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	21 February 2022

Results information

Result version number	v2 (current)
This version publication date	05 March 2023
First version publication date	11 October 2022
Version creation reason	

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 Healthcare KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, 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	05 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2022
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:

A total of 270 subjects were enrolled in the study from different trial sites across14 countries (Austria, Germany, Hungary, Poland, Czechia, Italy, Spain, France, United Kingdom of Great Britain and Northern Ireland, Finland, Sweden, Israel, Australia and Canada).

Pre-assignment

Screening details:

A total of 313 subjects were screened for eligibility and 270 subjects were enrolled and randomized.

Period 1

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

Arms

Arm title	Experimental: Mavenclad®

Arm description:

Participants 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	
Pharmaceutical forms	Tablet, Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Participants 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	Experimental: Mavenclad®
Started	270
Full Analysis Set (FAS)	270
Completed	270

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Mavenclad®
Reporting group description:	
Participants 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	Experimental: Mavenclad®	Total	
Number of subjects	270	270	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	270	270	
From 65-84 years	0	0	
85 years and over	0	0	
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	0	0	
Unknown or Not Reported	30	30	
Other	12	12	
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	Experimental: Mavenclad®

Reporting group description:

Participants 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 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)[1]

End point description:

CUA lesions were measured by using MRI scans. FAS included all subjects from the Intent to Treat (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 outcome measure and "Number Analyzed" signifies those subjects who were evaluable at specified categories.

End point type	Primary

End point timeframe:

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

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

End point values	Experimental: 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)[2]

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 outcome measure and "Number Analyzed" signifies those subjects who were evaluable at specified categories.

End point type	Primary

End point timeframe:

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

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

End point values	Experimental: 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

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)[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 outcome measure and "Number Analyzed" signifies those subjects who were evaluable at specified categories.

End point type	Primary

End point timeframe:

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

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

End point values	Experimental: 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

Secondary: Percent Change From Baseline in Counts of Immune Cell Subsets - B Cells at Month 3, 6, 12, 15, 18 and 24

End point title	Percent Change From Baseline in Counts of Immune Cell Subsets - B Cells at Month 3, 6, 12, 15, 18 and 24

End point description:

B cell population counts are: CD19 B cells (TBNK panel), CD20 B cells (B cell panel), Memory B cells (B cell panel), Activated B cells (B cell panel), Total plasma cells (B cell panel), Short-lived plasma cells (B cell panel), Naïve B cells (B cell panel), Transitional B cells (B cell panel), and Regulatory B cells (B cell panel). 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 outcome measure and "n" signifies those subjects who were evaluable at specified categories.

End point type	Secondary

End point timeframe:

Baseline, Month 3, 6, 12, 15, 18 and 24.

End point values	Experimental: Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
CD19 B cells(TBNK panel),Month 3:n=204	-80.14 (-85.85 to -73.65)			
CD19 B cells(TBNK panel),Month 6:n=200	-60.60 (-72.43 to -45.62)			
CD19 B cells(TBNK panel),Month 12:n=195	-26.88 (-46.67 to -3.70)			
CD19 B cells(TBNK panel),Month 15:n=161	-77.24 (-85.64 to -65.59)			
CD19 B cells(TBNK panel),Month 18:n=163	-55.30 (-69.55 to -39.30)			
CD19 B cells(TBNK panel),Month 24:n=172	-27.65 (-46.11 to 1.77)			
CD20 B cells(B cell panel),Month 3: n=200	-80.50 (-86.46 to -74.23)			
CD20 B cells(B cell panel),Month 6: n=196	-60.32 (-71.94 to -43.77)			
CD20 B cells(B cell panel),Month 12: n=191	-24.56 (-45.77 to -2.54)			
CD20 B cells(B cell panel),Month 15: n=159	-77.11 (-85.54 to -65.25)			
CD20 B cells(B cell panel),Month 18: n=163	-54.21 (-68.62 to -36.91)			
CD20 B cells(B cell panel),Month 24: n= 169	-24.77 (-43.43 to 8.84)			
Memory B cells(B cell panel),Month 3: n= 200	-92.69 (-95.56 to -88.52)			
Memory B cells(B cell panel), Month 6: n= 196	-91.56 (-94.14 to -86.80)			
Memory B cells(B cell panel), Month 12: n= 189	-86.90 (-91.57 to -80.14)			
Memory B cells(B cell panel), Month 15: n= 159	-96.47 (-97.75 to -93.25)			
Memory B cells(B cell panel), Month 18: n= 162	-94.67 (-96.70 to -91.41)			
Memory B cells(B cell panel), Month 24: n= 169	-89.29 (-93.61 to -84.91)			

Activated B cells(B cell panel), Month 3: n= 200	-74.02 (-83.29 to -61.45)			
Activated B cells(B cell panel), Month 6: n= 196	-60.91 (-74.77 to -38.25)			
Activated B cells(B cell panel), Month 12: n= 190	-28.82 (-52.68 to -1.85)			
Activated B cells(B cell panel), Month 15: n= 159	-73.02 (-83.81 to -62.22)			
Activated B cells(B cell panel), Month 18: n= 163	-51.87 (-65.00 to -28.54)			
Activated B cells(B cell panel), Month 24: n= 169	-15.95 (-40.82 to 29.33)			
Total plasma cells(B cell panel), Month 3: n= 200	-66.62 (-82.38 to -33.69)			
Total plasma cells(B cell panel), Month 6: n= 196	-59.00 (-78.63 to -28.51)			
Total plasma cells (B cell panel),Month 12:n= 190	-54.75 (-71.43 to -19.03)			
Total plasma cells(B cell panel), Month 15: n= 155	-78.02 (-89.68 to -60.13)			
Total plasma cells(B cell panel), Month 18: n= 158	-72.39 (-84.71 to -57.31)			
Total plasma cells(B cell panel), Month 24: n= 167	-62.47 (-80.79 to -36.26)			
Short-lived plasma cells(BCell panel)Month3:n=200	-68.18 (-84.72 to -43.46)			
Short-lived plasma cells(BCell panel)Month6:n=195	-56.55 (-77.83 to -31.98)			
Short-lived plasma cells(BCell panel)Month12:n=188	-56.70 (-76.20 to -23.22)			
Short-lived plasma cells(BCell panel)Month15:n=158	-82.96 (-93.23 to -69.90)			
Short-lived plasma cells(BCell panel)Month18:n=161	-79.54 (-90.76 to -65.70)			
Short-lived plasma cells(BCell panel)Month24:n=168	-70.10 (-83.17 to -45.12)			
Naïve B cells (B cell panel), Month 3: n= 200	-75.87 (-84.21 to -66.18)			
Naïve B cells (B cell panel), Month 6: n=196	-45.87 (-61.72 to -24.82)			
Naïve B cells (B cell panel), Month 12: n=189	1.63 (-20.85 to 35.59)			
Naïve B cells (B cell panel), Month 15: n=159	-69.17 (-79.40 to -51.59)			
Naïve B cells (B cell panel), Month 18: n=162	-39.73 (-57.61 to -5.27)			
Naïve B cells (B cell panel), Month 24: n=169	10.85 (-21.00 to 45.19)			
Transitional B cells(B cell panel), Month3:n=200	-4.06 (-38.65 to 56.25)			
Transitional B cells(B cell panel) Month6:n=196	14.82 (-26.68 to 63.34)			
Transitional B cells(B cell panel)Month12:n=191	11.92 (-26.75 to 64.99)			
Transitional B cells(B cell panel)Month15:n=159	28.69 (-29.88 to 92.02)			
Transitional B cells(B cell panel)Month18:n=163	11.27 (-22.94 to 67.22)			
Transitional B cells (B cell panel)Month24:n=170	6.30 (-27.06 to 69.12)			
Regulatory B cells(B cell panel), Month3:n=200	110.73 (17.78 to 290.50)			

Regulatory B cells(B cell panel), Month6:n=196	92.95 (19.07 to 231.41)			
Regulatory B cells(B cell panel), Month12:n= 191	30.64 (-18.33 to 134.17)			
Regulatory B cells(B cell panel), Month15:n=159	91.57 (15.05 to 288.71)			
Regulatory B cells(B cell panel), Month18:n=163	33.83 (-21.55 to 150.29)			
Regulatory B cells(B cell panel), Month24:n=170	1.62 (-36.85 to 98.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Counts of Immune Cell Subsets - T Cells at Month 3, 6, 12, 15, 18 and 24

End point title	Percent Change From Baseline in Counts of Immune Cell Subsets - T Cells at Month 3, 6, 12, 15, 18 and 24

End point description:

T cell population counts are: Total CD4 T cells (TBNK panel), CD4 Th1 cells (T cell panel), CD4 Th17 T cells (T cell panel), CD4 Regulatory T cells (T cell panel), and Total CD8 T cells (TBNK panel). 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 outcome measure and "n" signifies those subjects who were evaluable at specified categories.

End point type	Secondary

End point timeframe:

Baseline, Month 3, 6, 12, 15, 18 and 24.

End point values	Experimental: Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
Total CD4 T cells (TBNK panel), Month 3: n= 204	-48.60 (-62.55 to -37.05)			
Total CD4 T cells (TBNK panel), Month 6: n= 200	-47.18 (-59.72 to -34.68)			
Total CD4 T cells (TBNK panel), Month 12: n= 195	-40.16 (-55.59 to -27.74)			
Total CD4 T cells (TBNK panel), Month 15: n= 161	-69.04 (-79.78 to -58.61)			
Total CD4 T cells (TBNK panel), Month 18: n= 163	-66.98 (-75.03 to -55.24)			
Total CD4 T cells (TBNK panel), Month 24: n= 172	-57.51 (-67.54 to -47.47)			
CD4 Th1 cells (T cell panel), Month 3: n= 203	-44.35 (-61.62 to -30.01)			
CD4 Th1 cells (T cell panel), Month 6: n= 197	-43.20 (-56.95 to -28.94)			
CD4 Th1 cells (T cell panel), Month 12: n= 192	-35.55 (-50.76 to -17.71)			

CD4 Th1 cells (T cell panel), Month 15: n= 159	-63.68 (-77.41 to -51.43)			
CD4 Th1 cells (T cell panel), Month 18: n= 163	-63.01 (-74.41 to -49.62)			
CD4 Th1 cells (T cell panel), Month 24: n= 170	-52.86 (-62.71 to -40.22)			
CD4 Th17 T cells (T cell panel), Month 3: n= 200	-33.09 (-53.72 to -15.56)			
CD4 Th17 T cells (T cell panel), Month 6: n= 193	-30.26 (-46.84 to -10.70)			
CD4 Th17 T cells (T cell panel), Month 12: n= 185	-18.39 (-38.10 to 10.51)			
CD4 Th17 T cells (T cell panel), Month 15: n= 152	-44.77 (-59.51 to -28.43)			
CD4 Th17 T cells (T cell panel), Month 18: n= 157	-42.77 (-55.47 to -18.37)			
CD4 Th17 T cells (T cell panel), Month 24: n= 164	-31.74 (-46.81 to -3.84)			
CD4 Regulatory T cells(T cell panel),Month3:n=203	-25.98 (-42.82 to -11.42)			
CD4 Regulatory T cells(T cell panel),Month6:n=197	-29.84 (-41.82 to -11.66)			
CD4 Regulatory T cells(T cell panel),Month12:n=192	-25.60 (-38.18 to -10.45)			
CD4 Regulatory T cells(T cell panel),Month15:n=159	-48.40 (-59.80 to -35.82)			
CD4 Regulatory T cells(T cell panel),Month18:n=163	-48.73 (-60.71 to -34.86)			
CD4 Regulatory T cells(T cell panel)Month24:n=169	-40.30 (-52.78 to -27.15)			
Total CD8 T cells(TBNK panel), Month3:n=204	-42.33 (-54.55 to -22.17)			
Total CD8 T cells(TBNK panel), Month6:n=200	-39.42 (-52.98 to -19.88)			
Total CD8 T cells (TBNK panel), Month 12: n= 195	-36.28 (-51.42 to -15.79)			
Total CD8 T cells (TBNK panel), Month 15: n= 161	-57.08 (-69.20 to -38.74)			
Total CD8 T cells (TBNK panel), Month 18: n= 163	-54.44 (-67.77 to -35.12)			
Total CD8 T cells (TBNK panel), Month 24: n= 172	-45.93 (-58.41 to -30.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Counts of Immune Cell Subsets - NK Cells at Month 3, 6, 12, 15, 18 and 24

End point title	Percent Change From Baseline in Counts of Immune Cell Subsets - NK Cells at Month 3, 6, 12, 15, 18 and 24

End point description:

NK cell population counts are: CD16+ CD56-, NK Cells, CD16+ NK Cells, NK p46 cells, CD16lowCD56bright, and CD16brightCD56dim. 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 outcome measure and "n" signifies those subjects who were evaluable at specified categories.

End point type	Secondary

End point timeframe:
Baseline, Month 3, 6, 12, 15, 18 and 24.

End point values	Experimental: Mavenclad®			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: Percent change				
median (inter-quartile range (Q1-Q3))				
CD16+ CD56- NK cells, Month 3: n= 203	3.08 (-32.82 to 48.59)			
CD16+ CD56- NK cells, Month 6: n= 197	-8.88 (-35.60 to 40.41)			
CD16+ CD56- NK cells, Month 12: n= 192	9.44 (-38.02 to 65.90)			
CD16+ CD56- NK cells, Month 15: n= 159	27.70 (-24.44 to 104.4)			
CD16+ CD56- NK cells, Month 18: n= 163	7.89 (-31.60 to 55.64)			
CD16+ CD56- NK cells, Month 24: n= 170	-21.64 (-50.92 to 38.15)			
CD16+ NK cells, Month 3: n= 203	-32.50 (-49.49 to -12.61)			
CD16+ NK cells, Month 6: n= 197	-21.78 (-44.93 to 1.81)			
CD16+ NK cells, Month 12: n= 192	-8.10 (-33.88 to 14.37)			
CD16+ NK cells, Month 15: n= 159	-28.56 (-48.73 to -4.90)			
CD16+ NK cells, Month 18: n= 163	-21.47 (-40.28 to 2.74)			
CD16+ NK cells, Month 24: n= 170	-13.76 (-35.92 to 12.58)			
NK p46 cells, Month 3: n= 203	-20.85 (-47.77 to 17.63)			
NK p46 cells, Month 6: n= 197	-22.38 (-45.67 to 21.71)			
NK p46 cells, Month 12: n= 192	29.49 (-18.73 to 116.77)			
NK p46 cells, Month 15: n= 158	28.42 (-11.69 to 97.64)			
NK p46 cells, Month 18: n= 163	71.73 (2.68 to 154.75)			
NK p46 cells, Month 24: n= 170	77.70 (18.42 to 175.01)			
CD16low CD56bright, Month 3: n= 203	-8.94 (-36.65 to 31.46)			
CD16low CD56bright, Month 6: n= 197	3.72 (-26.06 to 42.24)			
CD16low CD56bright, Month 12: n= 192	2.56 (-20.62 to 41.41)			
CD16low CD56bright, Month 15: n= 159	4.77 (-23.35 to 49.22)			
CD16low CD56bright, Month 18: n= 163	30.13 (-8.52 to 75.67)			
CD16low CD56bright, Month 24: n= 170	17.21 (-20.09 to 82.09)			

CD16bright CD56dim, Month 3: n= 203	-36.13 (-55.16 to -14.13)			
CD16bright CD56dim, Month 6: n= 197	-25.61 (-46.87 to 1.97)			
CD16bright CD56dim, Month 12: n= 192	-11.05 (-38.53 to 16.63)			
CD16bright CD56dim, Month 15: n= 159	-35.05 (-55.45 to -8.85)			
CD16bright CD56dim, Month 18: n= 163	-24.99 (-45.87 to -0.29)			
CD16bright CD56dim, Month 24: n= 170	-12.94 (-37.36 to 10.95)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to Month 45	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0
Reporting groups	
Reporting group title	Experimental: Mavenclad®
Reporting group description:	
Participants 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	14 / 270 (5.19%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
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		
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		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Overdose			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
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		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
Ischaemic stroke			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
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			
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		
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		
Diplopia			
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		
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Interspinous osteoarthritis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			

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	225 / 270 (83.33%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 270 (7.41%)		
occurrences (all)	20		
Headache			
subjects affected / exposed	87 / 270 (32.22%)		
occurrences (all)	87		
Paraesthesia			
subjects affected / exposed	15 / 270 (5.56%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 270 (11.48%)		
occurrences (all)	31		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	28 / 270 (10.37%)		
occurrences (all)	28		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	26 / 270 (9.63%)		
occurrences (all)	26		

Nausea subjects affected / exposed occurrences (all)	31 / 270 (11.48%) 31		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	21 / 270 (7.78%) 21		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	16 / 270 (5.93%) 16 16 / 270 (5.93%) 16		
Musculoskeletal and connective tissue disorders Pain in extrimity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle Spasm subjects affected / exposed occurrences (all) Neck Pain subjects affected / exposed occurrences (all)	22 / 270 (8.15%) 22 19 / 270 (7.04%) 19 30 / 270 (11.11%) 30 17 / 270 (6.30%) 17 14 / 270 (5.19%) 14		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection	57 / 270 (21.11%) 57		

subjects affected / exposed	32 / 270 (11.85%)		
occurrences (all)	32		
Oral herpes			
subjects affected / exposed	20 / 270 (7.41%)		
occurrences (all)	20		
Upper respiratory tract infection			
subjects affected / exposed	27 / 270 (10.00%)		
occurrences (all)	27		

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