Clinical trial results:
A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-Active Relapsing Multiple Sclerosis Treated with Mavenclad® (CLARIFY MS)

Summary

EudraCT number	2017-002632-17
Trial protocol	LT HU AT SE ES CZ DK BE FI NO GB FR NL SK PT GR IT
Global end of trial date	26 August 2021

Results information

Result version number	v1 (current)
This version publication date	28 October 2022
First version publication date	28 October 2022

Trial information

Trial identification

Sponsor protocol code	MS700568_0021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03369665
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2021
Global end of trial reached?	Yes
Global end of trial date	26 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the health-related quality of life (HRQoL) through the multiple sclerosis quality of life-54 questionnaire (MSQoL-54) scale in highly-active Relapsing Multiple Sclerosis (RMS) subjects treated with Mavenclad for 2 years (24 months).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the ethical principles of the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki, as well as with applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 85
Country: Number of subjects enrolled	Czechia: 66
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Lithuania: 23
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Italy: 86
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	United Kingdom: 10

Country: Number of subjects enrolled	Belgium: 7
Worldwide total number of subjects	482
EEA total number of subjects	472

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)	480
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 485 subjects were enrolled in the study at Poland, Czechia, Slovakia, Hungary, Lithuania, Austria, Denmark, Finland, Sweden, Norway, Italy, Spain, Portugal, Greece, France, Netherlands, United Kingdom of Great Britain and Northern Ireland, and Belgium. Out of 485 subjects, 3 subjects were enrolled, but did not receive study medication.

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 with RMS 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. Each treatment course consisted of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.

Arm type	Experimental
Investigational medicinal product name	Cladribine
Investigational medicinal product code	
Other name	Mavenclad®
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	482
Full Analysis Set (FAS)	482
Safety Analysis Set (SAS)	482
Completed	452
Not completed	30
Consent withdrawn by subject	15
Adverse event, non-fatal	3
Not classified	3
Progression Disease	2
Lost to follow-up	7

Baseline characteristics

Reporting groups	
Reporting group title	Mavenclad®
Reporting group description:	
Subjects with RMS 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. Each treatment course consisted of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.	

Reporting group values	Mavenclad®	Total	
Number of subjects	482	482	
Age categorical Units:			
Age Continuous Units: Years arithmetic mean standard deviation	 37.4 ± 10.39	 -	
Sex: Female, Male Units: Subjects			
Female	338	338	
Male	144	144	
Race (NIH/OMB) Units: Subjects			
Asian	2	2	
White	360	360	
Not collected at this site	120	120	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21	21	
Not Hispanic or Latino	379	379	
Unknown or Not Reported	82	82	

End points

End points reporting groups

Reporting group title	Mavenclad®

Reporting group description:

Subjects with RMS 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. Each treatment course consisted of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.

Primary: Change From Baseline in Multiple Sclerosis Quality of Life-54 Questionnaire (MSQoL-54) Physical Health Composite Summary and Mental Health Composite Summary Scores at Month 24

End point title	Change From Baseline in Multiple Sclerosis Quality of Life-54 Questionnaire (MSQoL-54) Physical Health Composite Summary and Mental Health Composite Summary Scores at Month 24[1]

End point description:

MSQOL-54 was a multidimensional health-related QOL measure that combines both generic and MS-specific items into a single instrument. This 54-item instrument generates 12 sub-scales along with two summary scores, and two additional single-item measures. Sub-scales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The two summary scores physical health and mental health are derived from a weighted combination of scale scores. Each composite summary score has a range from 0-100 where higher scores indicate better QOL. A positive change from baseline indicates improvement. Full Analysis Set (FAS): all subjects from the ITT set treated with at least one dose of study medication. Here "number of subjects analysed" signifies those who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 24

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: No statistical and comparison analysis were performed in single arm for this endpoint.

End point values	Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	433			
Units: Score on a Scale				
least squares mean (standard error)				
Physical health composite summary	4.86 (± 0.769)			
Mental health composite summary	4.80 (± 0.845)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Global Satisfaction Determined by Treatment Satisfaction Questionnaire Medication Version 1.4 (TSQM v1.4) Scale at Month 6

End point title	Treatment Global Satisfaction Determined by Treatment

	Satisfaction Questionnaire Medication Version 1.4 (TSQM v1.4) Scale at Month 6

End point description:

TSQM was a global satisfaction scale used to assess the overall level of subject's satisfaction or dissatisfaction with their medications. It comprises of 14 items assessing the following 4 domains: effectiveness (1-3), side effects (4-8), convenience (9-11), global satisfaction (12-14). Global satisfaction- question 12 scored 1(not at all confident) to 5 (extremely confident); question 13 scored 1(not at all certain) to 5(extremely certain); and question 14 scored 1(extremely dissatisfied) to 7(extremely satisfied). The scores of the domain were added together and an algorithm was used to create a score of 0 to 100. Higher scores indicated greater satisfaction. FAS consisted of all subjects from the ITT set treated with at least one dose of study medication. Here "number of subjects analysed" signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Month 6

End point values	Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	477			
Units: Score on a Scale				
least squares mean (standard error)	72.02 (± 1.528)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline up to Month 24	
Adverse event reporting additional description:	
Safety Analysis Set (SAF) consisted of all subjects treated with at least one dose of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Mavenclad®
Reporting group description:	
Subjects with RMS received Mavenclad® 3.5 mg/kg of body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consisted of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.	

Serious adverse events	Mavenclad®		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 482 (5.39%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Clavicle fracture			

subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	3 / 482 (0.62%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Medication error				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 482 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm rupture				

subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovulation pain			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperventilation			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic disorder			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

COVID-19			
subjects affected / exposed	2 / 482 (0.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lyme disease			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 482 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Mavenclad®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	375 / 482 (77.80%)		
Nervous system disorders			
Headache			
subjects affected / exposed	105 / 482 (21.78%)		
occurrences (all)	105		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	73 / 482 (15.15%)		
occurrences (all)	73		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 482 (6.22%)		
occurrences (all)	30		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	25 / 482 (5.19%)		
occurrences (all)	25		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	26 / 482 (5.39%)		
occurrences (all)	26		
Back pain			
subjects affected / exposed	38 / 482 (7.88%)		
occurrences (all)	38		
Infections and infestations			
Influenza			
subjects affected / exposed	29 / 482 (6.02%)		
occurrences (all)	29		
Nasopharyngitis			
subjects affected / exposed	65 / 482 (13.49%)		
occurrences (all)	65		
Oral herpes			
subjects affected / exposed	25 / 482 (5.19%)		
occurrences (all)	25		
Urinary tract infection			
subjects affected / exposed	39 / 482 (8.09%)		
occurrences (all)	39		
Upper respiratory tract infection			
subjects affected / exposed	47 / 482 (9.75%)		
occurrences (all)	47		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2018	Protocol Amendment 1: - Revised trial country list. Israel, Switzerland and Ireland were removed from the trial centres list and Slovakia was added. - Change in the planned trial period. First subject first visit date was changed from Q1 2018 to Q2 2018 and last subject last visit date was changed to Q4 2021. - Section revised to clearly define endpoints. Tertiary endpoints revised to include "treatment effectiveness, side effects, and convenience assessed by TSQM at 6, 12 and 24 months". In addition, MSQoL-54 assessment schedule was updated to include 24 months. - Revised key exclusion criteria regarding immunosuppressive therapy to include mitoxantrone. In addition, sentences regarding hepatitis infection and PML were reworded for clarity. - Inclusion criterion number 5 was revised to introduce Appendix 15 which provides a list of highly effective birth control methods. In addition, definitions of WOCBP and postmenopausal women have been included and criterion 6 was combined with criterion 5. - Criteria 3: The phrase 'Presence or suspect of PML' was replaced with 'Presence of signs of PML detected by MRI, clinical and/or biomarker evaluations'. Criteria 7: Mitoxantrone was added to list of drugs. Addition of new exclusion criteria 13. - Treatment satisfaction scoring (TSQM v1.4) deleted from Baseline visit. - Revision of text for MRI assessment. - Included Screening as a timepoint for EDSS/KFS and updated definition for EDSS progression Section updated to ensure sites used only the forms provided in Appendix 6 for assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported