. A washout period (7 days) separated the 2 treatment periods. During the washout period, participants continued their current MS anti-spasticity medications. Each treatment period included a dose titration phase (~14 days) and maintenance-dose phase (~7 days) at optimized dose level.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Nabiximols

Arm description:

Participants who were randomized to receive GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received matching placebo treatment for 21 days (starting at Day 31; Treatment Period 2).

Arm type	Experimental
Investigational medicinal product name	Nabiximols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered GW-1000-02 (nabiximols) as an oromucosal spray for 21 days

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered placebo as an oromucosal spray for 21 days

Arm title	Placebo
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Arm description:

Participants who were randomized to receive matching placebo self-administered for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 31; Treatment Period 2).

Arm type	Active comparator
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered placebo as an oromucosal spray for 21 days

Investigational medicinal product name	Nabiximols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered GW-1000-02 (nabiximols) as an oromucosal spray for 21 days

Number of subjects in period 1	Nabiximols	Placebo
Started	33	35
Completed	30	33
Not completed	3	2
Adverse event, non-fatal	1	-
Decision by investigator, GW, or authority	-	1
Withdrawal of participant consent	2	1

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants who were randomized to receive matching placebo self-administered for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 31; Treatment Period 2).

Arm type	Active comparator
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered placebo as an oromucosal spray for 21 days

Investigational medicinal product name	Nabiximols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered GW-1000-02 (nabiximols) as an oromucosal spray for 21 days

Arm title	Nabiximols
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Arm description:

Participants who were randomized to receive GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received matching placebo treatment for 21 days (starting at Day 31; Treatment Period 2).

Arm type	Experimental
Investigational medicinal product name	Nabiximols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered GW-1000-02 (nabiximols) as an oromucosal spray for 21 days

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Patients self-administered placebo as an oromucosal spray for 21 days

Number of subjects in period 2	Placebo	Nabiximols
Started	33	30
Completed	30	28
Not completed	3	2
Adverse event, non-fatal	3	-
Not specified	-	2

Baseline characteristics

Reporting groups

Reporting group title	Nabiximols
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Reporting group description:

Participants who were randomized to receive GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received matching placebo treatment for 21 days (starting at Day 31; Treatment Period 2).

Reporting group title	Placebo
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Reporting group description:

Participants who were randomized to receive matching placebo self-administered for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 31; Treatment Period 2).

Reporting group values	Nabiximols	Placebo	Total
Number of subjects	33	35	68
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	35	66
From 65-84 years	2	0	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	49.7	49.7	
standard deviation	± 9.9	± 9.7	-
Gender categorical			
Units: Subjects			
Female	19	24	43
Male	14	11	25

End points

End points reporting groups

Reporting group title	Nabiximols
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Reporting group description:

Participants who were randomized to receive GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received matching placebo treatment for 21 days (starting at Day 31; Treatment Period 2).

Reporting group title	Placebo
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Reporting group description:

Participants who were randomized to receive matching placebo self-administered for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 31; Treatment Period 2).

Reporting group title	Placebo
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Reporting group description:

Participants who were randomized to receive matching placebo self-administered for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 31; Treatment Period 2).

Reporting group title	Nabiximols
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Reporting group description:

Participants who were randomized to receive GW-1000-02 (nabiximols) self-administered as an oromucosal spray for 21 days (starting on Day 1; Treatment Period 1), followed by at least a 7-day wash out period, and then received matching placebo treatment for 21 days (starting at Day 31; Treatment Period 2).

Subject analysis set title	Nabiximols
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Subject analysis set type	Full analysis
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Subject analysis set description:

Combined analysis of patients treated with nabiximols in both Treatment Period 1 and Treatment Period 2.

Subject analysis set title	Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Combined analysis of patients treated with placebo in both Treatment Period 1 and Treatment Period 2.

Primary: Change From Baseline in Lower Limb Muscle Tone-6 (LLMT-6)

End point title	Change From Baseline in Lower Limb Muscle Tone-6 (LLMT-6)
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End point description:

LLMT-6 is defined as the average of the 6 individual Modified Ashworth Scale (MAS) transformed scores of knee flexors, knee extensors, and plantar flexors on both sides of the body. Transformed MAS ranges from 0 (no increase in muscle tone) to 5 (affected part rigid in flexion or extension). The combined (treatment period 1 and treatment period 2) least square mean change from baseline in LLMT-6 score is being reported. Negative values indicate an improvement in muscle tone.

End point type	Primary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	68		
Units: units on a scale				
least squares mean (standard error)				
Change from baseline in LLMT-6	-0.23 (± 0.07)	-0.26 (± 0.07)		

Statistical analyses

Statistical analysis title	Nabiximols vs Placebo
Comparison groups	Nabiximols v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7152 ^[1]
Method	Mixed models analysis
Parameter estimate	Combined least square mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[1] - Pattern mixture model (PMM) control-based imputation, mixed model repeated measures (MMRM)

Secondary: Change From Baseline in Lower Limb Muscle Tone-4 (LLMT-4)

End point title	Change From Baseline in Lower Limb Muscle Tone-4 (LLMT-4)
End point description:	LLMT-4 is defined as the average of the 4 individual MAS transformed scores of knee flexors and knee extensors on both sides of the body. Transformed MAS ranges from 0 (no increase in muscle tone) to 5 (affected part rigid in flexion or extension). The combined (treatment period 1 and treatment period 2) least square mean change from baseline in LLMT-4 score is being reported. Negative values indicate an improvement in muscle tone.
End point type	Secondary
End point timeframe:	Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	68		
Units: units on a scale				
least squares mean (standard error)				
Change from baseline in LLMT-4	-0.23 (± 0.08)	-0.28 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Patients With Any Treatment-Emergent Adverse Events (TEAEs)
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End point description:

A TEAE is an adverse event that started, or worsened in severity or seriousness, following the first dose of the investigational medicinal product.

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	65		
Units: patients				
number (not applicable)				
Any TEAE	27	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Pressure

End point title	Change From Baseline in Blood Pressure
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic blood pressure	-3.7 (± 10.48)	-2.7 (± 10.85)		
Diastolic blood pressure	-3.6 (± 9.06)	-1.7 (± 8.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Heart Rate

End point title	Change From Baseline in Heart Rate
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: beats/minute				
arithmetic mean (standard deviation)				
Heart rate	-2.9 (± 8.12)	2.0 (± 9.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight

End point title	Change From Baseline in Weight
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	59		
Units: kg				
arithmetic mean (standard deviation)				
Weight	0.28 (± 1.73)	0.56 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI)

End point title	Change From Baseline in Body Mass Index (BMI)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	59		
Units: kg/m ²				
arithmetic mean (standard deviation)				
Body mass index (BMI)	0.09 (± 0.67)	0.19 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Laboratory Values

End point title	Change from Baseline in Clinical Laboratory Values
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: 10 ⁹ per liter				
arithmetic mean (standard deviation)				
Leukocytes (n=61; n=59)	-0.144 (± 1.57)	-0.324 (± 1.08)		
Neutrophils (n=60; n=59)	0.015 (± 1.57)	-0.316 (± 0.99)		
Basophils (n=60; n=58)	-0.001 (± 0.04)	0.000 (± 0.03)		
Eosinophils (n=60; n=58)	0.010 (± 0.08)	0.011 (± 0.08)		
Lymphocytes (n=60; n=58)	-0.172 (± 0.33)	-0.013 (± 0.31)		
Monocytes (n=60; n=58)	-0.003 (± 0.16)	-0.009 (± 0.15)		
Platelets (n=61; n=59)	1.0 (± 40.58)	1.7 (± 35.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Erythrocytes

End point title	Change From Baseline in Erythrocytes
End point description:	
End point type	Secondary
End point timeframe:	
Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)	

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: 10 ¹² per liter				
arithmetic mean (standard deviation)				
Erythrocytes	-0.101 (± 0.27)	-0.017 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin

End point title	Change From Baseline in Hemoglobin
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: g/dL				
arithmetic mean (standard deviation)				
Hemoglobin	-0.22 (± 0.79)	-0.03 (± 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hematocrit

End point title	Change From Baseline in Hematocrit
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: ratio				
arithmetic mean (standard deviation)				
Hematocrit	-0.006 (± 0.03)	-0.001 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Erythrocyte Mean Corpuscular Volume

End point title	Change From Baseline in Erythrocyte Mean Corpuscular Volume
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: fL				
arithmetic mean (standard deviation)				
Erythrocyte Mean Corpuscular Volume	0.64 (\pm 3.33)	0.17 (\pm 3.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Erythrocyte Mean Corpuscular Hemoglobin

End point title	Change From Baseline in Erythrocyte Mean Corpuscular Hemoglobin
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	59		
Units: pg				
arithmetic mean (standard deviation)				
Erythrocyte Mean Corpuscular Hemoglobin	0.14 (\pm 0.97)	0.04 (\pm 0.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Electrocardiogram Parameters

End point title	Change From Baseline in Electrocardiogram Parameters
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: msec				
arithmetic mean (standard deviation)				
PR interval	11.4 (± 102.54)	-1.7 (± 24.79)		
QRS duration	0 (± 13.61)	-1.0 (± 9.34)		
QT interval	2.4 (± 22.19)	-3.2 (± 32.57)		
QTcB interval	1.1 (± 56.32)	10.1 (± 51.80)		
QTcF interval	3.0 (± 55.83)	6.9 (± 50.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Electrocardiogram Pulse Rate

End point title	Change From Baseline in Electrocardiogram Pulse Rate
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: beats/minute				
arithmetic mean (standard deviation)				
Pulse rate	-6.6 (± 8.76)	-2.5 (± 9.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Suicidal Ideation or Behavior Based on The Columbia Suicide Severity Rating Scale (CSSRS)

End point title	Number of Patients With Suicidal Ideation or Behavior Based on The Columbia Suicide Severity Rating Scale (CSSRS)
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End point description:

The C-SSRS is a short questionnaire that is used to assess suicidal ideation (5 questions) and behavior (5 questions) since last patient visit. The questionnaire is completed by participants answering yes or no to each question.

End point type	Secondary
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End point timeframe:

Baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2)

End point values	Nabiximols	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	65		
Units: patients				
number (not applicable)				
Baseline: Ideation, Wish to be dead	0	0		
Baseline: Ideation, Non-specific active thoughts	0	0		
Baseline: Ideation: Active any method no intent	0	0		
Baseline: Ideation, Active intent to act no plan	0	0		
Baseline: Ideation, Active specific plan/intent	0	0		
Baseline: Behavior, Preparatory acts or behavior	0	0		
Baseline: Behavior, Aborted attempt	0	0		
Baseline: Behavior, Interrupted attempt	0	0		
Baseline: Behavior, Actual attempt (non-fatal)	0	0		
Baseline: Behavior, Completed suicide	0	0		
Baseline: Ideation or behavior	0	0		
Baseline: Self-injurious behavior without intent	0	0		
Day 15: Ideation, Wish to be dead	0	0		
Day 15: Ideation, Non-specific active thoughts	0	0		
Day 15: Ideation, Active any method no intent	0	0		
Day 15: Ideation, Active intent to act no plan	0	0		
Day 15: Ideation, Active specific plan/intent	0	0		
Day 15: Behavior, Preparatory acts or behavior	0	0		
Day 15: Behavior, Aborted attempt	0	0		
Day 15: Behavior, Interrupted attempt	0	0		

Day 15: Behavior, Actual attempt (non-fatal)	0	0		
Day 15 Behavior, Completed suicide	0	0		
Day 15: Ideation or behavior	0	0		
Day 15: Self-injurious behavior without intent	0	0		
Day 21: Ideation, Wish to be dead	0	0		
Day 21: Ideation, Non-specific active thoughts	0	0		
Day 21: Ideation, Active any method no intent	0	0		
Day 21: Ideation, Active intent to act no plan	0	0		
Day 21: Ideation, Active specific plan/intent	0	0		
Day 21: Behavior, Preparatory acts or behavior	0	0		
Day 21: Behavior, Aborted attempt	0	0		
Day 21: Behavior, Interrupted attempt	0	0		
Day 21: Behavior, Actual attempt (non-fatal)	0	0		
Day 21: Behavior, Completed suicide	0	0		
Day 21: Ideation or behavior	0	0		
Day 21: Self-injurious behavior without intent	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Δ9-tetrahydrocannabinol (THC)

End point title	Plasma Concentrations for Δ9-tetrahydrocannabinol (THC)
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End point description:

End point type	Secondary
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End point timeframe:

Period 1: Day 1: predose, 0-2 and 2-4 hours (hr) postdose. Day 15: 0-2 and 2-4 hr postdose. Day 21: predose, 0-1 and 2-3 hr postdose. Period 2: Day 31: predose, 0-2 and 2-4 hr postdose. Day 45: 0-2 and 2-4 hr postdose. Day 51: predose, 0-1, 2-3 hr postdose

End point values	Nabiximols			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, Predose (n=3)	1.60 (± 1.21)			
Day 1, 0-2H postdose (n=24)	0.78 (± 0.77)			
Day 1, 2-4H postdose (n=49)	0.91 (± 1.77)			
Day 15, 0-2H postdose (n=59)	1.13 (± 1.20)			
Day 15, 2-4H postdose (n=59)	2.07 (± 1.96)			

Day 21, Predose (n=59)	0.86 (± 0.66)			
Day 21, 0-2H postdose (n=58)	1.50 (± 1.77)			
Day 21, 2-4H postdose (n=60)	3.08 (± 2.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Relevant Metabolites, 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) and 11- carboxy-Δ9-tetrahydrocannabinol (11-COOH-THC), for Δ9-tetrahydrocannabinol (THC)

End point title	Plasma Concentrations for Relevant Metabolites, 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) and 11- carboxy-Δ9-tetrahydrocannabinol (11-COOH-THC), for Δ9-tetrahydrocannabinol (THC)
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End point description:

Plasma concentrations were assessed using blood samples collected at the timepoints specified.

End point type	Secondary
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End point timeframe:

Period 1:Day 1: predose,0-2 and 2-4 hours (hr) postdose. Day 15: 0-2 and 2-4 hr postdose. Day 21: predose,0-1 and 2-3 hr postdose. Period 2:Day 31: predose,0-2 and 2-4 hr postdose. Day 45: 0-2 and 2-4 hr postdose. Day 51: predose,0-1 and 2-3 hr postdose

End point values	Nabiximols			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
11-OH-THC: Day 1, Predose (n=4)	1.31 (± 1.87)			
11-OH-THC: Day 1, 0-2H postdose (n=23)	1.17 (± 1.52)			
11-OH-THC: Day 1, 2-4H postdose (n=51)	0.79 (± 1.00)			
11-OH-THC: Day 15, 0-2H postdose (n=58)	2.12 (± 1.92)			
11-OH-THC: Day 15, 2-4H postdose (n=58)	2.91 (± 2.23)			
11-OH-THC: Day 21, Predose (n=59)	1.77 (± 1.42)			
11-OH-THC: Day 21, 0-2H postdose (n=58)	2.22 (± 1.66)			
11-OH-THC: Day 21, 2-4H postdose (n=59)	3.75 (± 3.10)			
11-COOH-THC: Day 1 Predose (n=4)	19.54 (± 32.94)			
11-COOH-THC: Day 1, 0-2H postdose (n=25)	10.53 (± 24.16)			
11-COOH-THC: Day 1, 2-4H postdose (n=51)	6.49 (± 9.91)			
11-COOH-THC: Day 15, 0-2H postdose (n=59)	63.75 (± 47.02)			

11-COOH-THC: Day 15, 2-4H postdose (n=59)	66.86 (± 45.23)			
11-COOH-THC: Day 21, Predose (n=60)	77.59 (± 74.28)			
11-COOH-THC: Day 21, 0-2H postdose (n=60)	70.53 (± 68.49)			
11-COOH-THC: Day 21, 2-4H postdose (n=60)	76.31 (± 59.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Cannabidiol (CBD)

End point title	Plasma Concentrations for Cannabidiol (CBD)
End point description: Plasma concentrations were assessed using blood samples collected at the timepoints specified.	
End point type	Secondary
End point timeframe: Period 1:Day 1: predose,0-2 and 2-4 hours (hr) postdose. Day 15: 0-2 and 2-4 hr postdose. Day 21: predose,0-1 and 2-3 hr postdose. Period 2:Day 31: predose,0-2 and 2-4 hr postdose. Day 45: 0-2 and 2-4 hr postdose. Day 51: predose,0-1 and 2-3 hr postdose	

End point values	Nabiximols			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, Predose (n=4)	0.24 (± 0.16)			
Day 1, 0-2H postdose (n=21)	0.46 (± 0.55)			
Day 1, 2-4H postdose (n=45)	0.51 (± 0.94)			
Day 15, 0-2H postdose (n=59)	1.11 (± 0.84)			
Day 15, 2-4H postdose (n=59)	1.68 (± 1.29)			
Day 21, Predose (n=60)	1.01 (± 0.80)			
Day 21, 0-2H postdose (n=58)	1.40 (± 1.28)			
Day 21, 2-4H postdose (n=60)	2.42 (± 2.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations for Relevant Metabolites, 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD), for Cannabidiol (CBD)

End point title	Plasma Concentrations for Relevant Metabolites, 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD), for Cannabidiol (CBD)
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End point description:

Plasma concentrations were assessed using blood sample collected at the timepoints specified.

End point type	Secondary
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End point timeframe:

Period 1: Day 1: predose, 0-2 and 2-4 hours (hr) postdose. Day 15: 0-2 and 2-4 hr postdose. Day 21: predose, 0-1 and 2-3 hr postdose. Period 2: Day 31: predose, 0-2 and 2-4 hr postdose. Day 45: 0-2 and 2-4 hr postdose. Day 51: predose, 0-1 and 2-3 hr postdose

End point values	Nabiximols			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: ng/mL				
arithmetic mean (standard deviation)				
7-OH-CBD: Day 1, Predose (n=2)	0.18 (± 0.07)			
7-OH-CBD: Day 1, 0-2H postdose (n=13)	0.59 (± 1.00)			
7-OH-CBD: Day 1, 2-4H postdose (n=34)	0.27 (± 0.24)			
7-OH-CBD: Day 15, 0-2H postdose (n=59)	1.14 (± 0.66)			
7-OH-CBD: Day 15, 2-4H postdose (n=59)	1.33 (± 0.76)			
7-OH-CBD: Day 21, Predose (n=60)	1.15 (± 0.80)			
7-OH-CBD: Day 21, 0-2H postdose (n=58)	1.22 (± 0.82)			
7-OH-CBD: Day 21, 2-4H postdose (n=60)	1.59 (± 0.98)			
7-COOH-CBD: Day 1, Predose (n=60)	7.06 (± 4.91)			
7-COOH-CBD: Day 1, 0-2H postdose (n=60)	15.67 (± 47.41)			
7-COOH-CBD: Day 1, 2-4H postdose (n=60)	4.49 (± 3.50)			
7-COOH-CBD: Day 15, 0-2H postdose (n=60)	76.84 (± 47.81)			
7-COOH-CBD: Day 15, 2-4H postdose (n=60)	79.78 (± 46.27)			
7-COOH-CBD: Day 21, Predose (n=60)	88.95 (± 69.64)			
7-COOH-CBD: Day 21, 0-2H postdose (n=60)	78.04 (± 62.73)			
7-COOH-CBD: Day 21, 2-4H postdose (n=60)	88.32 (± 62.52)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse event (TEAE) data were collected from baseline (predose Day 1 of Treatment Period 1) up to Day 51 (end of treatment of Treatment Period 2).

Adverse event reporting additional description:

A TEAE is an adverse event that started, or worsened in severity or seriousness, following the first dose of the investigational medicinal product.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Nabiximols
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Nabiximols	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 66 (1.52%)	1 / 65 (1.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Facial spasm			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nabiximols	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 66 (28.79%)	3 / 65 (4.62%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 66 (15.15%)	1 / 65 (1.54%)	
occurrences (all)	10	1	
Somnolence			
subjects affected / exposed	4 / 66 (6.06%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 66 (7.58%)	1 / 65 (1.54%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2019	Clarified the use of a single central safety laboratory, implemented minor edits to the synopsis, and incorporated additional guidance on trial procedures
11 May 2020	Primary and secondary endpoints were updated and minor edits regarding trial procedures, statistical considerations, patient eligibility and prohibited therapy, and dose titrations were incorporated
02 September 2021	Minor updates were made to sections describing trial procedures, patient eligibility and prohibited therapy, statistical considerations, and trial monitoring

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported