



Clinical trial results:

Multicenter, Randomized, Double-blind, Parallel-group, Add-on, Superiority Study to Compare the Efficacy and Safety of Ponesimod to Placebo in Subjects with Active Relapsing Multiple Sclerosis Who Are Treated With Dimethyl Fumarate (Tecfidera)

Summary

| | |
|--------------------------|---|
| EudraCT number | 2012-000541-12 |
| Trial protocol | DE PT DK HU CZ AT ES GR BG FR PL FI BE HR |
| Global end of trial date | 30 March 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 08 April 2021 |
| First version publication date | 08 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-058B302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02907177 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.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 | 30 March 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine whether add-on therapy with ponesimod reduced relapse frequency as compared to placebo in subjects with active Relapsing Multiple Sclerosis (RMS) who were treated with dimethyl fumarate (DMF) (Tecfidera).

Protection of trial subjects:

The study was conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted. Safety evaluations included adverse events assessment through out the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 February 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Austria: 12 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Czechia: 33 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Mexico: 1 |
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | Russian Federation: 6 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 136 |
| EEA total number of subjects | 106 |

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) | 136 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 136 subjects were randomized, 68 in both arms (ponesimod 20mg plus DMF [dimethyl fumarate] & placebo plus DMF). Of 136 subjects, 107 (50 in ponesimod 20mg plus DMF; 57 in placebo plus DMF) completed study till early termination.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Ponesimod plus dimethyl fumarate (DMF) |

Arm description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ponesimod |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ponesimod 2-10 mg was administered as per titration sequence once daily from Day 1 to 14. Ponesimod 20 mg was administered once daily as maintenance dose from Day 15 to Week 156.

| | |
|--|-------------------------|
| Investigational medicinal product name | dimethyl fumarate (DMF) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subject continued receiving DMF as background therapy.

| | |
|------------------|--------------------------------------|
| Arm title | Placebo plus dimethyl fumarate (DMF) |
|------------------|--------------------------------------|

Arm description:

Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching Placebo was administered as per titration sequence once daily from Day 1 to 14 and

maintenance dose from Day 15 to Week 156.

| | |
|--|-------------------------|
| Investigational medicinal product name | dimethyl fumarate (DMF) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subject continued receiving DMF as background therapy.

| Number of subjects in period 1 | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) |
|---------------------------------------|--|--|
| Started | 68 | 68 |
| Treated | 67 | 68 |
| Randomized analysis set | 68 | 68 |
| Completed | 0 | 0 |
| Not completed | 68 | 68 |
| Adverse event, serious fatal | - | 1 |
| Physician decision | 3 | 3 |
| Sponsor's Decision | 50 | 57 |
| Withdrawal by subject | 15 | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Ponesimod plus dimethyl fumarate (DMF) |
|-----------------------|--|

Reporting group description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Placebo plus dimethyl fumarate (DMF) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| Reporting group values | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | Total |
|---|--|--------------------------------------|-------|
| Number of subjects | 68 | 68 | 136 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 68 | 68 | 136 |
| From 65 to 84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 37.8 | 38.1 | |
| standard deviation | ± 9.1 | ± 9.1 | - |
| Title for Gender Units: subjects | | | |
| Female | 43 | 46 | 89 |
| Male | 25 | 22 | 47 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Ponesimod plus dimethyl fumarate (DMF) |
| Reporting group description: Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy. | |
| Reporting group title | Placebo plus dimethyl fumarate (DMF) |
| Reporting group description: Subjects received matching placebo once daily during Days 1 to 14 and maintenance dose from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy. | |

Primary: Annualized Confirmed Relapse Rate (ARR)

| | |
|---|---|
| End point title | Annualized Confirmed Relapse Rate (ARR) |
| End point description: Relapse: occurrence of acute episode of one or more new worsened symptoms of Multiple sclerosis (MS), not linked to fever/infection, lasting 24 hours after stable 30 days. Confirmed relapse: increase from baseline at least 0.5 Expanded Disability Status Scale (EDSS) score or one point in 1, 2 or 3 Functional Systems (FS), excluding bowel/bladder and cerebral/mental FS. EDSS and FS scores are based on neurological examination (NE) for rating its impairment in MS. Among 8 FS, 7 are ordinal clinical rating scales range 0-5 or 6 with higher scale indicates overall functional impairment assessing Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel/Bladder functions. Rating individual FS scores used to rate EDSS in link with observations, information concerning gait and use of assistance. EDSS is ordinal clinical rating scale from 0 (normal NE) to 10 (deaths). Full Analysis Set (FAS) included all randomized subjects who had at least one dose of study treatment and post baseline efficacy | |
| End point type | Primary |
| End point timeframe: From randomization up to End of Study | |

| End point values | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | | |
|---|--|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 ^[1] | 67 ^[2] | | |
| Units: Relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.237 (0.144 to 0.391) | 0.187 (0.109 to 0.322) | | |

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Ponesimod plus dimethyl fumarate (DMF) v Placebo plus dimethyl fumarate (DMF) |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5252 |
| Method | Negative binomial regression |
| Parameter estimate | Treatment effect (Rate Ratio) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.608 |
| upper limit | 2.654 |

Secondary: 12-Week Confirmed Disability Accumulation (CDA) as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

| | |
|-----------------|--|
| End point title | 12-Week Confirmed Disability Accumulation (CDA) as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96) |
|-----------------|--|

End point description:

12-Week CDA as assessed by Kaplan Meier estimate (Percentage of Subjects Week 96) was defined as an increase of at least 1.5 in Expanded Disability Status Scale (EDSS) for subjects with a baseline EDSS score of 0.0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for participants with a baseline EDSS score greater than or equal to (\geq) 5.5, which was confirmed after 12 weeks. Baseline EDSS was defined as the last EDSS score recorded prior to randomization. EDSS is an ordinal clinical rating scale ranging from 0 (normal neurological examination) to 10 (death due to MS). FAS included all randomized subjects who had at least one dose of study treatment and had one post baseline efficacy assessment. Subjects were analyzed according to randomized treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 96

| End point values | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | | |
|--|--|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 ^[3] | 67 ^[4] | | |
| Units: Percentage of subjects with a CDA | | | | |
| number (confidence interval 95%) | 18.7 (8.7 to 37.6) | 11.9 (4.6 to 28.8) | | |

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96)

| | |
|--|--|
| End point title | Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96) |
| End point description: Time to First Confirmed Relapse as Assessed by Kaplan Meier Estimate (Percentage of Subjects at Week 96) was reported. The time to first confirmed relapse (in days) is defined as [Date of first confirmed relapse minus Date of randomization plus 1] in days. FAS included all randomized subjects who were treated with at least one dose of study treatment and had at least one post baseline efficacy assessment. Subjects were analyzed according to randomized treatment. | |
| End point type | Secondary |
| End point timeframe: Week 96 | |

| End point values | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | | |
|----------------------------------|--|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66 ^[5] | 67 ^[6] | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 33.6 (19.5 to 53.8) | 25.7 (13.4 to 46.1) | | |

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) as a Measure of Safety and Tolerability

| | |
|---|--|
| End point title | Number of Subjects With Adverse Events (AEs) as a Measure of Safety and Tolerability |
| End point description: An AE is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment. | |
| End point type | Secondary |
| End point timeframe: Up to 147 Weeks | |

| End point values | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | | |
|-----------------------------|--|--------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 68 | | |
| Units: Number of Subjects | 48 | 53 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to End of treatment + 15 days (maximum up to 147 Weeks)

Adverse event reporting additional description:

Treatment-Emergent Adverse Events (TEAEs) included deaths, Serious Adverse Events (SAEs), Adverse Events (AEs) leading to premature treatment discontinuation, and Adverse Events of Special Interest (AESIs) were summarized. Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Ponesimod plus dimethyl fumarate (DMF) |
|-----------------------|--|

Reporting group description:

Subjects were up-titrated during Days 1 to 14 with 2 to 10 mg of ponesimod once daily and maintenance dose of 20 mg ponesimod tablets once daily from Day 15 to end of treatment. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Placebo plus dimethyl fumarate (DMF) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects were up-titrated during Days 1 to 14 and maintenance dose form Day 15 to end of treatment with matching placebo once daily. In addition, subjects also continued receiving DMF capsules, orally, as background therapy.

| Serious adverse events | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | |
|---|--|--------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 7 / 68 (10.29%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Testicle Adenoma | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Multiple Injuries | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Procedural Nausea | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon Rupture | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| 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 | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status Epilepticus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide Attempt | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary Retention | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Exostosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastroenteritis Bacterial | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 68 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia Influenzal | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Pseudomonal | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 68 (1.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Ponesimod plus dimethyl fumarate (DMF) | Placebo plus dimethyl fumarate (DMF) | |
|---|--|--------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 67 (67.16%) | 41 / 68 (60.29%) | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 1 / 68 (1.47%) | |
| occurrences (all) | 6 | 3 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | 1 / 68 (1.47%) | |
| occurrences (all) | 7 | 1 | |
| Headache | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 6 / 68 (8.82%) | |
| occurrences (all) | 7 | 9 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 6 / 68 (8.82%) | |
| occurrences (all) | 0 | 7 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 68 (5.88%) | |
| occurrences (all) | 4 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 7 / 68 (10.29%) | |
| occurrences (all) | 4 | 7 | |
| Back Pain | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 6 / 68 (8.82%) | |
| occurrences (all) | 2 | 7 | |

| | | | |
|---|----------------------|------------------------|--|
| Pain in Extremity subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | 4 / 68 (5.88%) 4 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 5 | 3 / 68 (4.41%) 6 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 11 | 13 / 68 (19.12%) 16 | |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 3 / 67 (4.48%) 3 | 7 / 68 (10.29%) 7 | |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 5 | 5 / 68 (7.35%) 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 21 December 2017 | <p>The main reasons for the amendment are to make the following changes to inclusion criterion:</p> <p>1) To include the presence of at least one new or one unequivocally enlarging T2 lesion on magnetic resonance imaging (MRI) of the brain or spinal cord as an alternative criterion of disease activity. In order to assess this alternative criterion, two MRI scans have to be compared; the first MRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of dimethyl fumarate (DMF) treatment; the second MRI scan must be performed prior to randomization (i.e., MRI performed at Visit 2 [Baseline] may be used). The presence of at least one new or one unequivocally enlarging MRI T2 lesion has to be confirmed by the central MRI reading facility prior to randomization of the subject.</p> <p>2) To include the presence of MRI T1 gadolinium-enhancing (Gd+) lesions observed on the pre-randomization MRI scan of the brain as an alternative criterion of disease activity.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported