# 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<br>Units: Subjects | | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 37 | 36 | |
| standard deviation | ± 9.5 | ± 9.1 | - |
| Sex: Female, Male<br>Units: subjects | | | |
| Female | 370 | 413 | 783 |
| Male | 213 | 170 | 383 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 30 | 51 | 81 |
| Not Hispanic or Latino | 553 | 531 | 1084 |
| Unknown or Not Reported | 0 | 1 | 1 |
| Race<br>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 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 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 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 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 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) 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: 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 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 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 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 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 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 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 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: 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: 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 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 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 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: 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 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: 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.<br>• To clarify the process in the event of a female subject undergoing Accelerated elimination procedure (AEP).<br>• To clarify that this is a safety visit safety follow-up (SFU) visit must be >= 28 days after last study intervention Clarification.<br>• 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).<br>• 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.<br>• To avoid variability in interpretation of ECGs by non-cardiologists and in reports obtained from the locally sourced ECG machines.<br>• 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.<br>• 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.<br>• 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.<br>• 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<br>• Addition of the following exploratory endpoints:<br>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)<br>2. No evidence of progression (NEP) at Weeks 48, 96<br>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: