

**Clinical trial results:**

A phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group clinical trial to investigate the efficacy and safety of BX-1 for the symptomatic relief of spasticity in patients with multiple sclerosis

Summary

EudraCT number	2018-000001-23
Trial protocol	HU CZ ES
Global end of trial date	30 March 2021

Results information

Result version number	v1 (current)
This version publication date	23 March 2022
First version publication date	23 March 2022

Trial information**Trial identification**

Sponsor protocol code	DroSpas-1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03756974
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bionorica SE
Sponsor organisation address	Kerschensteinerstr. 11-15, Neumarkt, Germany, 92318
Public contact	R&D, Bionorica SE, 0049 918123190, info@bionorica.de
Scientific contact	Christine Neubauer, Bionorica SE, 0049 9181231541, christine.neubauer@bionorica.de

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	07 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2021
Global end of trial reached?	Yes
Global end of trial date	30 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial objective was to investigate the efficacy and safety of orally administered BX-1 compared to placebo in patients with spasticity due to multiple sclerosis not sufficiently controlled by current anti-spasticity medication.

Protection of trial subjects:

The trial was conducted in accordance with the protocol and its amendments, the ethical principles of the Declaration of Helsinki (2013) as well as with the valid national law(s) of the participating countries, with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (ICH-E6[R2]), and with the EU Commission Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 February 2019
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	Czechia: 218
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Hungary: 69
Country: Number of subjects enrolled	Poland: 188
Worldwide total number of subjects	507
EEA total number of subjects	507

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)	494
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

548 subjects planned to be enrolled in approximately 50 sites in 5 European countries to randomise 384 subjects. 507 subjects were enrolled in 39 active sites in 5 European countries: Poland (10 sites), Hungary (9 sites), Germany (5 sites), Czech Republic (11 sites) and Spain (4 sites), 397 subjects were randomised.

Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 507 subjects were enrolled to the trial. 41 subjects were screening failures, 14 subjects were Lead-in criterion failures, 1 subject met Lead-in criterion but without placebo intake, 9 subjects were Lead-in failures and 45 subjects were Randomisation criterion failures

Pre-assignment period milestones

Number of subjects started	507
Number of subjects completed	397

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failures: 41
Reason: Number of subjects	Lead-in criterion failures: 14
Reason: Number of subjects	Lead-in criterion but without placebo intake: 1
Reason: Number of subjects	Lead-in failures: 9
Reason: Number of subjects	Randomisation criterion failures: 45

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Overall - BX-1

Arm description:

BX-1 containing dronabinol 25 mg/ml, oral solution

Oral administration 3 times per day, starting with 2 strokes per intake time (equivalent to 5 mg dronabinol per day). During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day (equivalent to 30 mg dronabinol per day) for establishing individual optimal doses to be continued during the maintenance period.

Arm type	Active comparator
Investigational medicinal product name	Dronabinol (Delta-9-tetrahydrocannabinol; THC)
Investigational medicinal product code	BX-1
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

BX-1 containing dronabinol 25 mg/ml, oral solution

Dose dispenser: 1 stroke/drop corresponds to 33 µl (833 µg dronabinol)

Starting dosage: 6 strokes (3 x 2 strokes) per day, equivalent to 5 mg dronabinol per day
Maximum dosage: 36 strokes (3 x 12 strokes) per day, equivalent to 30 mg dronabinol per day

Arm title	Overall - Placebo
Arm description:	
Placebo, oral solution	
Oral administration 3 times per day, starting with 2 strokes per intake time. During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day for establishing individual optimal doses to be continued during the maintenance period.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

oral solution

Dose dispenser

Starting dosage: 6 strokes (3 x 2 strokes) per day

Maximum dosage: 36 strokes (3 x 12 strokes) per day

Number of subjects in period 1^[1]	Overall - BX-1	Overall - Placebo
Started	197	200
Completed	177	187
Not completed	20	13
Consent withdrawn by subject	7	4
Adverse event, non-fatal	9	5
Other	1	1
Adverse event, serious non-fatal	1	-
Lost to follow-up	-	1
Lack of efficacy	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Prior randomization there is a screening and placebo lead-in period. Therefore a total of 507 subjects have been enrolled/screened, but only 397 were randomized to BX-1 or placebo at baseline.

Baseline characteristics

Reporting groups

Reporting group title	Overall - BX-1
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Reporting group description:

BX-1 containing dronabinol 25 mg/ml, oral solution

Oral administration 3 times per day, starting with 2 strokes per intake time (equivalent to 5 mg dronabinol per day). During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day (equivalent to 30 mg dronabinol per day) for establishing individual optimal doses to be continued during the maintenance period.

Reporting group title	Overall - Placebo
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Reporting group description:

Placebo, oral solution

Oral administration 3 times per day, starting with 2 strokes per intake time. During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day for establishing individual optimal doses to be continued during the maintenance period.

Reporting group values	Overall - BX-1	Overall - Placebo	Total
Number of subjects	197	200	397
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 year)	0	0	0
From 18 - 64 years	195	196	391
From 65 – 84 years	2	4	6
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: years			
arithmetic mean	50.6	50	
standard deviation	± 8.52	± 8.85	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	61	64	125
Male	136	136	272

End points

End points reporting groups

Reporting group title	Overall - BX-1
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Reporting group description:

BX-1 containing dronabinol 25 mg/ml, oral solution

Oral administration 3 times per day, starting with 2 strokes per intake time (equivalent to 5 mg dronabinol per day). During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day (equivalent to 30 mg dronabinol per day) for establishing individual optimal doses to be continued during the maintenance period.

Reporting group title	Overall - Placebo
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Reporting group description:

Placebo, oral solution

Oral administration 3 times per day, starting with 2 strokes per intake time. During the titration period, individual doses could be increased up to a maximum dose of 12 strokes 3 times per day for establishing individual optimal doses to be continued during the maintenance period.

Subject analysis set title	Overall - BX-1 x Safety Set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety set (SAF) was defined as all patients who took at least one dose of IMP starting with V2. Patients in the SAF were analysed as treated based on treatment taken during Titration/Maintenance period. Respective safety analysis for the Lead-in phase are displayed separately. Details are given in the SAP.

Subject analysis set title	Overall - Placebo x Safety Set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety set (SAF) was defined as all patients who took at least one dose of IMP starting with V2. Patients in the SAF were analysed as treated based on treatment taken during Titration/Maintenance period. Respective safety analysis for the Lead-in phase are displayed separately. Details are given in the SAP.

Subject analysis set title	Overall - BX-1 x Full Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The full analysis set (FAS) set was defined as all randomised patients who received at least one dose of IMP during titration/maintenance period and had baseline measurement of NRS-S. Patients in the FAS are analysed as randomised.

Subject analysis set title	Overall - Placebo x Full Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The full analysis set (FAS) set was defined as all randomised patients who received at least one dose of IMP during titration/maintenance period and had baseline measurement of NRS-S. Patients in the FAS are analysed as randomised.

Subject analysis set title	Overall - BX-1 x Per Protocol Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The per-protocol set (PPS) was defined as patients from FAS who sufficiently complied with the study protocol. This set was defined prior to the unblinding of the treatment assignments. Major protocol violations were agreed at blind data review meeting prior to the database closure. Patients in the PPS were analysed as treated.

Subject analysis set title	Overall - Placebo x Per Protocol Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The per-protocol set (PPS) was defined as patients from FAS who sufficiently complied with the study protocol. This set was defined prior to the unblinding of the treatment assignments. Major protocol violations were agreed at blind data review meeting prior to the database closure. Patients in the PPS were analysed as treated.

Primary: NRS-S Response-Rate

End point title	NRS-S Response-Rate
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End point description:

Proportion of patients showing improvement in spasticity (change from baseline corresponding to the mean NRS-S score during 7 days prior to randomisation) of 18% or more in average NRS-S assessment at the end of treatment (mean NRS-S score during 7 days prior to Visit 6)

End point type	Primary
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End point timeframe:

16 weeks

End point values	Overall - BX-1 x Full Analysis Set	Overall - Placebo x Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	200		
Units: [%]				
number (not applicable)				
Response Rate	43.1	47		

Statistical analyses

Statistical analysis title	Fisher Exact, Full analysis set.
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Statistical analysis description:

The response rates and exact unconditional 95% confidence intervals will be presented for treatment groups. The difference of the response rates and p-value of Fisher's exact test will be presented. Number of non-responders due to missing assessments and due to < 18% improvement will be included. This percentage will be based on total number of non-responders.

Comparison groups	Overall - Placebo x Full Analysis Set v Overall - BX-1 x Full Analysis Set
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4805
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs with onset after the first IMP intake after randomisation (Visit 2) up to and including the last IMP intake (Visit 6/EOT) were defined as TEAEs in this trial.

Adverse event reporting additional description:

All AEs with onset after the first IMP intake after randomisation (Visit 2) up to and including the last IMP intake (Visit 6/EOT) were defined as TEAEs in this trial.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Overall - Placebo x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with Placebo

Reporting group title	Overall - BX-1 x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with BX-1

Serious adverse events	Overall - Placebo x Safety Set	Overall - BX-1 x Safety Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 200 (3.00%)	4 / 197 (2.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar syndrome			

subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
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	4 / 200 (2.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall - Placebo x Safety Set	Overall - BX-1 x Safety Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 200 (44.00%)	133 / 197 (67.51%)	
Vascular disorders			
Flushing			

subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	2 / 200 (1.00%)	2 / 197 (1.02%)	
occurrences (all)	2	2	
Hypotension			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 200 (4.00%)	22 / 197 (11.17%)	
occurrences (all)	9	24	
Chest discomfort			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	8 / 200 (4.00%)	10 / 197 (5.08%)	
occurrences (all)	8	10	
Gait disturbance			
subjects affected / exposed	2 / 200 (1.00%)	3 / 197 (1.52%)	
occurrences (all)	2	3	
Peripheral swelling			
subjects affected / exposed	1 / 200 (0.50%)	2 / 197 (1.02%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Feeling hot			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Feeling drunk			

subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 197 (0.51%) 1	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 197 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Respiratory tract inflammation subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1 1 / 200 (0.50%) 1	0 / 197 (0.00%) 0 0 / 197 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Apathy subjects affected / exposed occurrences (all) Hallucination, visual subjects affected / exposed occurrences (all) Disorientation subjects affected / exposed occurrences (all) Initial insomnia subjects affected / exposed occurrences (all) Insomnia	2 / 200 (1.00%) 2 0 / 200 (0.00%) 0 0 / 200 (0.00%) 0 1 / 200 (0.50%) 1 0 / 200 (0.00%) 0 0 / 200 (0.00%) 0 0 / 200 (0.00%) 0 0 / 200 (0.00%) 0	3 / 197 (1.52%) 3 1 / 197 (0.51%) 1 2 / 197 (1.02%) 2 0 / 197 (0.00%) 0 1 / 197 (0.51%) 1 1 / 197 (0.51%) 1 1 / 197 (0.51%) 1	

subjects affected / exposed	2 / 200 (1.00%)	1 / 197 (0.51%)	
occurrences (all)	2	1	
Mood altered			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Nervousness			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Psychomotor retardation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Tension			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Blood urine present			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Occult blood positive			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	

Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Medication error			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	3 / 200 (1.50%)	2 / 197 (1.02%)	
occurrences (all)	4	2	
Contusion			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Post-traumatic pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	3	
Balance disorder			
subjects affected / exposed	5 / 200 (2.50%)	7 / 197 (3.55%)	
occurrences (all)	5	9	
Cognitive disorder			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	3	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	

Disturbance in attention subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	3 / 197 (1.52%) 3
Headache subjects affected / exposed occurrences (all)	7 / 200 (3.50%) 8	5 / 197 (2.54%) 7
Dysarthria subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 197 (1.02%) 2
Dizziness subjects affected / exposed occurrences (all)	4 / 200 (2.00%) 4	33 / 197 (16.75%) 40
Neuralgia subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	1 / 197 (0.51%) 2
Muscle spasticity subjects affected / exposed occurrences (all)	8 / 200 (4.00%) 9	7 / 197 (3.55%) 7
Multiple sclerosis relapse subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	2 / 197 (1.02%) 2
Monoparesis subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 197 (0.51%) 1
Hypotonia subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 2	3 / 197 (1.52%) 3
Somnolence subjects affected / exposed occurrences (all)	4 / 200 (2.00%) 4	10 / 197 (5.08%) 10
Speech disorder subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 197 (0.51%) 1
Tension headache subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 197 (0.51%) 1

Sciatica			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Uhthoff's phenomenon			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 200 (4.50%)	22 / 197 (11.17%)	
occurrences (all)	9	25	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Anal incontinence			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	4 / 200 (2.00%)	4 / 197 (2.03%)	
occurrences (all)	4	4	
Aphthous ulcer			

subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)
occurrences (all)	1	0
Diarrhoea		
subjects affected / exposed	0 / 200 (0.00%)	9 / 197 (4.57%)
occurrences (all)	0	10
Dry mouth		
subjects affected / exposed	0 / 200 (0.00%)	6 / 197 (3.05%)
occurrences (all)	0	6
Diarrhoea haemorrhagic		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Flatulence		
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorder		
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)
occurrences (all)	1	0
Haemorrhoids		
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)
occurrences (all)	1	0
Paraesthesia oral		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	2
Nausea		
subjects affected / exposed	0 / 200 (0.00%)	5 / 197 (2.54%)
occurrences (all)	0	6
Irritable bowel syndrome		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Vomiting		
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)
occurrences (all)	0	2
Toothache		
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)
occurrences (all)	1	0
Skin and subcutaneous tissue disorders		

Dermatitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Urinary incontinence			

subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 200 (1.00%)	0 / 197 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	8 / 200 (4.00%)	4 / 197 (2.03%)	
occurrences (all)	9	4	
Bursitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Metatarsalgia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Muscle tightness			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			

subjects affected / exposed	3 / 200 (1.50%)	2 / 197 (1.02%)	
occurrences (all)	3	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	3 / 200 (1.50%)	10 / 197 (5.08%)	
occurrences (all)	3	12	
Tenosynovitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Synovial cyst			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 200 (1.00%)	2 / 197 (1.02%)	
occurrences (all)	2	2	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	3 / 200 (1.50%)	4 / 197 (2.03%)	
occurrences (all)	3	4	
Bronchitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Cystitis			
subjects affected / exposed	2 / 200 (1.00%)	2 / 197 (1.02%)	
occurrences (all)	2	2	
Herpes simplex			
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	

Hordeolum		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Laryngitis		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	3 / 200 (1.50%)	5 / 197 (2.54%)
occurrences (all)	3	6
Oral herpes		
subjects affected / exposed	2 / 200 (1.00%)	0 / 197 (0.00%)
occurrences (all)	2	0
Pharyngitis		
subjects affected / exposed	0 / 200 (0.00%)	2 / 197 (1.02%)
occurrences (all)	0	2
Pneumonia		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Pulpitis dental		
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Rhinitis		
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)
occurrences (all)	1	1
Tonsillitis		
subjects affected / exposed	1 / 200 (0.50%)	1 / 197 (0.51%)
occurrences (all)	1	1
Upper respiratory tract infection		
subjects affected / exposed	4 / 200 (2.00%)	2 / 197 (1.02%)
occurrences (all)	4	2

Viral infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	7 / 200 (3.50%)	4 / 197 (2.03%)	
occurrences (all)	7	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 200 (1.00%)	3 / 197 (1.52%)	
occurrences (all)	2	3	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Polydipsia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 197 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2018	<p>GLOBAL PROTOCOL AMENDMENT NO. 1: Section concerned: Changes/Modifications</p> <p>Section 9.1.8 Previous and concomitant therapy and non-drug therapy: - Previous and concomitant therapy item 6 was re-worded: in order to not interfere with treatment of MS relapses according to standard care alteration of systemic corticosteroid use is allowed in case of treatment of MS relapses - Not allowed previous and concomitant therapy item 5 parenteral and intrathecal corticosteroid use was deleted in order to not interfere with treatment of MS relapses according to standard care</p> <p>Section 9.4 Laboratory measurements: due to stability of investigated parameters in urine samples drug abuse screening tests have to be performed at the trial site instead of the central laboratory, therefore instructions were changed</p> <p>Section 11.3.2 Emergency Cases and Unblinding: it was deleted that need of unblinding has to be discussed in each individual case and specified that decision lies in the responsibility of the investigator with promptly information of the sponsor</p> <p>Further corrections and specifications: - Correction of minor spelling and formal errors - Completion and correction of chapter 2 "Administrative Structure" - For unification between documents IWRS was re-named as IVRS - For clarification section "concomitant therapy" was renamed to "previous and concomitant therapy" - Responder definition for primary endpoint was unified to improvement of 18% or more / at least 18% - Wording of in- and exclusion criteria was unified between trial synopsis and continuous text - Section 8.7 Screening failure, lead-in failure and randomisation failure: for randomisation criteria failure it was specified that end-of-treatment visit has to be performed and trial termination page need to be completed - Section 9.8.1 Visit 0 (V0): Screening Visit: it was added that the patient number has to be obtained via IVRS</p>

12 June 2019	<p>GLOBAL PROTOCOL AMENDMENT NO. 2: Section concerned: Changes/Modifications</p> <p>Section 8.3 Exclusion Criteria No. 11: for the evaluation of the renal function, the parameter was changed from creatinine clearance <50 mL/min to estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m².</p> <p>Section 9.3.3 Electrocardiogram (ECG): the specifications for recording the ECG were deleted, since no evaluation of individual parameters is required.</p> <p>Section 11.6 Drug Compliance: it was corrected that the compliance for the maintenance and treatment phase can be calculated according to the trial design only starting from visit 4.</p> <p>Statistical adaptations according to the Statistical Analysis Plan were performed in the following sections:</p> <ul style="list-style-type: none"> - 12.2.1 Analysis sets - 12.2.5 Other analysis - 12.2.6 Subgroup analyses <p>The following sections have been amended to provide a better understanding of the protocol:</p> <ul style="list-style-type: none"> - 7.5.2 Dosage schedule - 8.2 Inclusion Criteria No. 3, 7 and 8 - 8.4 Patients of childbearing potential - 8.7 Screening failure, lead-in failure and randomisation failure - 9.1.4 Multiple Sclerosis - 9.1.6 Expanded Disability Status Scale (EDSS) - 9.1.8 Previous and concomitant medication and non-drug therapy - 9.2.4 Timed 25-Foot Walk Test (T25-FW) - 11.6 Drug Compliance <p>Further corrections and specifications:</p> <ul style="list-style-type: none"> - Completion and correction of chapter 2 "Administrative Structure" - Adaptation of the time schedule <p>Correction of minor spelling and formal errors</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported