Clinical trial results:
A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With Teriflunomide, in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety (evolutionRMS 1)

Summary

EudraCT number	2019-004972-20
Trial protocol	DE GB AT HU BE CZ BG ES FI HR IT
Global end of trial date	08 March 2024

Results information

Result version number	v1 (current)
This version publication date	20 March 2025
First version publication date	20 March 2025

Trial information

Trial identification

Sponsor protocol code	MS200527_0080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04338022
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt Germany
Sponsor organisation address	Street Address: Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, 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	08 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 March 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study was to evaluate the efficacy and safety of evobrutinib administered orally twice daily versus Teriflunomide (Aubagio®), administered orally once daily in subjects with Relapsing Multiple Sclerosis (RMS). Subjects who complete the double-blind treatment period (DBTP) and double-blind extension period (DBEP) prior to approval of a separate long-term follow-up study in their country will get an option for evobrutinib treatment continuation through a 96-week open-label extension (OLE) period.

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	12 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 36
Country: Number of subjects enrolled	Bosnia and Herzegovina: 4
Country: Number of subjects enrolled	Czechia: 66
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Georgia: 133
Country: Number of subjects enrolled	Croatia: 47
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Poland: 105
Country: Number of subjects enrolled	Russian Federation: 163
Country: Number of subjects enrolled	Serbia: 29
Country: Number of subjects enrolled	Ukraine: 233
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 2

Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	Argentina: 55
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Taiwan: 6
Worldwide total number of subjects	1124
EEA total number of subjects	378

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)	1124
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1561 subjects with relapsing multiple sclerosis (RMS) were screened in this trial. Out of which 1124 subjects were randomized at a ratio of 1:1 (evobrutinib group: 560 and teriflunomide group: 564) in this trial.

Pre-assignment

Screening details:

3 subjects were enrolled in the Open Label Extension (OLE) Period after Double Blind Treatment Period (DBTP) Week 96 and they did not enter Double Blind Extension (DBE) period.

Period 1

Period 1 title	Double-blind treatment period: 156 weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide

Arm description:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.

Arm type	Active comparator
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP).

Arm title	Evobrutinib

Arm description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Arm type	Experimental
Investigational medicinal product name	Evobrutinib
Investigational medicinal product code	M2951
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP).

Number of subjects in period 1	Teriflunomide	Evobrutinib
Started	564	560
Completed	396	384
Not completed	168	176
Adverse event, serious fatal	1	1
Consent withdrawn by subject	56	55
Randomized, but not treated	1	1
Adverse event, non-fatal	56	72
Protocol Non-Compliance	5	5
Other Reason	24	14
Lost to follow-up	6	5
Lack of efficacy	19	23

Period 2

Period 2 title	Double-blind extension: 96 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide

Arm description:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.

Arm type	Active comparator
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Teriflunomide at a dose of 14 mg orally once daily up to 96 weeks in double blind extension (DBE) period.

Arm title	Evobrutinib

Arm description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Arm type	Experimental

Investigational medicinal product name	Evobrutinib
Investigational medicinal product code	M2951
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 96 weeks in double blind extension (DBE) period.

Number of subjects in period 2[1]	Teriflunomide	Evobrutinib
Started	377	359
Completed	371	346
Not completed	6	13
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	-
Other Reason	3	9
Lost to follow-up	-	1
Lack of efficacy	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: only 736 subjects (377 in Teriflunomide and 359 in Evobrutinib) started the DBE period.

Period 3

Period 3 title	Open Label Extension: 96 weeks
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Evobrutinib

Arm description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Arm type	Experimental
Investigational medicinal product name	Evobrutinib
Investigational medicinal product code	M2951
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 96 weeks in open label extension (OLE) period.

Number of subjects in period 3[2]	Evobrutinib
Started	3
Completed	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: only 3 subjects ("0" in Teriflunomide and "3" in Evobrutinib) started the OLE period.

Baseline characteristics

Reporting groups	
Reporting group title	Teriflunomide
Reporting group description:	
Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.	
Reporting group title	Evobrutinib
Reporting group description:	
Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.	

Reporting group values	Teriflunomide	Evobrutinib	Total
Number of subjects	564	560	1124
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	38	37	
standard deviation	± 9.5	± 9.6	-
Sex: Female, Male Units: subjects			
Female	374	377	751
Male	190	183	373
Ethnicity Units: Subjects			
Hispanic or Latino	60	63	123
Not Hispanic or Latino	504	497	1001
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	6	13	19
Asian	10	16	26
Black or African American	2	4	6
White	536	519	1055
More than one race	5	2	7
Unknown or Not Reported	5	6	11

End points

End points reporting groups

Reporting group title	Teriflunomide

Reporting group description:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.

Reporting group title	Evobrutinib

Reporting group description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Reporting group title	Teriflunomide

Reporting group description:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.

Reporting group title	Evobrutinib

Reporting group description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Reporting group title	Evobrutinib

Reporting group description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Primary: Double Blind Treatment Period (DBTP) and Double Blind Extension (DBE) Period: Annualized Relapse Rate (ARR)

End point title	Double Blind Treatment Period (DBTP) and Double Blind Extension (DBE) Period: Annualized Relapse Rate (ARR)[1]

End point description:

The qualifying relapse is the occurrence of new or worsening neurological symptoms attributable to Multiple Sclerosis (MS) (for more than [>] 24 hours, no fever, infection, injury, adverse events (AEs,) and preceded by a stable or improving neurological state for more than or equal to [>=] 30 days). Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Primary

End point timeframe:

From baseline to 172 weeks

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	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: relapses per year				
arithmetic mean (confidence interval 95%)	0.13 (0.11 to 0.15)	0.14 (0.12 to 0.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Open Label Extension (OLE) Period: Number of Subjects with Adverse Events (AEs) and Serious AEs

End point title	Open Label Extension (OLE) Period: Number of Subjects with Adverse Events (AEs) and Serious AEs[2][3]

End point description:

Adverse event (AE): Any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study drug. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. Serious AE: an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

From OLE Baseline (DBTP Week 96) to OLE Week 52

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 data was planned to be reported for this endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported only OLE period arms.

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects				
Subjects with AEs	1			
Subjects with Serious AEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Percentage of Subjects Without 12-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point title	DBTP and DBE Period: Percentage of Subjects Without 12-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point description:

Disability progression was defined as increase in EDSS of greater than or equal to [>=] 1 point from baseline EDSS score, if EDSS score at baseline is 5.0 or less and an increase of >=0.5 point, if the baseline score is 5.5. Disability progression is considered sustained for 12 weeks when the initial increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of neurological worsening. The total EDSS score ranges from 0 (normal) to 10 (death due to multiple sclerosis). Kaplan-Meier method was used to estimate the percentage of subjects without 12-week CDP. Full Analysis Set (FAS) included all subjects who were randomized to study treatment. The result reported for this endpoint are the results from data of combined DBTP and DBE periods.

End point type	Secondary

End point timeframe:

Week 96 and Week 156 (combined DBTP and DBE period)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	91.0 (88.0 to 93.3)	91.3 (88.3 to 93.5)		
Week 156	86.0 (81.5 to 89.5)	87.9 (83.5 to 91.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Percentage of Subjects with 24-Week Confirmed Disability Improvement (CDI) as Measured by Expanded Disability Status Scale (EDSS)

End point title	DBTP and DBE Period: Percentage of Subjects with 24-Week Confirmed Disability Improvement (CDI) as Measured by Expanded Disability Status Scale (EDSS)

End point description:

Disability improvement was defined as a reduction of 1 point from Baseline EDSS score when the Baseline score is >= 2 and less than or equal to [<=] 6 and a reduction of 0.5 point from Baseline EDSS score when the Baseline score is >= 6.5 and <= 9.5. Disability improvement is considered sustained when the initial reduction in the EDSS score is confirmed at a regularly scheduled visit at least 24 weeks after the initial reduction. The total EDSS score ranges from 0 (normal) to 10 (death due to multiple sclerosis). Kaplan-Meier method was used to estimate the percentage of subjects with 12-week CDI. Full Analysis Set (FAS) included all subjects who were randomized to study treatment. The result reported for this endpoint are the results from data of combined DBTP and DBE periods.

End point type	Secondary

End point timeframe:

Week 96 and Week 156 (combined DBTP and DBE period)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	7.9 (5.6 to 11.2)	9.4 (6.7 to 13.0)		
Week 156	8.8 (6.2 to 12.4)	10.1 (7.3 to 13.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Percentage of Subjects Without 24-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point title	DBTP and DBE Period: Percentage of Subjects Without 24-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point description:

Disability progression was defined as increase in EDSS of greater than or equal to [>=] 1 point from baseline EDSS score, if EDSS score at baseline is 5.0 or less and an increase of >=0.5 point, if the baseline score is 5.5. Disability progression is considered sustained for 24 weeks when the initial increase in the EDSS is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening. The total EDSS score ranges from 0 (normal) to 10 (death due to multiple sclerosis). Kaplan-Meier method was used to estimate the percentage of subjects without 24-week CDP. Full Analysis Set (FAS) included all subjects who were randomized to study treatment. The result reported for this endpoint are the results from data of combined DBTP and DBE periods.

End point type	Secondary

End point timeframe:

Week 96 and Week 156 (combined DBTP and DBE period)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	94.3 (91.9 to 96.1)	92.7 (89.9 to 94.7)		
Week 156	92.3 (89.2 to 94.5)	92.1 (89.2 to 94.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Score at Week 48, Week 96, Week 120, Week 144 and Week 156

End point title	DBTP and DBE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Score at Week 48, Week 96, Week 120, Week 144 and Week 156

End point description:

Physical function was assessed with PROMISnq Short Form v2.0 – Physical Function – Multiple Sclerosis 15a (PROMISnq PF(MS) 15a). PROMISnq PF(MS) 15a assesses a subject's abilities and limitations with respect to everyday physical activities. Results are reported as a T-score. In the general population, T-scores have a mean of 50, standard deviation of 10, and range from 10 to 65. Higher T-scores represent higher physical function. Change from baseline in PROMIS PF score was analyzed using Mixed Effect Model for Repeated Measures (MMRM) to evaluate the result of the 2 periods (DBTP and DBE). Full Analysis Set (FAS) included all subjects who were randomized to study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint. The result reported for this endpoint are the results from data of combined DBTP and DBE periods.

End point type	Secondary

End point timeframe:

Baseline, Week 48, Week 96, Week 120, Week 144 and Week 156 (combined DBTP and DBE period)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	551	545		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 48	-0.30 (-0.79 to 0.19)	0.05 (-0.45 to 0.55)		
Week 96	-0.76 (-1.35 to -0.16)	-0.14 (-0.74 to 0.46)		
Week 120	-0.29 (-0.95 to 0.37)	-0.25 (-0.92 to 0.42)		
Week 144	-1.04 (-1.82 to -0.25)	-0.70 (-1.53 to 0.14)		
Week 156	-1.61 (-2.70 to -0.51)	-1.44 (-2.66 to 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Total number of T1 Gadolinium-positive (Gd+) lesions

End point title	DBTP and DBE Period: Total number of T1 Gadolinium-positive (Gd+) lesions

End point description:

Analysis of Gadolinium-positive T1 lesions was done using magnetic resonance imaging (MRI) scans. Full

Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: lesions per scan				
arithmetic mean (confidence interval 95%)	0.35 (0.29 to 0.42)	0.52 (0.43 to 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Score at Week 48, Week 96, Week 120, Week 144 and Week 156

End point title	DBTP and DBE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Score at Week 48, Week 96, Week 120, Week 144 and Week 156

End point description:

PROMIS Fatigue score was assessed with PROMIS Short Form v1.0 – Fatigue – Multiple Sclerosis 8a (PROMIS Fatigue (MS) 8a). PROMIS Fatigue (MS) 8a assesses level of fatigue and its interference on daily activities. Results are reported as a T-score. In the general population, T-scores have a mean of 50, standard deviation of 10, and range from 33 to 85. Higher T-scores represent higher fatigue. Change from baseline in PROMIS fatigue score was analyzed using Mixed Effect Model for Repeated Measures (MMRM) to evaluate the result of the 2 periods (DBTP and DBE). Full Analysis Set (FAS) included all subjects who were randomized to study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint. The result reported for this endpoint are the results from data of combined DBTP and DBE periods.

End point type	Secondary

End point timeframe:

Baseline, Week 48, Week 96, Week 120, Week 144 and Week 156 (combined DBTP and DBE period)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	551	545		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 48	-1.39 (-1.98 to -0.81)	-1.82 (-2.41 to -1.23)		
Week 96	-1.60 (-2.32 to -0.87)	-2.14 (-2.88 to -1.41)		

Week 120	-1.44 (-2.25 to -0.63)	-1.32 (-2.15 to -0.50)		
Week 144	-1.88 (-2.90 to -0.86)	-0.98 (-2.06 to 0.10)		
Week 156	0.72 (-0.78 to 2.22)	-0.21 (-1.90 to 1.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE periods: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) by Severity

End point title	DBTP and DBE periods: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) by Severity

End point description:

Severity of adverse events (AE) were assessed by the investigator per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0. Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death. Number of subjects with Grades 1, 2, 3, 4 and 5 were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	482		
Units: subjects				
Subjects with Grade 1	50	56		
Subjects with Grade 2	349	327		
Subjects with Grade 3	82	88		
Subjects with Grade 4	3	10		
Subjects with Grade 5	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE periods: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Adverse Events of Special Interest (AESIs)

End point title	DBTP and DBE periods: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Adverse Events of Special Interest (AESIs)

End point description:

Adverse event (AE): Any untoward medical occurrence in a subject which does not necessarily have a

causal relationship with the study drug. Serious AE: an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs: those AEs with an onset date on or after the date of first study intervention administration, or AEs present prior to any study intervention administration but exacerbating after. TEAEs included both Serious TEAEs and non-serious TEAEs. AESIs included liver AEs (possible drug-induced, non-infectious, non-alcoholic, and immune-mediated), infections (serious and opportunistic infections), lipase and amylase elevation, and seizure. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	563	559		
Units: subjects				
Subjects with TEAEs	485	482		
Subjects with AESIs	120	117		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP Period: Neurofilament Light Chain Concentration (NfL) at Week 12

End point title	DBTP Period: Neurofilament Light Chain Concentration (NfL) at Week 12

End point description:

NfL is a biomarker of neuro-axonal damage whose concentration was assessed in blood at Week 12. Full Analysis Set (FAS) included all subjects who were randomized to study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	528		
Units: nanogram per liter (ng/L)				
geometric mean (confidence interval 95%)	12.90 (12.48 to 13.34)	12.88 (12.46 to 13.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Period: New or Enlarging T2 Lesions Rate

End point title	DBTP and DBE Period: New or Enlarging T2 Lesions Rate

End point description:

Analysis of new or enlarging T2 lesions rate was done using magnetic resonance imaging (MRI) scans. Negative binomial model for lesion count (summed over scans) includes treatment and covariates based on randomization strata and baseline volume of T2 lesion (continuous), with offset equal to the log of the time in years between the last available MRI scan and the baseline scan. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	560		
Units: lesions per year				
arithmetic mean (confidence interval 95%)	5.78 (5.02 to 6.65)	5.45 (4.73 to 6.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Vital Signs: Diastolic Blood Pressure and Systolic Blood Pressure

End point title	DBTP and DBE Periods: Change From Baseline in Vital Signs: Diastolic Blood Pressure and Systolic Blood Pressure

End point description:

Diastolic blood pressure and systolic blood pressure were measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: diastolic blood pressure and systolic blood pressure from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic Blood Pressure	2.6 (± 11.18)	0.2 (± 10.83)		

Diastolic Blood Pressure	1.8 (± 8.35)	0.0 (± 8.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Vital Signs: Pulse Rate

End point title	DBTP and DBE Periods: Change From Baseline in Vital Signs: Pulse Rate

End point description:

Pulse rate was measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: pulse rate from baseline up to baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	443		
Units: beats per minute				
arithmetic mean (standard deviation)	2.6 (± 10.22)	1.9 (± 9.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs) Parameter: Heart Rate

End point title	DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs) Parameter: Heart Rate

End point description:

Heart rate was measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: heart rate from baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	50		
Units: beats per minute				
arithmetic mean (standard deviation)	3.0 (± 10.90)	-0.1 (± 12.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Vital Signs: Temperature

End point title	DBTP and DBE Periods: Change From Baseline in Vital Signs: Temperature

End point description:

Temperature was measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: Temperature from baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	442		
Units: degree Celsius				
arithmetic mean (standard deviation)	0.00 (± 0.326)	0.02 (± 0.319)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Vital Signs: Respiratory Rate

End point title	DBTP and DBE Periods: Change From Baseline in Vital Signs: Respiratory Rate

End point description:

Respiratory rate was measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: respiratory rate from baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	442		
Units: breaths per minute				
arithmetic mean (standard deviation)	-0.1 (± 1.76)	-0.2 (± 1.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Vital Signs: Weight

End point title	DBTP and DBE Periods: Change From Baseline in Vital Signs: Weight

End point description:

Changes in vital signs: weight from baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	443		
Units: kilograms (kg)				
arithmetic mean (standard deviation)	-0.21 (± 5.867)	0.48 (± 5.490)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs) Parameters: QT Interval - Fridericia's Correction Formula, PR Interval and QRS Duration

End point title	DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs) Parameters: QT Interval - Fridericia's Correction Formula, PR Interval and QRS Duration

End point description:

QT Interval - Fridericia's Correction Formula, PR Interval and QRS Duration was measured after at least 5 minutes of rest for the subject in a quiet sitting without distractions. Changes in vital signs: QT Interval - Fridericia's Correction Formula, PR Interval and QRS Duration from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	50		
Units: milliseconds (msec)				
arithmetic mean (standard deviation)				
QT Interval - Fridericia's Correction Formula	-2.77 (± 16.005)	-1.37 (± 12.053)		
PR Interval	-5.2 (± 14.31)	-2.5 (± 14.65)		
QRS Duration	-3.7 (± 7.48)	-1.5 (± 10.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Hemoglobin and Erythrocytes Mean Corpuscular Hemoglobin (HGB) Concentration [Ery. Mean Corp. HGB conc.]

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Hemoglobin and Erythrocytes Mean Corpuscular Hemoglobin (HGB) Concentration [Ery. Mean Corp. HGB conc.]

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the hematology parameters: erythrocytes mean corpuscular HGB concentration and hemoglobin. Changes in hematology parameters: erythrocytes mean corpuscular HGB concentration and hemoglobin from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this outcome measure and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	432		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
Hemoglobin: n = 433, 432	-3.5 (± 10.74)	-2.8 (± 11.34)		
Ery. Mean Corp. HGB conc.: n = 422, 416	-2.7 (± 12.43)	-1.0 (± 11.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Platelets, Leukocytes, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes and Reticulocytes

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Platelets, Leukocytes, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes and Reticulocytes

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the hematology parameters: Platelets, Leukocytes, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes and Reticulocytes. Changes in hematology parameters: Platelets, Leukocytes, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes and Reticulocytes from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	430		
Units: 10^9 cells per liter				
arithmetic mean (standard deviation)				
Platelets: n = 428, 428	-4.8 (± 47.09)	8.8 (± 53.83)		
Leukocytes: n = 433, 430	-0.17 (± 2.165)	-0.09 (± 1.958)		
Neutrophils: n = 358, 353	-0.316 (± 1.8846)	-0.210 (± 1.8356)		
Eosinophils: n = 424, 424	0.0510 (± 0.15999)	0.0203 (± 0.15853)		
Basophils: n = 424, 424	-0.0009 (± 0.03657)	-0.0003 (± 0.03786)		
Monocytes: n = 424, 424	0.0785 (± 0.18171)	0.0656 (± 0.17816)		
Lymphocytes: n = 424, 424	-0.0307 (± 0.58566)	-0.0401 (± 0.58108)		
Reticulocytes: n = 411, 411	0.488 (± 20.2014)	-0.827 (± 17.6824)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Bilirubin and Creatinine

End point title	DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Bilirubin and Creatinine

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the biochemistry parameters: Bilirubin and Creatinine. Changes in biochemistry parameters: Bilirubin and Creatinine from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	439		
Units: micromoles per liter (mcmol/L)				
arithmetic mean (standard deviation)				
Bilirubin: n = 433, 439	-0.08 (± 4.792)	0.15 (± 4.792)		
Creatinine: n = 435, 438	0.6 (± 12.76)	2.4 (± 8.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Erythrocytes Mean Corpuscular Volume

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Erythrocytes Mean Corpuscular Volume

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the hematology parameter: Erythrocytes Mean Corpuscular Volume. Changes in hematology parameter: Erythrocytes Mean Corpuscular Volume from baseline up to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	417		
Units: femtoliters				
arithmetic mean (standard deviation)	-1.42 (± 5.999)	-1.75 (± 4.895)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Erythrocytes Mean Corpuscular Hemoglobin

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Erythrocytes Mean Corpuscular Hemoglobin

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the hematology parameter: Erythrocytes Mean Corpuscular Hemoglobin. Changes in hematology parameter: Erythrocytes Mean Corpuscular Hemoglobin from baseline to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	429		
Units: picogram (pg)				
arithmetic mean (standard deviation)	-0.61 (± 1.588)	-0.62 (± 1.956)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Hematocrit

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameter: Hematocrit

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the hematology parameter: Hematocrit. Changes in hematology parameter: Hematocrit from baseline to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	426	419		
Units: percentage of cells				
arithmetic mean (standard deviation)	-0.0069 (± 0.03359)	-0.0076 (± 0.03238)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Gamma Glutamyl Transferase and Lactate Dehydrogenase

End point title	DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Gamma Glutamyl Transferase and Lactate Dehydrogenase

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the biochemistry parameters: Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Gamma Glutamyl Transferase and Lactate Dehydrogenase. Changes in biochemistry parameters: Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Amylase, Lipase, Gamma Glutamyl Transferase and Lactate Dehydrogenase from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	440		
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
Aspartate Aminotransferase: n = 433, 433	2.32 (± 18.190)	6.49 (± 64.249)		
Alanine Aminotransferase: n = 433, 438	4.06 (± 23.308)	8.55 (± 52.866)		
Alkaline Phosphatase: n = 435, 440	4.20 (± 23.289)	7.65 (± 20.252)		
Amylase: n = 434, 439	-0.5 (± 17.04)	2.8 (± 16.84)		
Lipase: n = 435, 438	-2.5 (± 33.36)	3.5 (± 17.33)		
Gamma Glutamyl Transferase: n = 375, 390	4.28 (± 21.091)	5.51 (± 40.098)		
Lactate Dehydrogenase: n = 431, 430	6.16 (± 28.235)	-4.53 (± 26.014)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Sodium, Potassium, Calcium, Magnesium, Glucose, Chloride, Urea Nitrogen, Phosphate, Bicarbonate and Corrected Calcium

End point title	DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Sodium, Potassium, Calcium, Magnesium, Glucose, Chloride, Urea Nitrogen, Phosphate, Bicarbonate and Corrected Calcium

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the biochemistry parameters: Sodium, Potassium, Calcium, Magnesium, Glucose, Chloride, Urea Nitrogen, Phosphate, Bicarbonate and Corrected Calcium. Changes in biochemistry parameters: Sodium, Potassium, Calcium, Magnesium, Glucose, Chloride, Urea Nitrogen, Phosphate, Bicarbonate and Corrected Calcium from baseline up to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	439		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Sodium: n = 436, 439	0.9128 (± 2.34334)	0.7904 (± 2.28990)		
Potassium: n = 436, 438	0.0320 (± 0.43741)	0.0893 (± 0.42341)		

Calcium: n = 435, 438	0.004 (± 0.1139)	-0.002 (± 0.1029)		
Magnesium: n = 435, 438	0.004 (± 0.0682)	0.002 (± 0.0656)		
Glucose: n = 432, 437	0.06 (± 0.928)	0.25 (± 1.146)		
Chloride: n = 435, 438	1.8 (± 3.42)	1.7 (± 2.95)		
Urea Nitrogen: n = 434, 437	0.222 (± 1.2668)	0.114 (± 1.2654)		
Phosphate: n = 432, 435	-0.053 (± 0.2048)	-0.026 (± 0.1724)		
Bicarbonate: n = 359, 375	0.05 (± 2.561)	0.04 (± 2.725)		
Corrected Calcium: n = 434, 437	0.0297 (± 0.09428)	0.0317 (± 0.09071)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Total Protein and Albumin

End point title	DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Total Protein and Albumin

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the biochemistry parameters: Total Protein and Albumin. Changes in biochemistry parameters: Total Protein and Albumin from baseline to 176 weeks were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	439		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
Total protein: n = 432, 438	-1.26 (± 4.865)	-0.47 (± 4.417)		
Albumin: n = 436, 439	-1.28 (± 3.520)	-1.67 (± 3.284)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Biochemistry

Parameters: Glomerular Filtration Rate

End point title	DBTP and DBE Periods: Change From Baseline in Biochemistry Parameters: Glomerular Filtration Rate

End point description:

Blood samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the biochemistry parameter: Glomerular Filtration Rate. Changes in biochemistry parameter: Glomerular Filtration Rate from baseline to 176 weeks were reported. The Glomerular Filtration Rate will be measured as milliliter per minute per 1.73 square meter (mL/min/1.73m^2). Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	374		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-3.3 (± 13.82)	-5.6 (± 13.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Urinalyses Parameter: Potential of Hydrogen (pH) of Urine

End point title	DBTP and DBE Periods: Change From Baseline in Urinalyses Parameter: Potential of Hydrogen (pH) of Urine

End point description:

Urine samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the urinalyses parameter: pH. pH is measured on a numeric scale ranging from 0 to 14; values on the scale refer to the degree of alkalinity or acidity. A pH of 7 is neutral. A pH less than 7 is acidic, and a pH greater than 7 is basic. Normal urine has a slightly acid pH (5.0 - 6.0). Changes in urinalyses parameter: pH from baseline to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	436		
Units: pH				
arithmetic mean (standard deviation)	-0.08 (± 0.886)	0.01 (± 0.913)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Absolute Concentrations of Immunoglobulin (Ig) Levels

End point title	DBTP and DBE Periods: Absolute Concentrations of Immunoglobulin (Ig) Levels

End point description:

Absolute Concentrations serum levels of IgG, IgA, IgM were assessed. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 176

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	366		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
IgA	1.750 (± 0.7987)	2.503 (± 1.0582)		
IgG	9.693 (± 2.1096)	10.529 (± 2.2363)		
IgM	1.101 (± 0.6096)	1.181 (± 0.6619)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change From Baseline in Urinalyses Parameter: Specific Gravity of Urine

End point title	DBTP and DBE Periods: Change From Baseline in Urinalyses Parameter: Specific Gravity of Urine

End point description:

Urine samples were collected in a fasted condition (after a fast of at least 12 hours) to analyze the urinalyses parameter: Specific Gravity of Urine. Changes in urinalyses parameter: Specific Gravity of Urine from baseline to 176 weeks was reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	436		
Units: Kilogram per cubic meter				
arithmetic mean (standard deviation)	0.0006 (± 0.03891)	0.0011 (± 0.02189)		

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Percentage of Subjects with 24-Week Confirmed Disability Improvement (CDI) as Measured by Expanded Disability Status Scale (EDSS)

End point title	OLE Period: Percentage of Subjects with 24-Week Confirmed Disability Improvement (CDI) as Measured by Expanded Disability Status Scale (EDSS)

End point description:

Disability improvement was defined as a reduction of 1 point from Baseline EDSS score when the Baseline score is >= 2 and less than or equal to [<=] 6 and a reduction of 0.5 point from Baseline EDSS score when the Baseline score is >= 6.5 and <= 9.5. Disability improvement is considered sustained when the initial reduction in the EDSS score is confirmed at a regularly scheduled visit at least 24 weeks after the initial reduction. The total EDSS score ranges from 0 (normal) to 10 (death due to multiple sclerosis). Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[4] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Percentage of Subjects without 24-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point title	OLE Period: Percentage of Subjects without 24-Week Confirmed Disability Progression (CDP) as Measured by Expanded Disability Status Scale (EDSS)

End point description:

Disability progression was defined as increase in EDSS of greater than or equal to [>=] 1 point from baseline EDSS score, if EDSS score at baseline is 5.0 or less and an increase of >=0.5 point, if the baseline score is 5.5. Disability progression is considered sustained for 24 weeks when the initial increase in the EDSS is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening. The total EDSS score ranges from 0 (normal) to 10 (death due to multiple sclerosis). Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: percentage of subjects				
number (confidence interval 95%)	(to)			

Notes:

[5] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Annualized Relapse Rate (ARR)

End point title	OLE Period: Annualized Relapse Rate (ARR)

End point description:

The qualifying relapse is the occurrence of new or worsening neurological symptoms attributable to Multiple Sclerosis (MS) (for more than [>] 24 hours, no fever, infection, injury, AEs, and preceded by a stable or improving neurological state for more than or equal to [>=] 30 days). Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: relapses per year				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[6] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: DBTP and DBE Periods: Change from Baseline in Immunoglobulin (Ig) Levels

End point title	DBTP and DBE Periods: Change from Baseline in Immunoglobulin (Ig) Levels

End point description:

Change from baseline serum levels of IgG, IgA, IgM were assessed. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment. Here, Overall number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to 176 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	362		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
IgA	-0.262 (± 0.3572)	0.483 (± 0.5320)		
IgG	-0.733 (± 1.4414)	0.105 (± 1.4556)		
IgM	-0.165 (± 0.2979)	-0.187 (± 0.2794)		

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue (MS) 8a Score at Week 52

End point title	OLE Period: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue (MS) 8a Score at Week 52

End point description:

PROMIS Fatigue score was assessed with PROMIS Short Form v1.0 – Fatigue – Multiple Sclerosis 8a (PROMIS Fatigue (MS) 8a). PROMIS Fatigue (MS) 8a assesses level of fatigue and its interference on daily activities. Results are reported as a T-score. In the general population, T-scores have a mean of 50, standard deviation of 10, and range from 33 to 85. Higher T-scores represent higher fatigue. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

OLE Baseline (DBTP Week 96), OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)			

Notes:

[7] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects with Abnormalities in Laboratory Parameters

End point title	OLE Period: Number of Subjects with Abnormalities in Laboratory Parameters

End point description:

Laboratory investigation included hematology, biochemistry and coagulation. The number of subjects with abnormalities in laboratory parameters were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: subjects				

Notes:

[8] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects with Abnormalities in Vital Signs

End point title	OLE Period: Number of Subjects with Abnormalities in Vital Signs

End point description:

Vital signs included temperature, pulse rate, respiration rate and blood pressure and weight (taken after 5 minutes in the sitting position). The number of subjects with abnormalities in vital signs were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: subjects				

Notes:

[9] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects with Abnormalities in Electrocardiograms (ECGs) Findings

End point title	OLE Period: Number of Subjects with Abnormalities in Electrocardiograms (ECGs) Findings

End point description:

ECG recordings included, heart rate, PR interval and QRS duration. ECG recordings were obtained after the subjects have rested for at least 5 minutes in supine position. The number of subjects with abnormalities in ECG findings were reported. Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: subjects				

Notes:

[10] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Total Number of New or Enlarging T2 Lesions

End point title	OLE Period: Total Number of New or Enlarging T2 Lesions

End point description:

Analysis of new or enlarging T2 lesions rate was done using magnetic resonance imaging (MRI) scans. Negative binomial model for lesion count (summed over scans) includes treatment and covariates based on randomization strata and baseline volume of T2 lesion (continuous), with offset equal to the log of the time in years between the last available MRI scan and the baseline scan. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: lesions per year				
arithmetic mean (confidence interval 95%)	(to)			

Notes:

[11] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Change from Baseline in T2 lesion Volume

End point title	OLE Period: Change from Baseline in T2 lesion Volume

End point description:

Change from baseline in T2 lesion volume was reported. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: cubic centimeters (cm^3)				
arithmetic mean (standard deviation)	()			

Notes:

[12] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Symbol Digit Modalities Test (SDMT)

End point title	OLE Period: Symbol Digit Modalities Test (SDMT)

End point description:

The SDMT is a test of information processing speed. It consists of 9 abstract symbols. Each symbol is paired with a single digit. The subject is provided with a "key", showing each symbol digit pair. In addition, the subjects are shown several rows of the 9 symbols, which are arranged pseudo-randomly, without the digit. Subjects are asked to voice the digit associated with each symbol as rapidly as possible for 90 seconds. The SDMT score ranges from 0 to 110 where higher scores indicated improvement and lower scores indicated worsening. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From OLE baseline (DBTP Week 96) to OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[13] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Change From Baseline in PROMISnq Physical Function (PF) Multiple Sclerosis (MS) 15a at Week 52

End point title	OLE Period: Change From Baseline in PROMISnq Physical Function (PF) Multiple Sclerosis (MS) 15a at Week 52

End point description:

Physical function was assessed with PROMISnq Short Form v2.0 – Physical Function – Multiple Sclerosis 15a (PROMISnq PF(MS) 15a). PROMISnq PF(MS) 15a assesses a subject's abilities and limitations with respect to everyday physical activities. Results are reported as a T-score. In the general population, T-scores have a mean of 50, standard deviation of 10, and range from 10 to 65. Higher T-scores represent higher physical function. Full Analysis Set (FAS) included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

OLE Baseline (DBTP Week 96), OLE Week 52

End point values	Evobrutinib			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: units on a scale				
least squares mean (confidence interval 95%)	(to)			

Notes:

[14] - Due to the early termination of the study, data for this endpoint was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to 176 weeks

Adverse event reporting additional description:

Safety (SAF) analysis set included all subjects who received at least one dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Evobrutinib

Reporting group description:

Subjects received Evobrutinib at a dose of 45 mg orally twice daily up to 156 weeks in Double blind treatment period (DBTP) followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in double blind extension (DBE) period and followed by twice daily oral doses of Evobrutinib 45 mg up to 96 weeks in open label extension (OLE) period.

Reporting group title	Teriflunomide

Reporting group description:

Subjects received Teriflunomide at a dose of 14 milligrams (mg) orally once daily up to 156 weeks in Double blind treatment period (DBTP) followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in double blind extension (DBE) period and followed by once daily oral doses of Teriflunomide 14 mg up to 96 weeks in open label extension (OLE) period.

Serious adverse events	Evobrutinib	Teriflunomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 559 (8.05%)	33 / 563 (5.86%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 559 (0.36%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 559 (0.18%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion complete			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexa uteri cyst			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal uterine bleeding			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 559 (0.36%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual bleeding			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Paranasal cyst			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic movement disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Suicide attempt			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blast injury			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 559 (0.36%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impacted fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervicobrachial syndrome			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurologic neglect syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 559 (0.72%)	3 / 563 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyskinesia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess oral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative abscess			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 559 (0.18%)	2 / 563 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	2 / 563 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 559 (0.54%)	4 / 563 (0.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 559 (0.54%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 559 (0.00%)	1 / 563 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 559 (0.18%)	0 / 563 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Evobrutinib	Teriflunomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	361 / 559 (64.58%)	409 / 563 (72.65%)	
Investigations			
White blood cell count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	7 / 559 (1.25%)	29 / 563 (5.15%)	
occurrences (all)	8	38	
Neutrophil count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	25 / 559 (4.47%)	50 / 563 (8.88%)	
occurrences (all)	34	83	
Lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 559 (4.11%)	35 / 563 (6.22%)	
occurrences (all)	31	50	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	51 / 559 (9.12%)	54 / 563 (9.59%)	
occurrences (all)	66	71	
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	77 / 559 (13.77%)	86 / 563 (15.28%)	
occurrences (all)	131	134	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	15 / 559 (2.68%)	32 / 563 (5.68%)	
occurrences (all)	19	40	

Nervous system disorders Headache alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 81 / 559 (14.49%) 151	 75 / 563 (13.32%) 175	
Blood and lymphatic system disorders Neutropenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) Leukopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 20 / 559 (3.58%) 23 13 / 559 (2.33%) 15	 41 / 563 (7.28%) 87 39 / 563 (6.93%) 66	
General disorders and administration site conditions Fatigue alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 29 / 559 (5.19%) 33	 32 / 563 (5.68%) 34	
Gastrointestinal disorders Diarrhoea alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 15 / 559 (2.68%) 20	 53 / 563 (9.41%) 71	
Skin and subcutaneous tissue disorders Alopecia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 32 / 559 (5.72%) 34	 59 / 563 (10.48%) 63	
Musculoskeletal and connective tissue disorders Back pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 34 / 559 (6.08%) 46	 25 / 563 (4.44%) 28	
Infections and infestations			

Upper respiratory tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	36 / 559 (6.44%)	42 / 563 (7.46%)	
occurrences (all)	56	62	
Nasopharyngitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	67 / 559 (11.99%)	61 / 563 (10.83%)	
occurrences (all)	105	82	
COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	121 / 559 (21.65%)	108 / 563 (19.18%)	
occurrences (all)	142	117	
Urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	36 / 559 (6.44%)	26 / 563 (4.62%)	
occurrences (all)	56	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2020	• To allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization • To clarify the process in the event of a female subject undergoing AEP • Medical history is collected at Screening; any changes thereafter are recorded as AEs • A urine pregnancy test is sufficient at this visit unless there has been a gap of >=1 month since the last test • Tmax removed from list of PK parameters for evaluation • Objectives and endpoints added for biomarkers collected during the OLE • False positive results were not addressed in the original protocol
19 May 2021	• To be aligned with the inclusion of an optional IA for BSSR. • Due to unexpectedly rapid enrollment, the trigger for the IA for USSR is projected to occur months after the completion of enrollment, considered too late to implement changes following outcome of IA from an operational perspective. The optional IA for BSSR, triggered prior to completion of enrollment, does not have this disadvantage • Due to the removal of the IA for USSR, the role played by the IDMC in making the sample size increase recommendation is no longer required. • Due to removing the IA for USSR, there is no need to control type-1 error in the 12-week CDP analysis using the Cui, Hung, Wang method. Thus, 12-week CDP and 24-week CDP will be analyzed in the same manner.
03 April 2022	• Revision of the treatment duration from fixed 96 weeks to variable duration up to 156 weeks • CDI endpoint added to secondary endpoints to explore treatment effect on additional clinically relevant endpoint for disability. Week 12 NfL concentration added to investigate early impact of treatment on reducing neuronal damage. • A new study will allow subjects who completed the double blind treatment period in the current protocol to enroll in a new, single-arm long-term follow-up study, which will also include subjects who completed other RMS studies with evobrutinib. The text of the protocol has been amended to describe a transition opportunity to this long-term follow-up study • NfL has emerged as a potential biomarker for disease activity and treatment monitoring of patients with MS. Additional information added to support the inclusion of NfL as secondary endpoint.
06 December 2022	• Introduction of an OLE period for subjects completing the DBTP prior to approval of the long-term follow-up study in their country to enable an option for evobrutinib treatment continuation • Addition of the following exploratory endpoints: Time to PIRA and time to PIRMA (to evaluate the effect of treatment on progression not driven by relapse events or MRI activity); NEP at Weeks 48, 96; Level of anti-SARS-CoV-2 antibodies.
26 April 2023	• To reflect the recent update to the risk profile of evobrutinib (i.e. important identified risk of drug-induced liver injury) by adapting liver-related eligibility criteria, monitoring, and discontinuation criteria as well as language on tolerability and safety of evobrutinib across the protocol. • To allow subjects to stay on blinded IMP after DBTP in a DBE period to delay the switch of subjects naïve to evobrutinib treatment to the OLE period. This will also allow to generate additional data on efficacy and safety over an extended period of time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Final Analysis represents analysis of cumulative data collected up to Primary Analysis trigger and beyond through DBE up to final database lock. Therefore, endpoints were evaluated considering a time period from start of DBTP to end of DBE Period.

Notes: