# Clinical trial results:
# A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis

## Summary

| | |
|---|---|
| EudraCT number | 2017-002631-42 |
| Trial protocol | SE GB HU AT CZ ES FR BE FI IT |
| Global end of trial date | 30 September 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 11 October 2022 |
| First version publication date | 11 October 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | MS700568_0022 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03364036 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Merck KGaA,, Germany |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293 |
| Public contact | Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@emdgroup.com |
| Scientific contact | Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@emdgroup.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 05 May 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of the study was to determine the onset of Mavenclad® action by frequent magnetic resonance imaging (MRI) assessment of the combined unique active (CUA) lesions in subjects with highly active relapsing multiple sclerosis (MS).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 28 May 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Czechia: 89 |
| Country: Number of subjects enrolled | Spain: 40 |
| Country: Number of subjects enrolled | Germany: 25 |
| Country: Number of subjects enrolled | France: 23 |
| Country: Number of subjects enrolled | Poland: 20 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Australia: 12 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Sweden: 9 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Finland: 4 |
| Worldwide total number of subjects | 270 |
| EEA total number of subjects | 225 |

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) | 270 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 270 subjects were enrolled in the study from different trial sites across Europe (including, but not limited to Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Poland, Spain, Sweden, the United Kingdom), as well as Australia, Canada and Israel.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Mavenclad® |

Arm description:

Subjects received Mavenclad® 3.5 milligram per kilogram (mg/kg) of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Mavenclad |
| Investigational medicinal product code | |
| Other name | Cladribine |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Mavenclad® 3.5 milligram per kilogram (mg/kg) of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year.

| **Number of subjects in period 1** | Mavenclad® |
|---|---|
| Started | 270 |
| Full Analysis Set (FAS) | 270 |
| Completed | 264 |
| Not completed | 6 |
| Withdrew Consent | 1 |
| Adverse event, non-fatal | 1 |
| Protocol Non-Compliance | 1 |
| Unspecified | 2 |
| Lost to follow-up | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Mavenclad® |
| Reporting group description: | |
| Subjects received Mavenclad® 3.5 milligram per kilogram (mg/kg) of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. | |

| Reporting group values | Mavenclad® | Total | |
|---|---|---|---|
| Number of subjects | 270 | 270 | |
| Age categorical<br>Units: | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 37.7 | | |
| standard deviation | ± 9.75 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 180 | 180 | |
| Male | 90 | 90 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 2 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 1 | 1 | |
| White | 225 | 225 | |
| More than one race | 12 | 12 | |
| Unknown or Not Reported | 30 | 30 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 7 | 7 | |
| Not Hispanic or Latino | 246 | 246 | |
| Unknown or Not Reported | 17 | 17 | |

## End points

### End points reporting groups

| Reporting group title | Mavenclad® |
|---|---|

Reporting group description:

Subjects received Mavenclad® 3.5 milligram per kilogram (mg/kg) of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year.

### Primary: Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 3 (Month 3-6)

| End point title | Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 3 (Month 3-6)[1] |
|---|---|

End point description:

CUA lesions were measured by using MRI scans. Full analysis set (FAS) included all subjects from the intent-to-treat (ITT [ITT population included all participants classified as eligible]) set who received at least one dose of the study treatment. Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this end point.

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

End point timeframe:

Baseline period (the period screening to Baseline), Period 3 (Month 3-6)

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: Only descriptive statistics data was planned to be reported for this endpoint.

| End point values | Mavenclad® | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 246 | | | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | -1.499 (± 3.4244) | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 1 (Month 1-6)

| End point title | Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 1 (Month 1-6)[2] |
|---|---|

End point description:

CUA lesions were measured by using MRI scans. FAS included all participants from the ITT set who received at least one dose of the study treatment. Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this end point.

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

End point timeframe:

Baseline period (the period screening to Baseline), Period 1 (Month 1-6)

Notes:

[2] - 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: Only descriptive statistics data was planned to be reported for this endpoint.

| **End point values** | Mavenclad® | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 252 | | | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | -1.211 (± 3.4413) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 2 (Month 2-6)

| End point title | Change From Baseline Period (Period Screening to Baseline) in Counts of Combined Unique Active (CUA) Magnetic Resonance Imaging (MRI) Lesions at Period 2 (Month 2-6)[3] |
|---|---|

End point description:

CUA lesions were measured by using MRI scans. FAS included all subjects from the ITT set who received at least one dose of the study treatment. Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this end point.

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

End point timeframe:

Baseline period (the period screening to Baseline), Period 2 (Month 2-6)

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: Only descriptive statistics data was planned to be reported for this endpoint.

| **End point values** | Mavenclad® | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 252 | | | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | -1.521 (± 4.0558) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From baseline up to Month 6 | |
| Assessment type | Non-systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |
| **Reporting groups** | |
| Reporting group title | Experimental: Mavenclad® |
| Reporting group description: | |
| Subjects received Mavenclad® 3.5 milligram per kilogram (mg/kg) of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. | |

| Serious adverse events | Experimental: Mavenclad® | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 270 (2.59%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Carotid endarterectomy | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 270 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Experimental: Mavenclad® | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 123 / 270 (45.56%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 69 / 270 (25.56%) | | |
| occurrences (all) | 69 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 22 / 270 (8.15%) | | |
| occurrences (all) | 22 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 19 / 270 (7.04%) | | |
| occurrences (all) | 19 | | |
| Nausea | | | |
| subjects affected / exposed | 22 / 270 (8.15%) | | |
| occurrences (all) | 22 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | | |
| occurrences (all) | 16 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 37 / 270 (13.70%) | | |
| occurrences (all) | 37 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 15 / 270 (5.56%) | | |
| occurrences (all) | 15 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 February 2019 | • Revised the primary endpoint analyses and the primary population for analyses from the ITT Set to the FAS. • Updated to include a risk-benefit evaluation for subjects with prior malignancy. • Inclusion criterion was added to include subjects with previous exposure and immunity to varicella virus. • Section 8 (including several sub-sections) was amended to provide more detail on the planned analyses. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported