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 2)

Summary

EudraCT number	2019-004980-36
Trial protocol	PT LT SK LV GR BG PL NO ES DE SI IT RO CZ
Global end of trial date	19 March 2024

Results information

Result version number	v1 (current)
This version publication date	21 March 2025
First version publication date	21 March 2025

Trial information

Trial identification

Sponsor protocol code	MS200527_0082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04338061
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	19 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 March 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial 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	02 July 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: 74
Country: Number of subjects enrolled	Belarus: 54
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Moldova, Republic of: 12
Country: Number of subjects enrolled	Poland: 191
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 161
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Ukraine: 351
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Italy: 23

Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Malaysia: 23
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	Saudi Arabia: 4
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Türkiye: 23
Country: Number of subjects enrolled	South Africa: 18
Worldwide total number of subjects	1166
EEA total number of subjects	414

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)	1166
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1581 subjects with relapsing multiple sclerosis (RMS) were screened in this trial. Out of which 1166 subjects were randomized at a ratio of 1:1 (583 per treatment group) in this trial.

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, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide

Arm description:

Participants 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.

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:

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

Arm title	Evobrutinib

Arm description:

Participants 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.

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:

Participants 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	583	583
Completed	409	410
Not completed	174	173
Consent withdrawn by subject	59	52
Randomized, but not treated	-	2
Other Reasons	17	22
Adverse event, non-fatal	67	70
Protocol Non-Compliance	9	8
Lost to follow-up	11	3
Lack of efficacy	11	16

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide

Arm description:

Participants 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.

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:

Participants 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:

Participants 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.

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:

Participants 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	390	389
Completed	381	377
Not completed	9	12
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1
Other Reasons	4	8
Protocol Non-Compliance	1	-
Lost to follow-up	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 779 subjects (390 in Teriflunomide and 389 in Evobrutinib) started the DBE period.

Baseline characteristics

Reporting groups	
Reporting group title	Teriflunomide
Reporting group description:	
Participants 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.	
Reporting group title	Evobrutinib
Reporting group description:	
Participants 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.	

Reporting group values	Teriflunomide	Evobrutinib	Total
Number of subjects	583	583	1166
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	37	36	
standard deviation	± 9.5	± 9.1	-
Sex: Female, Male Units: subjects			
Female	370	413	783
Male	213	170	383
Ethnicity Units: Subjects			
Hispanic or Latino	30	51	81
Not Hispanic or Latino	553	531	1084
Unknown or Not Reported	0	1	1
Race Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	17	15	32
Black or African American	4	4	8
White	551	556	1107
More than one race	7	2	9
Unknown or Not Reported	3	4	7
Native Hawaiian or Other Pacific Islander	0	1	1

End points

End points reporting groups

Reporting group title	Teriflunomide
Reporting group description:	
Participants 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.	
Reporting group title	Evobrutinib
Reporting group description:	
Participants 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.	
Reporting group title	Teriflunomide
Reporting group description:	
Participants 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.	
Reporting group title	Evobrutinib
Reporting group description:	
Participants 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.	

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:	
Baseline up to 170 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 statistical 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	583	583		
Units: relapses per year				
arithmetic mean (confidence interval 95%)	0.11 (0.09 to 0.13)	0.11 (0.09 to 0.13)		

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 periods)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	583		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	91.6 (88.7 to 93.8)	93.6 (91.0 to 95.5)		
Week 156	89.7 (86.5 to 92.2)	90.9 (87.8 to 93.3)		

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 periods)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	583		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	88.9 (85.7 to 91.4)	91.8 (88.9 to 93.9)		
Week 156	82.3 (76.0 to 87.1)	85.0 (77.8 to 90.0)		

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 periods)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	583		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 96	11.4 (8.6 to 15.0)	7.6 (5.4 to 10.7)		
Week 156	12.5 (9.5 to 16.4)	8.4 (6.0 to 11.6)		

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). FAS was used. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint. Here, "9999" = Week 156 is not evaluable in the modelling due to the lack of subjects in some of the covariate categories at that visit. 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 periods)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	572	572		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 48	0.25 (-0.22 to 0.72)	0.31 (-0.16 to 0.78)		
Week 96	-0.31 (-0.88 to 0.26)	-0.45 (-1.03 to 0.13)		
Week 120	-0.56 (-1.23 to 0.11)	-0.19 (-0.86 to 0.48)		
Week 144	-0.38 (-1.12 to 0.35)	-0.57 (-1.31 to 0.17)		
Week 156	9999 (9999 to 9999)	9999 (9999 to 9999)		

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 periods)

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	572	572		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 48	-2.20 (-2.81 to -1.60)	-2.59 (-3.19 to -1.98)		
Week 96	-2.17 (-2.85 to -1.49)	-2.12 (-2.81 to -1.44)		
Week 120	-2.24 (-3.00 to -1.48)	-2.59 (-3.35 to -1.83)		
Week 144	-2.41 (-3.35 to -1.48)	-2.16 (-3.10 to -1.22)		
Week 156	-2.21 (-3.62 to -0.81)	-2.34 (-3.83 to -0.86)		

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. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	544	544		
Units: lesions per scan				
arithmetic mean (confidence interval 95%)	0.29 (0.24 to 0.34)	0.51 (0.43 to 0.60)		

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. Here, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	544	544		
Units: lesions per year				
arithmetic mean (confidence interval 95%)	6.88 (6.01 to 7.87)	6.17 (5.38 to 7.07)		

Statistical analyses

No statistical analyses for this end point

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

End point title	DBTP Period: Neurofilament Light Chain (NfL) Concentration 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	544	544		
Units: nanogram per liter (ng/L)				
geometric mean (confidence interval 95%)	13.09 (12.69 to 13.50)	12.51 (12.13 to 12.90)		

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 participant 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	581		
Units: subjects				
Subjects with TEAEs	524	508		
Subjects with AESIs	144	135		

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.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	583	581		
Units: subjects				
Subjects with Grade 1	41	59		
Subjects with Grade 2	389	351		
Subjects with Grade 3	87	92		
Subjects with Grade 4	7	6		
Subjects with Grade 5	0	0		

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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	454		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic Blood Pressure	2.4 (± 11.0)	1.0 (± 11.50)		
Diastolic Blood Pressure	1.4 (± 8.73)	-0.5 (± 8.38)		

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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	454		
Units: kilograms (kg)				
arithmetic mean (standard deviation)	-0.51 (± 5.447)	1.06 (± 5.310)		

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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	454		
Units: breaths per minute				
arithmetic mean (standard deviation)	-0.3 (± 1.75)	-0.5 (± 1.87)		

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 participant in a quiet sitting without distractions. Changes in vital signs: pulse rate from baseline up to 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	454		
Units: beats per minute				
arithmetic mean (standard deviation)	2.2 (± 10.19)	3.0 (± 10.15)		

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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	454		
Units: degree Celsius				
arithmetic mean (standard deviation)	-0.02 (± 0.340)	-0.03 (± 0.350)		

Statistical analyses

No statistical analyses for this end point

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

End point title	DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs): 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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	69		
Units: beats per minute				
arithmetic mean (standard deviation)	-0.1 (± 10.36)	2.6 (± 10.20)		

Statistical analyses

No statistical analyses for this end point

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

End point title	DBTP and DBE Periods: Change From Baseline in Electrocardiograms (ECGs): 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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	69		
Units: milliseconds (msec)				
arithmetic mean (standard deviation)				
QT Interval - Fridericia's Correction Formula	-2.14 (± 16.459)	-0.07 (± 14.935)		
PR Interval	-4.2 (± 16.82)	-3.1 (± 14.51)		
QRS Duration	-2.8 (± 6.77)	-1.1 (± 8.94)		

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

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

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 (Con.) and hemoglobin. Changes in hematology parameters: erythrocytes mean corpuscular HGB concentration and hemoglobin from baseline up to 170 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 and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447	436		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
Erythrocytes Mean Corpuscular HGB Con.: n=438, 428	0.0 (± 11.07)	-1.9 (± 12.42)		
Hemoglobin: n = 447, 436	-3.4 (± 11.40)	-3.4 (± 11.43)		

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 170 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 and "n"= subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	437		
Units: 10^9 cells per liter				
arithmetic mean (standard deviation)				
Platelets: n = 441, 432	-8.4 (± 48.38)	9.8 (± 52.24)		
Leukocytes: n = 446, 437	-0.39 (± 1.954)	0.24 (± 1.883)		
Neutrophils: n = 331, 324	-0.471 (± 1.7550)	0.156 (± 1.7796)		
Eosinophils: n = 438, 431	0.0198 (± 0.14809)	0.0238 (± 0.14945)		
Basophils: n = 438, 431	-0.0081 (± 0.03882)	-0.0042 (± 0.03902)		

Monocytes: n = 438, 432	0.0797 (± 0.19710)	0.0772 (± 0.20715)		
Lymphocytes: n = 442, 434	-0.0241 (± 0.57564)	0.0311 (± 0.57810)		
Reticulocytes: n = 436, 430	2.001 (± 23.3886)	-0.841 (± 20.2200)		

Statistical analyses

No statistical analyses for this end point

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

End point title	DBTP and DBE Periods: Change From Baseline in Hematology Parameters: 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 up to 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	431		
Units: percentage of cells				
arithmetic mean (standard deviation)	-0.0107 (± 0.03199)	-0.0085 (± 0.03311)		

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 up to 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	435		
Units: picogram				
arithmetic mean (standard deviation)	-0.44 (± 1.603)	-0.93 (± 1.941)		

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 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	431		
Units: femtoliters				
arithmetic mean (standard deviation)	-1.48 (± 4.150)	-2.53 (± 5.217)		

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 170 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 and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	455	446		
Units: micromoles per liter (mcmol/L)				
arithmetic mean (standard deviation)				
Bilirubin: n = 455, 446	-0.02 (± 4.649)	0.33 (± 4.212)		
Creatinine: n = 449, 442	1.6 (± 8.93)	2.4 (± 12.06)		

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 170 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 and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	455	446		
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
Aspartate Aminotransferase: n = 454, 444	2.64 (± 15.365)	1.74 (± 13.219)		
Alanine Aminotransferase: n = 455, 446	4.40 (± 33.878)	2.75 (± 32.018)		
Alkaline Phosphatase: n = 447, 445	2.32 (± 15.875)	6.69 (± 15.659)		
Amylase: n = 450, 441	1.3 (± 14.42)	2.1 (± 15.91)		
Lipase: n = 449, 442	-0.3 (± 18.35)	2.3 (± 17.26)		
Gamma Glutamyl Transferase: n = 359, 385	3.71 (± 26.084)	1.98 (± 20.207)		
Lactate Dehydrogenase: n = 436, 439	7.08 (± 27.049)	-5.41 (± 27.637)		

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 170 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 and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	450	446		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Sodium: n = 448, 440	0.9286 (± 2.56796)	0.7750 (± 3.21185)		
Potassium: n = 449, 439	0.0405 (± 0.48750)	0.0376 (± 0.44331)		

Calcium: n = 448, 440	-0.006 (± 0.1197)	-0.008 (± 0.1121)		
Magnesium: n = 449, 441	-0.002 (± 0.0656)	-0.006 (± 0.0667)		
Glucose: n = 448, 440	0.09 (± 0.949)	0.16 (± 0.812)		
Chloride: n = 450, 440	2.3 (± 3.30)	2.1 (± 3.53)		
Urea Nitrogen: n = 447, 441	0.126 (± 1.2759)	0.122 (± 1.1651)		
Phosphate: n = 428, 434	-0.047 (± 0.1944)	-0.024 (± 0.1799)		
Bicarbonate: n = 324, 348	0.44 (± 2.592)	0.17 (± 2.980)		
Corrected Calcium: n = 446, 437	0.0290 (± 0.10405)	0.0292 (± 0.09775)		

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 up to 170 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 and "n" = subjects who were evaluable for the specified categories.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	444		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
Total protein: n = 448, 437	-1.31 (± 4.905)	-0.59 (± 4.998)		
Albumin: n = 448, 444	-1.75 (± 3.497)	-1.83 (± 3.287)		

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 up to 170 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, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	351		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-4.7 (± 13.41)	-5.7 (± 13.81)		

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 up to 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	438		
Units: pH				
arithmetic mean (standard deviation)	-0.03 (± 0.936)	-0.04 (± 0.973)		

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 up to 170 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:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	428		
Units: Kilogram per cubic meter				
arithmetic mean (standard deviation)	-0.0015 (± 0.04460)	-0.0017 (± 0.03748)		

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, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 170

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	341		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
IgA	1.899 (± 0.7787)	2.581 (± 1.1201)		
IgG	10.082 (± 2.1551)	10.990 (± 2.4844)		
IgM	1.251 (± 0.6445)	1.196 (± 0.6151)		

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, number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 170 weeks

End point values	Teriflunomide	Evobrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	339		
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				
IgA	-0.203 (± 0.5704)	0.500 (± 0.7197)		
IgG	-0.645 (± 1.6188)	0.146 (± 1.8712)		
IgM	-0.167 (± 0.5094)	-0.175 (± 0.3888)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 170 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.	
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.	

Serious adverse events	Evobrutinib	Teriflunomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 581 (8.78%)	37 / 583 (6.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma of liver			

alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 581 (0.69%)	2 / 583 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial sarcoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	2 / 583 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Subgaleal haematoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy of partner			

alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miscarriage of partner			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 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 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
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 / 581 (0.00%)	1 / 583 (0.17%)	
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 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal uterine bleeding			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal sinus inflammation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropsychiatric symptoms			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (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	7 / 581 (1.20%)	3 / 583 (0.51%)	
occurrences causally related to treatment / all	4 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 581 (0.52%)	2 / 583 (0.34%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	2 / 583 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic neuropathy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral radiculopathy			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	2 / 581 (0.34%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 581 (0.52%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Chalazion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus spastic			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Symphysiolysis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (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			
Acute sinusitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 581 (0.34%)	2 / 583 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 581 (0.34%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 581 (0.34%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 581 (0.34%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Salpingo-oophoritis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 581 (0.00%)	1 / 583 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 581 (0.17%)	0 / 583 (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	409 / 581 (70.40%)	455 / 583 (78.04%)	
Investigations			
Lymphocyte count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	27 / 581 (4.65%)	39 / 583 (6.69%)	
occurrences (all)	40	73	
Lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	33 / 581 (5.68%)	33 / 583 (5.66%)	
occurrences (all)	55	39	
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	31 / 581 (5.34%)	29 / 583 (4.97%)	
occurrences (all)	37	70	
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	99 / 581 (17.04%)	126 / 583 (21.61%)	
occurrences (all)	168	227	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	61 / 581 (10.50%)	80 / 583 (13.72%)	
occurrences (all)	84	123	
White blood cell count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 581 (3.96%)	63 / 583 (10.81%)	
occurrences (all)	39	122	
Neutrophil count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	40 / 581 (6.88%)	92 / 583 (15.78%)	
occurrences (all)	52	156	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	96 / 581 (16.52%)	103 / 583 (17.67%)	
occurrences (all)	198	169	
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	37 / 581 (6.37%)	47 / 583 (8.06%)	
occurrences (all)	46	66	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	34 / 581 (5.85%)	23 / 583 (3.95%)	
occurrences (all)	54	35	
Neutropenia			
alternative dictionary used:			

MedDRA 26.0			
subjects affected / exposed	22 / 581 (3.79%)	47 / 583 (8.06%)	
occurrences (all)	33	112	
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	29 / 581 (4.99%)	36 / 583 (6.17%)	
occurrences (all)	39	39	
Diarrhoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	24 / 581 (4.13%)	47 / 583 (8.06%)	
occurrences (all)	28	59	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	35 / 581 (6.02%)	84 / 583 (14.41%)	
occurrences (all)	38	87	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	49 / 581 (8.43%)	61 / 583 (10.46%)	
occurrences (all)	63	79	
Pain in extremity			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	30 / 581 (5.16%)	32 / 583 (5.49%)	
occurrences (all)	46	40	
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	58 / 581 (9.98%)	67 / 583 (11.49%)	
occurrences (all)	89	103	
COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	105 / 581 (18.07%)	121 / 583 (20.75%)	
occurrences (all)	119	139	

Respiratory tract infection viral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 581 (3.96%)	37 / 583 (6.35%)	
occurrences (all)	36	52	
Urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	39 / 581 (6.71%)	33 / 583 (5.66%)	
occurrences (all)	49	46	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	55 / 581 (9.47%)	45 / 583 (7.72%)	
occurrences (all)	83	81	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 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 Accelerated elimination procedure (AEP). • To clarify that this is a safety visit safety follow-up (SFU) visit must be >= 28 days after last study intervention Clarification. • Assessment required at Week 108 for subjects for whom this is also D1 of the OLE.
19 May 2021	• To be aligned with the inclusion of an optional Interim analysis (IA) for Blinded Sample Size Re-estimation (BSSR). • Due to unexpectedly rapid enrollment, the trigger for the IA for Unblinded Sample Size Re-estimation (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. • To avoid variability in interpretation of ECGs by non-cardiologists and in reports obtained from the locally sourced ECG machines. • Due to the removal of the IA for USSR, the role played by the Independent Data Monitoring Committee (IDMC) in making the sample size increase recommendation is no longer required.
03 April 2022	• To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in Ukraine, Russian Federation, and Belarus. • Due to the extended study duration and the planned transition of all eligible study completers to the long-term follow-up study under a new protocol, the OLE Period is no longer needed. • To ensure consistency after removal of the OLE Period, and to ensure consistency in evaluation of safety and efficacy for all subjects entering the long-term follow-up study. Furthermore, removal of the OLE Period and the mandatory AEP related to teriflunomide reduces the risk of unblinding due to the variable AEP duration. • 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.
08 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: 1. Time to Progression Independent of Relapse Activity (PIRA) and time to Progression Independent of Relapse and Brain Magnetic Resonance (PIRMA) (to evaluate the effect of treatment on progression not driven by relapse events or MRI activity) 2. No evidence of progression (NEP) at Weeks 48, 96 3. Level of anti- Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) antibodies
27 April 2023	• To reflect recent update to 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 Investigational medicinal product (IMP) after DBTP in a DBE period to delay the switch of participants 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: