Clinical trial results:
A 2-year Follow-up Study to Assess Cognition and Health-related Quality of Life in Participants With Highly-active Relapsing Multiple Sclerosis, Having Participated in the CLARIFY MS Trial (CLARIFY MS Extension)

Summary

EudraCT number	2020-003874-30
Trial protocol	CZ HU SK DK AT FR IT
Global end of trial date	20 June 2023

Results information

Result version number	v1 (current)
This version publication date	18 May 2024
First version publication date	18 May 2024

Trial information

Trial identification

Sponsor protocol code	MS700568_0158

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04776213
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	20 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was the evaluation of the effect of a treatment for highly-active relapsing multiple sclerosis (RMS). This was the extension study to CLARIFY MS (NCT03369665), to assess cognitive impairment and health related quality of life (HRQoL) in subjects with highly active RMS, at 4 years after initial dose of Mavenclad® tablets.

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	23 February 2021
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	Poland: 54
Country: Number of subjects enrolled	Czechia: 51
Country: Number of subjects enrolled	Slovakia: 25
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Netherlands: 5
Worldwide total number of subjects	280
EEA total number of subjects	280

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	273
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 280 subjects were enrolled in the study from different trial sites.

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:

This low interventional extension study involves the follow up of subjects in the parent study (NCT03369665). The subjects were followed up for an additional 2 year period (until 4 years after initial administration of Mavenclad® tablets), during which the subjects are not treated with Mavenclad®, as per European Medicines Agency (EMA) label of Mavenclad®.

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

Dosage and administration details:

Subjects were followed up for an additional 2 year period (until 4 years after initial administration of Mavenclad® tablets), during which the subjects are not treated with Mavenclad®, as per European Medicines Agency (EMA) label of Mavenclad®.

Number of subjects in period 1	Mavenclad®
Started	280
Completed	269
Not completed	11
Consent withdrawn by subject	7
Unspecified	1
Lost to follow-up	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Mavenclad®

Reporting group description:

This low interventional extension study involves the follow up of subjects in the parent study (NCT03369665). The subjects were followed up for an additional 2 year period (until 4 years after initial administration of Mavenclad® tablets), during which the subjects are not treated with Mavenclad®, as per European Medicines Agency (EMA) label of Mavenclad®.

Reporting group values	Mavenclad®	Total	
Number of subjects	280	280	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	41.4		
standard deviation	± 10.44	-	
Sex: Female, Male Units: subjects			
Female	201	201	
Male	79	79	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	248	248	
More than one race	0	0	
Unknown or Not Reported	31	31	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	18	18	
Not Hispanic or Latino	202	202	
Unknown or Not Reported	60	60	

End points

End points reporting groups

Reporting group title	Mavenclad®

Reporting group description:

This low interventional extension study involves the follow up of subjects in the parent study (NCT03369665). The subjects were followed up for an additional 2 year period (until 4 years after initial administration of Mavenclad® tablets), during which the subjects are not treated with Mavenclad®, as per European Medicines Agency (EMA) label of Mavenclad®.

Primary: Percentage of Subjects With No or Minimal Decline in Cognitive Function, Defined As an Improved or Stable Symbol Digit Modalities Test (SDMT) Score or a Decline of 4 points or Less in the SDMT Score, From Baseline of Parent Study to Month 48

End point title	Percentage of Subjects With No or Minimal Decline in Cognitive Function, Defined As an Improved or Stable Symbol Digit Modalities Test (SDMT) Score or a Decline of 4 points or Less in the SDMT Score, From Baseline of Parent Study to Month 48[1]

End point description:

The SDMT was a test of information processing speed. It consists of 9 abstract symbols. Each symbol was paired with a single digit. The subject was provided with a "key", showing each symbol digit pair. In addition, the subjects were shown several rows of the 9 symbols, which were arranged pseudo-randomly, without the digit. Subjects were asked to voice the digit associated with each symbol as rapidly as possible for 90 seconds. The SDMT score ranges from 0 to 110 higher scores indicated improvement and lower scores indicated worsening. Full analysis set (FAS) included all eligible subjects, for whom any Visit data had been collected after end date of CLARIFY MS (NCT03369665) Year 2 Visit (Month 24 Visit).

End point type	Primary

End point timeframe:

Baseline (baseline of parent study [NCT03369665]) and Month 48 after initial dose of Mavenclad® in parent study (NCT03369665)

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 data was planned to be reported for this endpoint.

End point values	Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	280			
Units: percentage of subjects				
number (confidence interval 95%)	68.6 (62.9 to 73.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Related Quality of Life (HRQoL) as Measured by Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) Physical and Mental Health Composite Summary Scores at 4 Years

End point title	Change From Baseline in Health Related Quality of Life

	(HRQoL) as Measured by Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) Physical and Mental Health Composite Summary Scores at 4 Years

End point description:

The 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) was used. Here, "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (baseline of parent study [NCT03369665]), 4 years after initial dose of Mavenclad® in parent study (NCT03369665)

End point values	Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	265			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Physical health composite score	3.69 (1.71 to 5.67)			
Mental health composite score	5.13 (2.73 to 7.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Month 24 in Health Related Quality of Life (HRQoL) as Measured by Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) Physical and Mental Health Composite Summary Scores at 4 Years

End point title	Change From Month 24 in Health Related Quality of Life (HRQoL) as Measured by Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) Physical and Mental Health Composite Summary Scores at 4 Years

End point description:

The 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) was used. Here, "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Month 24 after initial dose of Mavenclad® in parent study (NCT03369665), 4 years after initial dose of Mavenclad® in parent study (NCT03369665)

End point values	Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	232			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Physical health composite score	-2.02 (-3.81 to -0.22)			
Mental health composite score	-0.36 (-2.65 to 1.92)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4 years after initial dose of Mavenclad® in parent study (NCT03369665).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0.

Reporting groups

Reporting group title	Mavenclad®

Reporting group description:

This low interventional extension study involves the follow up of subjects in the parent study (NCT03369665). The subjects were followed up for an additional 2 year period (until 4 years after initial administration of Mavenclad® tablets), during which the subjects are not treated with Mavenclad®, as per European Medicines Agency (EMA) label of Mavenclad®.

Serious adverse events	Mavenclad®		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 280 (5.36%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid tumour benign			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			

subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulum intestinal			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Stress urinary incontinence			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bartholin's abscess			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 280 (0.36%)		
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	Mavenclad®		
Total subjects affected by non-serious adverse events subjects affected / exposed	110 / 280 (39.29%)		
Nervous system disorders Headache subjects affected / exposed	21 / 280 (7.50%)		
occurrences (all)	21		
Infections and infestations COVID-19 subjects affected / exposed	84 / 280 (30.00%)		
occurrences (all)	84		
Urinary tract infection subjects affected / exposed	16 / 280 (5.71%)		
occurrences (all)	16		
Nasopharyngitis subjects affected / exposed	16 / 280 (5.71%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2021	1. To collect data on the potential impact of COVID-19 on the study endpoints. 2. KFS assessments should be performed along with Expanded Disability Status Scale (EDSS) assessments, as done in the CLARIFY MS parent study. 3. Details of pregnancy occurring during the gap period need to be collected in the adverse event (AE) page and reported to Global Patient Safety. 4. A drop-out rate during the CLARIFY MS trial of 20% was expected. However, it was observed that the current actual drop-out rate was around 10%, which results in more subjects available for enrollment in the extension study. With a drop-out rate of 10%, approximately 380 subjects may be eligible to enroll into the extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported