



## Clinical trial results:

**A 24-week, multicenter, exploratory, two arm study to assess the effect of Dimethyl fumarate on Immune-Modulatory Action on T cells in patients with relapsing remitting Multiple Sclerosis**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003481-25 |
| Trial protocol           | DE             |
| Global end of trial date | 07 May 2018    |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 04 January 2020 |
| First version publication date | 04 January 2020 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | DIMAT-MS |
|-----------------------|----------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | -               |
| WHO universal trial number (UTN)   | U1111-1164-2476 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Universitätsklinikum Münster  |
| Sponsor organisation address | Albert-Schweitzer-Campus 1, Gebäude D5, Münster, Germany, 48149                           |
| Public contact               | Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, Luisa.Klotz@ukmuenster.de |
| Scientific contact           | Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, Luisa.Klotz@ukmuenster.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 May 2018 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 07 May 2018 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 07 May 2018 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

This is an exploratory study design, which allows analysis of multiple immune parameters derived from peripheral blood mononuclear cells (PBMCs) from patients with relapsing remitting multiple sclerosis before and during immune-modulatory treatment with dimethyl fumarate (Tecfidera) in comparison to PBMCs from healthy subjects.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis was allowed for treatment of relapses at any time during the study as clinically warranted. Steroid treatment should consist of 3-5 days and up to 1,000 mg methylprednisolone/day intravenously.

Evidence for comparator:

Healthy subjects were used as a reference group and were not treated.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 05 June 2015 |
| 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 | Germany: 67 |
| Worldwide total number of subjects   | 67          |
| EEA total number of subjects         | 67          |

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)      | 67 |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The RRMS (relapsing remitting multiple sclerosis) patients were recruited from three university hospitals and one neurological specialist practice throughout Germany. Healthy subjects were only recruited at the Universitätsklinikum Münster. The recruitment period was from June 2015 to January 2018.

### Pre-assignment

Screening details:

The study included untreated healthy subjects and patients with RRMS according to the 2010 revised McDonald's criteria who were either treatment-naïve (i.e. no dimethyl fumarate treatment for at least 1 month) or willing to switch from conventional first-line immunomodulatory therapy (beta-interferons, glatiramer acetate) to dimethyl fumarate.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 67 |
| Number of subjects completed | 58 |

### Pre-assignment subject non-completion reasons

|                            |                                   |
|----------------------------|-----------------------------------|
| Reason: Number of subjects | Not meeting inclusion criteria: 8 |
| Reason: Number of subjects | Consent withdrawn by subject: 1   |

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |   |
|------------------|---|
| <b>Arm title</b> | Dimethyl fumarate (DMF) (RRMS patients) |
|------------------|---|

Arm description:

RRMS patients treated with dimethyl fumarate.

|  |                                |
|--|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Tecfidera                      |
| Investigational medicinal product code |                                |
| Other name                             | Dimethyl fumarate              |
| Pharmaceutical forms                   | Gastro-resistant capsule, hard |
| Routes of administration               | Oral use                       |

Dosage and administration details:

RRMS patients received dimethyl fumarate (Tecfidera) from week 0 to week 24. Dimethyl fumarate (Tecfidera®) treatment was initiated by daily administration of 120 mg Tecfidera® p.o. in the morning in week 0. At week 1, the dose was increased to 120 mg Tecfidera® p.o. twice daily, split into a morning and an evening dose. At week 2, the daily dose was further increased to 240 mg Tecfidera® p.o. in the morning and 120 mg Tecfidera® p.o. in the evening. Finally at week 3, the dose was increased to the final daily dose of 240 mg Tecfidera® p.o. in the morning and 240 mg Tecfidera® p.o. in the evening and maintained throughout the study. Study participants were able to perform an optional 24-week follow-up Phase. No study treatment was performed in the follow-up phase. However, RRMS patients were able to continue treatment with dimethyl fumarate (Tecfidera).

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | No treatment (Healthy subjects) |
|------------------|---------------------------------|

Arm description:

Healthy subjects who have not been treated.

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

| Number of subjects in period 1 <sup>[1]</sup> | Dimethyl fumarate (DMF) (RRMS patients) | No treatment (Healthy subjects) |
|---|---|---------------------------------|
|   |   |                                 |
| Started                                       | 42                                      | 16                              |
| End of core study phase (Week 24)             | 37                                      | 14                              |
| Completed                                     | 33                                      | 14                              |
| Not completed                                 | 9                                       | 2                               |
| Consent withdrawn by subject                  | 1                                       | 1                               |
| Relapse                                       | 1                                       | -                               |
| End of study after core study phase           | 2                                       | -                               |
| Adverse event, non-fatal                      | 2                                       | -                               |
| Pregnancy                                     | 2                                       | 1                               |
| Lost to follow-up                             | 1                                       | -                               |

---

**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: 51 RRMS patients were enrolled in the study and assessed for eligibility. Because 8 patients did not meet the inclusion criteria and one patient withdrew consent before start of treatment, only 42 RRMS patients entered the baseline period.

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | Dimethyl fumarate (DMF) (RRMS patients) |
| Reporting group description:<br>RRMS patients treated with dimethyl fumarate. |   |
| Reporting group title   | No treatment (Healthy subjects)         |
| Reporting group description:<br>Healthy subjects who have not been treated.   |   |

| Reporting group values                             | Dimethyl fumarate (DMF) (RRMS patients) | No treatment (Healthy subjects) | Total |
|--|---|---------------------------------|-------|
| Number of subjects                                 | 42                                      | 16                              | 58    |
| Age categorical<br>Units: Subjects                 |   |                                 |       |
| In utero   | 0                                       | 0                               | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                                       | 0                               | 0     |
| Newborns (0-27 days)                               | 0                                       | 0                               | 0     |
| Infants and toddlers (28 days-23 months)           | 0                                       | 0                               | 0     |
| Children (2-11 years)                              | 0                                       | 0                               | 0     |
| Adolescents (12-17 years)                          | 0                                       | 0                               | 0     |
| Adults (18-64 years)                               | 42                                      | 16                              | 58    |
| From 65-84 years                                   | 0                                       | 0                               | 0     |
| 85 years and over                                  | 0                                       | 0                               | 0     |
| Gender categorical<br>Units: Subjects              |   |                                 |       |
| Female   | 28                                      | 11                              | 39    |
| Male   | 14                                      | 5                               | 19    |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Dimethyl fumarate (DMF) (RRMS patients) |
| Reporting group description:<br>RRMS patients treated with dimethyl fumarate. |   |
| Reporting group title   | No treatment (Healthy subjects)         |
| Reporting group description:<br>Healthy subjects who have not been treated.   |   |

### Primary: Number of lymphocytes in PBMCs

|  |  |
|--|--|
| End point title  | Number of lymphocytes in PBMCs <sup>[1][2]</sup> |
| End point description:<br>The number of lymphocytes in the PBMC (peripheral blood mononuclear cell) population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Lymphocytes (percent of PBMCs) |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 79.13 (74.27 to 84.97)                  |  |  |  |
| Month 2 (n = 19)                      | 76.78 (73.23 to 85.05)                  |  |  |  |
| Month 4 (n = 19)                      | 77.14 (72.71 to 81.83)                  |  |  |  |
| Month 6 (n = 34)                      | 72.75 (68.18 to 81.91)                  |  |  |  |
| Month 11 (n = 19)                     | 73.76 (68.59 to 80.86)                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

**Primary: Absolute change of lymphocytes in PBMCs**

|   |   |
|---|---|
| End point title   | Absolute change of lymphocytes in PBMCs <sup>[3]</sup> <sup>[4]</sup> |
| End point description:<br>Absolute change of lymphocytes from baseline (month 0) within the PBMC population during DMF treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Lymphocytes (percent of PBMCs) |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -2.13 (-4.62 to 2.74)                   |  |  |  |
| Month 4 (n = 19)                      | -3.09 (-11.95 to 3.22)                  |  |  |  |
| Month 6 (n = 34)                      | -7.16 (-16.40 to 2.98)                  |  |  |  |
| Month 11 (n = 19)                     | -3.50 (-13.94 to 2.15)                  |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of monocytes in PBMCs**

|  |  |
|--|--|
| End point title  | Number of monocytes in PBMCs <sup>[5]</sup> <sup>[6]</sup> |
| End point description:<br>The number of monocytes in the PBMC population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.



| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Monocytes (percent of PBMCs)   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 20.83 (14.96 to 25.66)                  |  |  |  |
| Month 2 (n = 19)                      | 23.20 (14.91 to 26.71)                  |  |  |  |
| Month 4 (n = 19)                      | 22.83 (18.09 to 27.11)                  |  |  |  |
| Month 6 (n = 34)                      | 27.20 (17.62 to 31.74)                  |  |  |  |
| Month 11 (n = 19)                     | 26.08 (19.10 to 31.33)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of monocytes in PBMCs

|   |   |
|---|---|
| End point title   | Absolute change of monocytes in PBMCs <sup>[7][8]</sup> |
| End point description:<br>Absolute change of monocytes from baseline (month 0) within the PBMC population during DMF treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Monocytes (percent of PBMCs)   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | 2.15 (-2.72 to 4.54)                    |  |  |  |
| Month 4 (n = 19)                      | 2.93 (-3.22 to 11.96)                   |  |  |  |
| Month 6 (n = 34)                      | 7.13 (-2.98 to 16.24)                   |  |  |  |

|                   |                       |  |  |  |
|-------------------|-----------------------|--|--|--|
| Month 11 (n = 19) | 3.49 (-2.29 to 13.97) |  |  |  |
|-------------------|-----------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of T cells in lymphocytes

|                 |   |
|-----------------|---|
| End point title | Number of T cells in lymphocytes <sup>[9][10]</sup> |
|-----------------|---|

End point description:

The number of T cells in the lymphocyte population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: T cells (percent of Lymphocytes) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 0 (n = 34)                        | 69.17 (56.87 to 72.39)                  |  |  |  |
| Month 2 (n = 19)                        | 66.47 (63.96 to 72.69)                  |  |  |  |
| Month 4 (n = 19)                        | 69.68 (63.21 to 71.54)                  |  |  |  |
| Month 6 (n = 34)                        | 64.53 (53.87 to 71.01)                  |  |  |  |
| Month 11 (n = 19)                       | 65.23 (59.75 to 72.86)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of T cells in lymphocytes

|                 |   |
|-----------------|---|
| End point title | Absolute change of T cells in lymphocytes <sup>[11][12]</sup> |
|-----------------|---|

End point description:

Absolute change of T cells from baseline (month 0) within the lymphocytes population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: T cells (percent of Lymphocytes) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 2 (n = 19)                        | -0.21 (-3.65 to 3.30)                   |  |  |  |
| Month 4 (n = 19)                        | 2.61 (-2.69 to 6.68)                    |  |  |  |
| Month 6 (n = 34)                        | -0.91 (-10.28 to 4.37)                  |  |  |  |
| Month 11 (n = 19)                       | 0.77 (-4.19 to 7.19)                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of CD4 T cells in T cells

|                 |  |
|-----------------|--|
| End point title | Number of CD4 T cells in T cells <sup>[13][14]</sup> |
|-----------------|--|

End point description:

The number of CD4 T cells in the T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: CD4 T cells (percent of T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 0 (n = 34)                        | 72.10 (67.29 to 79.42)                  |  |  |  |
| Month 2 (n = 19)                        | 74.66 (66.82 to 81.78)                  |  |  |  |
| Month 4 (n = 19)                        | 80.64 (69.42 to 86.15)                  |  |  |  |
| Month 6 (n = 34)                        | 76.47 (72.55 to 82.83)                  |  |  |  |
| Month 11 (n = 19)                       | 80.70 (69.58 to 84.73)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of CD4 T cells in T cells

|   |   |
|---|---|
| End point title   | Absolute change of CD4 T cells in T cells <sup>[15][16]</sup> |
| End point description:<br>Absolute change of CD4 T cells from baseline (month 0) within the T cell population during DMF treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: CD4 T cells (percent of T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 2 (n = 19)                        | 0.49 (-1.61 to 2.88)                    |  |  |  |
| Month 4 (n = 19)                        | 2.60 (-1.75 to 5.52)                    |  |  |  |
| Month 6 (n = 34)                        | 4.31 (0.37 to 6.02)                     |  |  |  |

|                   |                     |  |  |  |
|-------------------|---------------------|--|--|--|
| Month 11 (n = 19) | 3.62 (1.65 to 9.15) |  |  |  |
|-------------------|---------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of CD8 T cells in T cells

|                 |  |
|-----------------|--|
| End point title | Number of CD8 T cells in T cells <sup>[17][18]</sup> |
|-----------------|--|

End point description:

The number of CD8 T cells in the T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: CD8 T cells (percent of T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 0 (n = 34)                        | 17.78 (13.55 to 23.34)                  |  |  |  |
| Month 2 (n = 19)                        | 16.62 (11.03 to 25.79)                  |  |  |  |
| Month 4 (n = 19)                        | 12.96 (7.28 to 25.02)                   |  |  |  |
| Month 6 (n = 34)                        | 15.85 (9.84 to 20.16)                   |  |  |  |
| Month 11 (n = 19)                       | 12.44 (8.00 to 22.06)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of CD8 T cells in T cells

|                 |   |
|-----------------|---|
| End point title | Absolute change of CD8 T cells in T cells <sup>[19][20]</sup> |
|-----------------|---|

End point description:

Absolute change of CD8 T cells from baseline (month 0) within the T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                        | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                         |  |  |  |
| Number of subjects analysed             | 34                                      |  |  |  |
| Units: CD8 T cells (percent of T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3))   |   |  |  |  |
| Month 2 (n = 19)                        | 0.09 (-2.15 to 2.04)                    |  |  |  |
| Month 4 (n = 19)                        | -2.13 (-4.01 to 0.30)                   |  |  |  |
| Month 6 (n = 34)                        | -2.18 (-5.16 to -0.56)                  |  |  |  |
| Month 11 (n = 19)                       | -3.63 (-8.05 to -1.22)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of naive CD4 T cells in CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Number of naive CD4 T cells in CD4 T cells <sup>[21][22]</sup> |
|-----------------|--|

End point description:

The number of naive CD4 T cells in the CD4 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 94.78 (81.69 to 95.99)                  |  |  |  |
| Month 2 (n = 19)                      | 93.82 (91.63 to 96.14)                  |  |  |  |
| Month 4 (n = 19)                      | 94.59 (91.90 to 95.73)                  |  |  |  |
| Month 6 (n = 34)                      | 91.82 (81.57 to 95.73)                  |  |  |  |
| Month 11 (n = 19)                     | 94.35 (91.52 to 95.72)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of naive CD4 T cells in CD4 T cells

|                        |   |
|------------------------|---|
| End point title        | Absolute change of naive CD4 T cells in CD4 T cells <sup>[23][24]</sup>   |
| End point description: | Absolute change of naive CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF treatment. |
| End point type         | Primary   |
| End point timeframe:   | Months 0, 2, 4, 6 and 11.   |

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.93 (-2.61 to 0.91)                   |  |  |  |
| Month 4 (n = 19)                      | -0.73 (-2.68 to 1.14)                   |  |  |  |
| Month 6 (n = 34)                      | -0.16 (-5.57 to 4.72)                   |  |  |  |

|                   |                       |  |  |  |
|-------------------|-----------------------|--|--|--|
| Month 11 (n = 19) | -0.46 (-5.63 to 6.38) |  |  |  |
|-------------------|-----------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of central memory CD4 T cells in CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Number of central memory CD4 T cells in CD4 T cells <sup>[25][26]</sup> |
|-----------------|---|

End point description:

The number of central memory CD4 T cells in the CD4 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 137.04 (67.28 to 262.87)                |  |  |  |
| Month 2 (n = 19)                      | 145.88 (77.15 to 204.24)                |  |  |  |
| Month 4 (n = 19)                      | 88.42 (46.43 to 232.67)                 |  |  |  |
| Month 6 (n = 34)                      | 71.08 (44.93 to 168.54)                 |  |  |  |
| Month 11 (n = 17)                     | 62.28 (41.54 to 95.99)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of central memory CD4 T cells in CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Absolute change of central memory CD4 T cells in CD4 T |
|-----------------|--|



End point description:

Absolute change of central memory CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF Treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -28.74 (-57.11 to 8.29)                 |  |  |  |
| Month 4 (n = 19)                      | -44.34 (-97.71 to 17.85)                |  |  |  |
| Month 6 (n = 34)                      | -69.46 (-120.78 to 9.88)                |  |  |  |
| Month 11 (n = 17)                     | -83.50 (-167.00 to -56.30)              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of effector memory CD4 T cells in CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Number of effector memory CD4 T cells in CD4 T cells <sup>[29]</sup> <sup>[30]</sup> |
|-----------------|--|

End point description:

The number of effector memory CD4 T cells in the CD4 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 113.40 (53.26 to 155.11)                |  |  |  |
| Month 2 (n = 19)                      | 126.91 (57.30 to 162.66)                |  |  |  |
| Month 4 (n = 19)                      | 67.56 (43.60 to 128.14)                 |  |  |  |
| Month 6 (n = 34)                      | 59.14 (18.41 to 123.99)                 |  |  |  |
| Month 11 (n = 17)                     | 34.47 (17.07 to 53.70)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of effector memory CD4 T cells in CD4 T cells

|  |   |
|--|---|
| End point title  | Absolute change of effector memory CD4 T cells in CD4 T |
| End point description:<br>Absolute change of memory CD4 T cells from baseline (month 0) within the CD4 T cell population during DMF Treatment. |   |
| End point type   | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |   |

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | 12.96 (-59.83 to 32.89)                 |  |  |  |
| Month 4 (n = 19)                      | -46.18 (-77.48 to 10.63)                |  |  |  |
| Month 6 (n = 34)                      | -64.68 (-94.91 to -4.67)                |  |  |  |

|                   |                            |  |  |  |
|-------------------|----------------------------|--|--|--|
| Month 11 (n = 17) | -86.80 (-115.07 to -49.35) |  |  |  |
|-------------------|----------------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of CD4 RTEs in CD4 T cells

|   |   |
|---|---|
| End point title   | Number of CD4 RTEs in CD4 T cells <sup>[33]</sup> <sup>[34]</sup> |
| End point description:<br>The number of CD4 RTEs (Recent Thymic Emigrants) in the CD4 T cell population during DMF treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 248.37 (177.33 to 395.43)               |  |  |  |
| Month 2 (n = 19)                      | 241.99 (186.56 to 323.91)               |  |  |  |
| Month 4 (n = 19)                      | 245.58 (152.32 to 307.67)               |  |  |  |
| Month 6 (n = 34)                      | 200.22 (126.39 to 332.06)               |  |  |  |
| Month 11 (n = 17)                     | 225.50 (139.55 to 316.22)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of CD4 RTEs in CD4 T cells

|  |  |
|--|--|
| End point title  | Absolute change of CD4 RTEs in CD4 T cells <sup>[35]</sup> <sup>[36]</sup> |
| End point description:<br>Absolute change of CD4 RTEs from baseline (month 0) within the CD4 T cell population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -33.79 (-79.50 to 31.02)                |  |  |  |
| Month 4 (n = 19)                      | -5.73 (-110.75 to 19.93)                |  |  |  |
| Month 6 (n = 34)                      | -47.01 (-130.13 to 18.15)               |  |  |  |
| Month 11 (n = 17)                     | -39.23 (-69.11 to 10.93)                |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of naive CD8 T cells in CD8 T cells

|  |  |
|--|--|
| End point title  | Number of naive CD8 T cells in CD8 T cells <sup>[37]</sup> <sup>[38]</sup> |
| End point description:<br>The number of naive CD8 T cells in the CD8 T cell population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 60.85 (37.58 to 138.80)                 |  |  |  |
| Month 2 (n = 19)                      | 65.60 (22.20 to 126.16)                 |  |  |  |
| Month 4 (n = 19)                      | 40.48 (22.08 to 97.46)                  |  |  |  |
| Month 6 (n = 34)                      | 37.74 (22.53 to 77.30)                  |  |  |  |
| Month 11 (n = 17)                     | 37.70 (21.14 to 81.52)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Absolute change of naive CD8 T cells in CD8 T cells

|   |   |
|---|---|
| End point title   | Absolute change of naive CD8 T cells in CD8 T cells <sup>[39][40]</sup> |
| End point description:<br>Absolute change of naive CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment. |   |
| End point type  | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |

|                   |                          |  |  |  |
|-------------------|--------------------------|--|--|--|
| Month 2 (n = 19)  | -9.70 (-31.05 to 7.18)   |  |  |  |
| Month 4 (n = 19)  | -15.71 (-67.91 to 2.29)  |  |  |  |
| Month 6 (n = 34)  | -18.93 (-49.83 to 0.89)  |  |  |  |
| Month 11 (n = 17) | -25.49 (-55.25 to -4.10) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of central memory CD8 T cells in CD8 T cells

|                 |   |
|-----------------|---|
| End point title | Number of central memory CD8 T cells in CD8 T cells <sup>[41]</sup> <sup>[42]</sup> |
|-----------------|---|

End point description:

The number of central memory CD8 T cells in the CD8 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 1.97 (0.75 to 4.72)                     |  |  |  |
| Month 2 (n = 19)                      | 1.73 (0.67 to 2.80)                     |  |  |  |
| Month 4 (n = 19)                      | 0.89 (0.63 to 2.31)                     |  |  |  |
| Month 6 (n = 34)                      | 0.64 (0.36 to 2.25)                     |  |  |  |
| Month 11 (n = 17)                     | 0.35 (0.25 to 0.69)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of central memory CD8 T cells in CD8 T cells

|  |  |
|--|--|
| End point title  | Absolute change of central memory CD8 T cells in CD8 T |
| End point description:<br>Absolute change of central memory CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.81 (-1.37 to 0.02)                   |  |  |  |
| Month 4 (n = 19)                      | -0.86 (-1.91 to 0.15)                   |  |  |  |
| Month 6 (n = 34)                      | -1.16 (-1.96 to 0.16)                   |  |  |  |
| Month 11 (n = 17)                     | -1.22 (-2.29 to -0.52)                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of effector memory CD8 T cells in CD8 T cells

|  |  |
|--|--|
| End point title  | Number of effector memory CD8 T cells in CD8 T cells <sup>[45][46]</sup> |
| End point description:<br>The number of effector memory CD8 T cells in the CD8 T cell population during DMF treatment. |  |
| End point type   | Primary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 14.19 (7.65 to 27.84)                   |  |  |  |
| Month 2 (n = 19)                      | 11.65 (6.62 to 22.08)                   |  |  |  |
| Month 4 (n = 19)                      | 6.97 (3.53 to 21.58)                    |  |  |  |
| Month 6 (n = 34)                      | 5.95 (2.60 to 14.22)                    |  |  |  |
| Month 11 (n = 17)                     | 2.30 (1.63 to 5.61)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Absolute change of effector memory CD8 T cells in CD8 T cells

|                 |   |
|-----------------|---|
| End point title | Absolute change of effector memory CD8 T cells in CD8 T |
|-----------------|---|

End point description:

Absolute change of effector memory CD8 T cells from baseline (month 0) within the CD8 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[47] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |



|                   |                          |  |  |  |
|-------------------|--------------------------|--|--|--|
| Month 2 (n = 19)  | -1.05 (-10.45 to 2.85)   |  |  |  |
| Month 4 (n = 19)  | -4.77 (-11.87 to -1.17)  |  |  |  |
| Month 6 (n = 34)  | -8.58 (-16.34 to -0.57)  |  |  |  |
| Month 11 (n = 17) | -12.49 (-24.05 to -4.54) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of TEMRA in CD8 T cells

|                 |  |
|-----------------|--|
| End point title | Number of TEMRA in CD8 T cells <sup>[49]</sup> <sup>[50]</sup> |
|-----------------|--|

End point description:

The number of TEMRAs (Effector Memory RA T cells) in the CD8 T cell population during DMF treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 14.01 (6.36 to 26.86)                   |  |  |  |
| Month 2 (n = 19)                      | 5.40 (4.34 to 16.98)                    |  |  |  |
| Month 4 (n = 19)                      | 5.96 (3.55 to 23.16)                    |  |  |  |
| Month 6 (n = 34)                      | 7.27 (3.55 to 11.26)                    |  |  |  |
| Month 11 (n = 17)                     | 3.14 (1.75 to 4.86)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Absolute change of TEMRA in CD8 T cells

|  |   |
|--|---|
| End point title  | Absolute change of TEMRA in CD8 T cells <sup>[51][52]</sup> |
| End point description:<br>Absolute change of TEMRAs from baseline (month 0) within the CD8 T cell population during DMF treatment. |   |
| End point type   | Primary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |   |

Notes:

[51] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Since this is an explorative study, the endpoints were only evaluated descriptively.

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -1.00 (-6.16 to 0.39)                   |  |  |  |
| Month 4 (n = 19)                      | -2.30 (-8.56 to -0.41)                  |  |  |  |
| Month 6 (n = 34)                      | -4.79 (-15.47 to 1.82)                  |  |  |  |
| Month 11 (n = 17)                     | -6.02 (-14.17 to -2.77)                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of GM-CSF-producing CD4 T cells

|  |  |
|--|--|
| End point title  | Number of GM-CSF-producing CD4 T cells <sup>[53]</sup> |
| End point description:<br>CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of granulocyte-macrophage colony-stimulating factor (GM-CSF). |  |
| End point type   | Secondary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.  |  |

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not

evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 1.43 (0.94 to 1.76)                     |  |  |  |
| Month 2 (n = 19)                      | 1.13 (0.89 to 1.65)                     |  |  |  |
| Month 4 (n = 19)                      | 0.97 (0.71 to 1.36)                     |  |  |  |
| Month 6 (n = 34)                      | 1.02 (0.68 to 1.56)                     |  |  |  |
| Month 11 (n = 19)                     | 0.98 (0.75 to 1.25)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change of GM-CSF-producing CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Absolute change of GM-CSF-producing CD4 T cells <sup>[54]</sup> |
|-----------------|---|

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of granulocyte-macrophage colony-stimulating factor (GM-CSF).

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu\text{L}$   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.24 (-0.63 to 0.18)                   |  |  |  |
| Month 4 (n = 19)                      | -0.44 (-0.87 to -0.15)                  |  |  |  |

|                   |                        |  |  |  |
|-------------------|------------------------|--|--|--|
| Month 6 (n = 34)  | -0.16 (-0.81 to 0.37)  |  |  |  |
| Month 11 (n = 19) | -0.47 (-0.65 to -0.11) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of IFN-gamma-producing CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Number of IFN-gamma-producing CD4 T cells <sup>[55]</sup> |
|-----------------|---|

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of interferon (IFN)-gamma.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 10.15 (7.02 to 13.78)                   |  |  |  |
| Month 2 (n = 19)                      | 11.25 (4.20 to 15.58)                   |  |  |  |
| Month 4 (n = 19)                      | 7.94 (2.13 to 12.24)                    |  |  |  |
| Month 6 (n = 34)                      | 6.97 (2.27 to 10.06)                    |  |  |  |
| Month 11 (n = 19)                     | 3.15 (2.04 to 8.85)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change of IFN-gamma-producing CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Absolute change of IFN-gamma-producing CD4 T cells <sup>[56]</sup> |
|-----------------|--|

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow

cytometry for the intracellular amount of interferon (IFN)-gamma.

|                           |           |
|---------------------------|-----------|
| End point type            | Secondary |
| End point timeframe:      |           |
| Months 0, 2, 4, 6 and 11. |           |

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.12 (-3.02 to 2.29)                   |  |  |  |
| Month 4 (n = 19)                      | -2.34 (-5.84 to 1.50)                   |  |  |  |
| Month 6 (n = 34)                      | -3.73 (-6.81 to -0.04)                  |  |  |  |
| Month 11 (n = 19)                     | -4.85 (-8.34 to -1.24)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of IL-17A-producing CD4 T cells

|   |  |
|---|--|
| End point title   | Number of IL-17A-producing CD4 T cells <sup>[57]</sup> |
| End point description:  |  |
| CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-17A. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Months 0, 2, 4, 6 and 11.   |  |

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |

|                   |                     |  |  |  |
|-------------------|---------------------|--|--|--|
| Month 0 (n = 34)  | 0.84 (0.51 to 1.27) |  |  |  |
| Month 2 (n = 19)  | 0.81 (0.49 to 1.10) |  |  |  |
| Month 4 (n = 19)  | 0.75 (0.41 to 0.88) |  |  |  |
| Month 6 (n = 34)  | 0.65 (0.40 to 0.96) |  |  |  |
| Month 11 (n = 19) | 0.51 (0.26 to 0.90) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change of IL17A-producing CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Absolute change of IL17A-producing CD4 T cells <sup>[58]</sup> |
|-----------------|--|

End point description:

CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL17A.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.07 (-0.25 to 0.13)                   |  |  |  |
| Month 4 (n = 19)                      | -0.06 (-0.36 to 0.01)                   |  |  |  |
| Month 6 (n = 34)                      | -0.24 (-0.39 to 0.01)                   |  |  |  |
| Month 11 (n = 19)                     | -0.31 (-0.52 to -0.04)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of IL-4-producing CD4 T cells

|   |  |
|---|--|
| End point title   | Number of IL-4-producing CD4 T cells <sup>[59]</sup> |
| End point description:<br>CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-4. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |  |

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per µL              |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 34)                      | 1.73 (1.28 to 2.17)                     |  |  |  |
| Month 2 (n = 19)                      | 1.50 (1.27 to 2.29)                     |  |  |  |
| Month 4 (n = 19)                      | 1.48 (1.16 to 1.94)                     |  |  |  |
| Month 6 (n = 34)                      | 1.56 (1.18 to 2.35)                     |  |  |  |
| Month 11 (n = 19)                     | 1.35 (1.10 to 1.97)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change of IL-4-producing CD4 T cells

|   |   |
|---|---|
| End point title   | Absolute change of IL-4-producing CD4 T cells <sup>[60]</sup> |
| End point description:<br>CD4 T cells were stimulated with leukocyte activation Cocktail for 6 hours and analyzed by flow cytometry for the intracellular amount of IL-4. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Months 0, 2, 4, 6 and 11.   |   |

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Cell count per $\mu$ L         |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.05 (-0.36 to 0.17)                   |  |  |  |
| Month 4 (n = 19)                      | -0.10 (-0.53 to 0.18)                   |  |  |  |
| Month 6 (n = 34)                      | -0.05 (-0.26 to 0.17)                   |  |  |  |
| Month 11 (n = 19)                     | -0.32 (-0.56 to 0.08)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change of thymus derived regulatory T cells in memory CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Absolute change of thymus derived regulatory T cells in memory CD4 T cells <sup>[61]</sup> |
|-----------------|--|

End point description:

Absolute change of thymus derived regulatory T cells (tTreg) from baseline (month 0) within the memory CD4 T cell (CD4 Mem) population during DMF treatment.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: tTreg (percent of CD4 Mem)     |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.12 (-0.64 to 1.49)                   |  |  |  |
| Month 4 (n = 19)                      | 0.39 (-0.48 to 1.66)                    |  |  |  |
| Month 6 (n = 34)                      | 0.59 (-0.23 to 2.27)                    |  |  |  |
| Month 11 (n = 19)                     | 1.78 (-0.19 to 3.32)                    |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change of regulatory T cells in CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Absolute change of regulatory T cells in CD4 T cells <sup>[62]</sup> |
|-----------------|--|

End point description:

Absolute change of regulatory T cells (Treg) from baseline (month 0) within the CD4 T cell population during DMF treatment.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: Treg (percent of CD4 T cells)  |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -2.00 (-6.97 to 2.49)                   |  |  |  |
| Month 4 (n = 19)                      | -3.96 (-9.89 to 1.32)                   |  |  |  |
| Month 6 (n = 34)                      | -7.20 (-10.68 to 0.61)                  |  |  |  |
| Month 11 (n = 19)                     | -8.49 (-13.64 to -6.67)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change of thymus derived regulatory T cells in CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Absolute change of thymus derived regulatory T cells in CD4 T cells <sup>[63]</sup> |
|-----------------|---|

End point description:

Absolute change of thymus derived regulatory T cells (tTreg) from baseline (month 0) within the CD4 T cell population during DMF Treatment.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: tTreg (percent of CD4 T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 2 (n = 19)                      | -0.15 (-0.39 to 0.42)                   |  |  |  |
| Month 4 (n = 19)                      | -0.17 (-0.57 to 0.34)                   |  |  |  |
| Month 6 (n = 34)                      | 0.04 (-0.51 to 0.31)                    |  |  |  |
| Month 11 (n = 19)                     | -0.26 (-0.88 to 0.15)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change of peripheral derived regulatory T cells in CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Absolute change of peripheral derived regulatory T cells in CD4 T cells <sup>[64]</sup> |
|-----------------|---|

End point description:

Absolute change of peripheral derived regulatory T cells (pTreg) from baseline (month 0) within the CD4 T cell population during DMF treatment.

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

End point timeframe:

Months 0, 2, 4, 6 and 11.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 34                                      |  |  |  |
| Units: pTreg (percent of CD4 T cells) |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |

|                   |                        |  |  |  |
|-------------------|------------------------|--|--|--|
| Month 2 (n = 19)  | -0.02 (-0.09 to 0.05)  |  |  |  |
| Month 4 (n = 19)  | -0.03 (-0.15 to 0.05)  |  |  |  |
| Month 6 (n = 34)  | -0.03 (-0.10 to 0.03)  |  |  |  |
| Month 11 (n = 19) | -0.06 (-0.14 to -0.02) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mitochondrial energy metabolism of unstimulated (ex vivo) CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Mitochondrial energy metabolism of unstimulated (ex vivo) CD4 T cells <sup>[65]</sup> |
|-----------------|---|

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of unstimulated (ex vivo) CD4 T cells using seahorse agilent technology during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

|  |   |  |  |  |
|--|---|--|--|--|
| <b>End point values</b>                    | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
| Subject group type                         | Reporting group                         |  |  |  |
| Number of subjects analysed                | 14                                      |  |  |  |
| Units: oxygen consumption rate in pmol/min |   |  |  |  |
| median (inter-quartile range (Q1-Q3))      |   |  |  |  |
| Month 0 (n = 14)                           | 60.14 (41.57 to 101.45)                 |  |  |  |
| Month 6 (n = 14)                           | 62.20 (51.39 to 92.01)                  |  |  |  |
| Month 11 (n = 14)                          | 65.18 (28.63 to 75.57)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mitochondrial energy metabolism of short-term stimulated CD4 T cells

|                 |  |
|-----------------|--|
| End point title | Mitochondrial energy metabolism of short-term stimulated CD4 T cells <sup>[66]</sup> |
|-----------------|--|

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of short-term stimulated CD4 T cells using seahorse agilent technology during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                           | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|--|---|--|--|--|
| Subject group type                         | Reporting group                         |  |  |  |
| Number of subjects analysed                | 14                                      |  |  |  |
| Units: oxygen consumption rate in pmol/min |   |  |  |  |
| median (inter-quartile range (Q1-Q3))      |   |  |  |  |
| Month 0 (n = 14)                           | 49.26 (38.33 to 69.60)                  |  |  |  |
| Month 6 (n = 14)                           | 34.79 (16.78 to 57.62)                  |  |  |  |
| Month 11 (n = 14)                          | 34.41 (16.44 to 44.32)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mitochondrial energy metabolism of unstimulated (ex vivo) CD8 T cells

|                 |   |
|-----------------|---|
| End point title | Mitochondrial energy metabolism of unstimulated (ex vivo) CD8 T cells <sup>[67]</sup> |
|-----------------|---|

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of unstimulated (ex vivo) CD8 T cells using seahorse agilent technology during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                           | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|--|---|--|--|--|
| Subject group type                         | Reporting group                         |  |  |  |
| Number of subjects analysed                | 14                                      |  |  |  |
| Units: oxygen consumption rate in pmol/min |   |  |  |  |
| median (inter-quartile range (Q1-Q3))      |   |  |  |  |
| Month 0 (n = 14)                           | 86.12 (60.22 to 132.35)                 |  |  |  |
| Month 6 (n = 14)                           | 62.07 (36.14 to 81.76)                  |  |  |  |
| Month 11 (n = 14)                          | 66.66 (34.79 to 121.96)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mitochondrial energy metabolism of short-term stimulated CD8 T cells

|                 |  |
|-----------------|--|
| End point title | Mitochondrial energy metabolism of short-term stimulated CD8 T cells <sup>[68]</sup> |
|-----------------|--|

End point description:

Measurement of mitochondrial energy metabolism (i.e. oxidative phosphorylation) of short-term stimulated CD8 T cells using seahorse agilent technology during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                           | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|--|---|--|--|--|
| Subject group type                         | Reporting group                         |  |  |  |
| Number of subjects analysed                | 14                                      |  |  |  |
| Units: oxygen consumption rate in pmol/min |   |  |  |  |
| median (inter-quartile range (Q1-Q3))      |   |  |  |  |
| Month 0 (n = 14)                           | 34.90 (16.80 to 63.01)                  |  |  |  |
| Month 6 (n = 14)                           | 19.99 (6.75 to 38.75)                   |  |  |  |
| Month 11 (n = 14)                          | 21.90 (8.43 to 27.43)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Migratory capacity of CD4 T cells

|                 |   |
|-----------------|---|
| End point title | Migratory capacity of CD4 T cells <sup>[69]</sup> |
|-----------------|---|

End point description:

Migration analysis in an in vitro model of the blood-brain-barrier of unstimulated CD4 T cells during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

| End point values                      | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 20                                      |  |  |  |
| Units: Percentage of migrated cells   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 20)                      | 19.77 (1.92 to 64.27)                   |  |  |  |
| Month 6 (n = 19)                      | 19.64 (2.31 to 56.85)                   |  |  |  |
| Month 11 (n = 10)                     | 1.66 (0.82 to 2.82)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Migratory capacity of CD8 T cells

|                 |   |
|-----------------|---|
| End point title | Migratory capacity of CD8 T cells <sup>[70]</sup> |
|-----------------|---|

End point description:

Migration analysis in an in vitro model of the blood-brain-barrier of unstimulated CD8 T cells during DMF treatment.

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

End point timeframe:

Months 0, 6 and 11.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Because there were not enough samples from healthy subjects, this arm was not evaluated.

|                                       |   |  |  |  |
|---------------------------------------|---|--|--|--|
| <b>End point values</b>               | Dimethyl fumarate (DMF) (RRMS patients) |  |  |  |
| Subject group type                    | Reporting group                         |  |  |  |
| Number of subjects analysed           | 20                                      |  |  |  |
| Units: Percentage of migrated cells   |   |  |  |  |
| median (inter-quartile range (Q1-Q3)) |   |  |  |  |
| Month 0 (n = 20)                      | 11.50 (0.82 to 148.75)                  |  |  |  |
| Month 6 (n = 19)                      | 19.44 (0.69 to 173.56)                  |  |  |  |
| Month 11 (n = 10)                     | 0.83 (0.37 to 0.97)                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From enrollment in the study to the final study visit.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Safety group |
|-----------------------|--------------|

Reporting group description:

RRMS patients who received at least one dose of dimethyl fumarate.

| Serious adverse events                            | Safety group   |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 3 / 42 (7.14%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Investigations                                    |                |  |  |
| Weight decreased                                  |                |  |  |
| subjects affected / exposed                       | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Injury, poisoning and procedural complications    |                |  |  |
| Radius fracture                                   |                |  |  |
| subjects affected / exposed                       | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Pregnancy, puerperium and perinatal conditions    |                |  |  |
| Abortion  |                |  |  |
| subjects affected / exposed                       | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Nervous system disorders                          |                |  |  |
| Cerebral ischaemia                                |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Safety group     |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 37 / 42 (88.10%) |  |  |
| Vascular disorders                                    |                  |  |  |
| Flushing  |                  |  |  |
| subjects affected / exposed                           | 24 / 42 (57.14%) |  |  |
| occurrences (all)                                     | 28               |  |  |
| Hot flush   |                  |  |  |
| subjects affected / exposed                           | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Fatigue   |                  |  |  |
| subjects affected / exposed                           | 4 / 42 (9.52%)   |  |  |
| occurrences (all)                                     | 4                |  |  |
| Feeling hot   |                  |  |  |
| subjects affected / exposed                           | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Oedema peripheral                                     |                  |  |  |
| subjects affected / exposed                           | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Reproductive system and breast disorders              |                  |  |  |
| Menopausal symptoms                                   |                  |  |  |
| subjects affected / exposed                           | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Respiratory, thoracic and mediastinal disorders       |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                           | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Oropharyngeal pain                                    |                  |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 42 (2.38%)<br>1  |  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)   | 1 / 42 (2.38%)<br>1  |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Protein urine present<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1 |  |  |
| Injury, poisoning and procedural complications<br>Cartilage injury<br>subjects affected / exposed<br>occurrences (all)<br><br>Foot fracture<br>subjects affected / exposed<br>occurrences (all)   | 1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1   |  |  |
| Cardiac disorders<br>Arrhythmia<br>subjects affected / exposed<br>occurrences (all)<br><br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1   |  |  |
| Nervous system disorders<br>Ataxia  |  |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Dizziness                            |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Dysgeusia                            |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Headache                             |                |  |  |
| subjects affected / exposed          | 4 / 42 (9.52%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Hypertonia                           |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Hypoaesthesia                        |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Sensory loss                         |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Tremor                               |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Blood and lymphatic system disorders |                |  |  |
| Iron deficiency anaemia              |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Leukopenia                           |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Lymphopenia                          |                |  |  |
| subjects affected / exposed          | 3 / 42 (7.14%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Ear and labyrinth disorders          |                |  |  |
| Vertigo                              |                |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 42 (2.38%)<br>1  |  |  |
| Eye disorders<br>Visual impairment<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 42 (4.76%)<br>2  |  |  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1  |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 42 (2.38%)<br>1  |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 42 (9.52%)<br>4  |  |  |
| Aphthous ulcer<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 42 (2.38%)<br>1  |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 5 / 42 (11.90%)<br>6 |  |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)  | 1 / 42 (2.38%)<br>1  |  |  |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 42 (2.38%)<br>1  |  |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)   | 3 / 42 (7.14%)<br>3  |  |  |
| Gastric disorder<br>subjects affected / exposed<br>occurrences (all)                                   | 3 / 42 (7.14%)<br>3  |  |  |
| Gastrointestinal disorder  |                      |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 3 / 42 (7.14%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 4 / 42 (9.52%)  |  |  |
| occurrences (all)                               | 4               |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Erythema  |                 |  |  |
| subjects affected / exposed                     | 4 / 42 (9.52%)  |  |  |
| occurrences (all)                               | 7               |  |  |
| Pruritus  |                 |  |  |
| subjects affected / exposed                     | 6 / 42 (14.29%) |  |  |
| occurrences (all)                               | 7               |  |  |
| Skin irritation                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Skin warm                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Proteinuria                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Joint lock                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Muscular weakness                               |                 |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Osteoarthritis                                  |                 |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pain in extremity           |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Infections and infestations |                  |  |  |
| Acute sinusitis             |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Bronchitis                  |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Folliculitis                |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Gastric infection           |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Gastroenteritis             |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Hand-foot-and-mouth disease |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Infection                   |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Nasal herpes                |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Nasopharyngitis             |                  |  |  |
| subjects affected / exposed | 14 / 42 (33.33%) |  |  |
| occurrences (all)           | 17               |  |  |
| Oral herpes                 |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |

|                                |                 |  |  |
|--------------------------------|-----------------|--|--|
| Rhinitis                       |                 |  |  |
| subjects affected / exposed    | 1 / 42 (2.38%)  |  |  |
| occurrences (all)              | 1               |  |  |
| Tonsillitis                    |                 |  |  |
| subjects affected / exposed    | 1 / 42 (2.38%)  |  |  |
| occurrences (all)              | 1               |  |  |
| Urinary tract infection        |                 |  |  |
| subjects affected / exposed    | 6 / 42 (14.29%) |  |  |
| occurrences (all)              | 6               |  |  |
| Vulvovaginal mycotic infection |                 |  |  |
| subjects affected / exposed    | 1 / 42 (2.38%)  |  |  |
| occurrences (all)              | 1               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 06 October 2015 | <p>Inclusion and exclusion criteria of the protocol have been amended:</p> <ul style="list-style-type: none"><li>• The time limit for disease-modifying treatment before the start of the trial was reduced from 6 months to one month (the procedure remained unchanged for patients who received IFN <math>\beta</math>-1 or glatiramer acetate at the time of screening).</li><li>• Previously, the test for tuberculosis, HIV and hepatitis B and C had to be performed during screening. After the amendment, test results not older than 3 months at the time of screening were also allowed.</li><li>• Limit values for certain laboratory parameters have been removed. Only clinical significant deviations of the laboratory values lead to the exclusion of the patient (decision of the investigator).</li></ul> <p>In addition, the following has been modified in the protocol:</p> <ul style="list-style-type: none"><li>• In order to exclude pregnancy at the time of screening, a urine pregnancy test should now also be allowed (previously only a blood test was allowed).</li><li>• The analysis of laboratory parameters (clinical chemistry) which are not recommended or obligatory according to the summary of product characteristics or the Krankheitsbezogenen Kompetenznetzes Multiple Sklerose should no longer be performed.</li></ul> |
| 25 April 2017   | <p>Secondary objectives have been modified:</p> <ul style="list-style-type: none"><li>• In order to examine the cytokine production of the cells, only the cytokines GM-CSF, IFN<math>\gamma</math>, TNF-<math>\alpha</math>, IL-22 und IL-17A should be examined (the analysis of IL-2, IL-4, IL-10 and IL-21 was removed from the protocol).</li></ul> <p>Secondary objectives have been removed:</p> <ul style="list-style-type: none"><li>• Investigating the differentiation capability of T cells and the ability of regulatory T cells to suppress the effector T cell response were removed from the protocol.</li></ul> <p>Secondary objectives have been added:</p> <ul style="list-style-type: none"><li>• Evaluation of changes in mitochondrial energy metabolism was added to the protocol.</li></ul> <p>Sample size / change to the power analyses:</p> <ul style="list-style-type: none"><li>• Initially, it was planned to recruit 60 RRMS patients. Due to new external information concerning the mean change in Th17 cells, the number of RRMS patients was decreased to 50 patients and the power analysis was repeated.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported