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 Units:			
Age Continuous Units: years			
arithmetic mean	37.7		
standard deviation	± 9.75	-	
Sex: Female, Male Units: Participants			
Female	180	180	
Male	90	90	
Race (NIH/OMB) 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) 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