



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 |
|-----------------------|-----------|

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 |
|-----------------------|----------------|

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 |
|-----------------------|-------------------|

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 |
|-----------------------|----------------|

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 |
|-----------------------|-------------------|

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 |
|----------------------------|-----------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

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 |
|----------------------------|--------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

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 |
|----------------------------|------------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

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 |
|----------------------------|---------------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

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 |
|----------------------------|-----------------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

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 |
|----------------------------|--------------------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

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 |
|-----------------|---------------------|

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 |
|----------------|---------|

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. |
|----------------------------|----------------------------------|

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 |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Overall - Placebo x Safety Set |
|-----------------------|--------------------------------|

Reporting group description:

Subjects in the Safety Set treated with Placebo

| | |
|-----------------------|-----------------------------|
| Reporting group title | Overall - BX-1 x Safety Set |
|-----------------------|-----------------------------|

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

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|-----------------------------|-----------------|-----------------|--|
| 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 | | | |

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|---|-----------------|-----------------|--|
| 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> |

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| 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> |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported