



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 With a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients With Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-001448-21 |
| Trial protocol | SK ES CZ PL BG |
| Global end of trial date | 02 April 2024 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 17 April 2025 |
| First version publication date | 17 April 2025 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | MS200527-0086 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02975349 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Healthcare KGaA, Darmstadt Germany |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293 |
| Public contact | Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com |
| Scientific contact | Communication 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 | 02 April 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 April 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The aim of this study was to find out about the safety and effectiveness of M2951 in subjects with relapsing multiple sclerosis. Subjects were placed into 1 of 3 groups to receive M2951, placebo or tefidera for 24 weeks. After 24 weeks, the subjects on placebo were given M2951.

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 | 07 March 2017 |
| 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: 47 |
| Country: Number of subjects enrolled | Czechia: 26 |
| Country: Number of subjects enrolled | Poland: 83 |
| Country: Number of subjects enrolled | Russian Federation: 19 |
| Country: Number of subjects enrolled | Serbia: 17 |
| Country: Number of subjects enrolled | Slovakia: 10 |
| Country: Number of subjects enrolled | Ukraine: 62 |
| Country: Number of subjects enrolled | Spain: 3 |
| Worldwide total number of subjects | 267 |
| EEA total number of subjects | 169 |

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 | 0 |

| | |
|---------------------------|-----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 267 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a 24-week active treatment period, 24-week blinded extension (BE) period and a 336-week open-label extension period. A total of 333 subjects with Relapsing Multiple Sclerosis (RMS) were screened, and 267 subjects were randomized and received treatment in the study.

Period 1

| | |
|------------------------------|------------------------------------|
| Period 1 title | Active Treatment Period (24 Weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo (period 1) |

Arm description:

Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1.

| | |
|------------------|---------------------------------------|
| Arm title | Evobrutinib 25 mg QD (Period 1 and 2) |
|------------------|---------------------------------------|

Arm description:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

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

Dosage and administration details:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|---------------------------------------|
| Arm title | Evobrutinib 75 mg QD (Period 1 and 2) |
|------------------|---------------------------------------|

Arm description:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|--|
| Arm title | Evobrutinib 75 mg BID (Period 1 and 2) |
|------------------|--|

Arm description:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|----------------------------|
| Arm title | Tecfidera (Period 1 and 2) |
|------------------|----------------------------|

Arm description:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tecfidera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

| Number of subjects in period 1 | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|---------------------------------------|--------------------|---------------------------------------|---------------------------------------|
| Started | 54 | 52 | 53 |
| Completed | 49 | 47 | 48 |
| Not completed | 5 | 5 | 5 |
| Consent withdrawn by subject | - | 3 | 3 |
| Adverse event, non-fatal | 4 | 2 | 2 |
| Lost to follow-up | 1 | - | - |

| Number of subjects in period 1 | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) |
|---------------------------------------|--|----------------------------|
| Started | 54 | 54 |
| Completed | 48 | 52 |
| Not completed | 6 | 2 |

| | | |
|------------------------------|---|---|
| Consent withdrawn by subject | - | - |
| Adverse event, non-fatal | 6 | 2 |
| Lost to follow-up | - | - |

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Blinded Extension Period (24 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo Then Evobrutinib 25 mg QD (Period 2) |

Arm description:

Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1 received Evobrutinib 25 milligram (mg) orally, once daily (QD) in blinded extension (BE) period from week 25 to week 48.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo +Evobrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1 received Evobrutinib 25 milligram (mg) orally, once daily (QD) in blinded extension (BE) period from week 25 to week 48.

| | |
|------------------|---------------------------------------|
| Arm title | Evobrutinib 25 mg QD (Period 1 and 2) |
|------------------|---------------------------------------|

Arm description:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

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

Dosage and administration details:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|---------------------------------------|
| Arm title | Evobrutinib 75 mg QD (Period 1 and 2) |
|------------------|---------------------------------------|

Arm description:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|--|
| Arm title | Evobrutinib 75 mg BID (Period 1 and 2) |
|------------------|--|

Arm description:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

| | |
|------------------|----------------------------|
| Arm title | Tecfidera (Period 1 and 2) |
|------------------|----------------------------|

Arm description:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tecfidera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

| Number of subjects in period 2 | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|---------------------------------------|--|---------------------------------------|---------------------------------------|
| Started | 49 | 47 | 48 |
| Completed | 42 | 43 | 44 |
| Not completed | 7 | 4 | 4 |
| Consent withdrawn by subject | 5 | 2 | 1 |

| | | | |
|--------------------------|---|---|---|
| Adverse event, non-fatal | 1 | 1 | 3 |
| Progressive Disease | 1 | - | - |
| Lack of efficacy | - | 1 | - |

| Number of subjects in period 2 | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) |
|--------------------------------|--|----------------------------|
| Started | 48 | 52 |
| Completed | 46 | 52 |
| Not completed | 2 | 0 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | 1 | - |
| Progressive Disease | - | - |
| Lack of efficacy | - | - |

Period 3

| | |
|------------------------------|---|
| Period 3 title | Open-label Extension Period (336 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo + Evobrutinib 25 mg QD (Period 3) |

Arm description:

Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period received Evobrutinib 25 mg orally, QD from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo +Evobrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1 received Evobrutinib 25 mg orally, QD from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|------------------|---------------------------------|
| Arm title | Evobrutinib 25 mg QD (Period 3) |
|------------------|---------------------------------|

Arm description:

Subjects received Evobrutinib 25 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

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

Dosage and administration details:

Subjects received Evobrutinib 25 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|------------------|---------------------------------|
| Arm title | Evobrutinib 75 mg QD (Period 3) |
|------------------|---------------------------------|

Arm description:

Subjects received Evobrutinib 75 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|------------------|----------------------------------|
| Arm title | Evobrutinib 75 mg BID (Period 3) |
|------------------|----------------------------------|

Arm description:

Subjects Evobrutinib 75 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

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

Dosage and administration details:

Subjects received Evobrutinib 75 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|------------------|----------------------|
| Arm title | Tecfidera (Period 3) |
|------------------|----------------------|

Arm description:

Subjects received Tecfidera 120 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tecfidera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Tecfidera 120 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| Number of subjects in period 3 ^[1] | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) |
|---|---|---------------------------------|---------------------------------|
| | | | |
| Started | 39 | 39 | 42 |
| Completed | 28 | 25 | 33 |
| Not completed | 11 | 14 | 9 |
| Adverse event, serious fatal | - | 1 | - |
| Consent withdrawn by subject | 4 | 7 | 2 |
| Study reached its predefined end | - | - | 1 |
| Adverse event, non-fatal | 3 | 2 | 2 |
| Unspecified | 3 | 3 | 1 |
| Lost to follow-up | 1 | - | - |
| COVID-19 Related | - | 1 | 1 |
| Lack of efficacy | - | - | 2 |

| Number of subjects in period 3 ^[1] | Evobrutinib 75 mg BID (Period 3) | Tecfidera (Period 3) |
|---|----------------------------------|----------------------|
| | | |
| Started | 44 | 49 |
| Completed | 35 | 39 |
| Not completed | 9 | 10 |
| Adverse event, serious fatal | - | - |
| Consent withdrawn by subject | 4 | 2 |
| Study reached its predefined end | - | - |
| Adverse event, non-fatal | 1 | 2 |
| Unspecified | 2 | 3 |
| Lost to follow-up | 1 | - |
| COVID-19 Related | 1 | 2 |
| Lack of efficacy | - | 1 |

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 213 subjects started the OLE period.

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Placebo (period 1) |
| Reporting group description: Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1. | |
| Reporting group title | Evobrutinib 25 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg BID (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Tecfidera (Period 1 and 2) |
| Reporting group description: Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period. | |

| Reporting group values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|--|--------------------|---------------------------------------|---------------------------------------|
| Number of subjects | 54 | 52 | 53 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 54 | 52 | 53 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 0 | 0 | 0 |
| standard deviation | ± 0 | ± 0 | ± 0 |
| Sex: Female, Male Units: subjects | | | |
| Female | 39 | 32 | 35 |
| Male | 14 | 18 | 16 |
| Unknown or Not Reported | 1 | 2 | 2 |

| | | | |
|------------------------|--|----------------------------|-------|
| Reporting group values | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) | Total |
|------------------------|--|----------------------------|-------|

| | | | |
|---|-----|-----|-----|
| Number of subjects | 54 | 54 | 267 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 54 | 54 | 267 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 0 | 0 | |
| standard deviation | ± 0 | ± 0 | - |
| Sex: Female, Male | | | |
| Units: subjects | | | |
| Female | 36 | 39 | 181 |
| Male | 17 | 15 | 80 |
| Unknown or Not Reported | 1 | 0 | 6 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Placebo (period 1) |
| Reporting group description: Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1. | |
| Reporting group title | Evobrutinib 25 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg BID (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Tecfidera (Period 1 and 2) |
| Reporting group description: Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Placebo Then Evobrutinib 25 mg QD (Period 2) |
| Reporting group description: Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1 received Evobrutinib 25 milligram (mg) orally, once daily (QD) in blinded extension (BE) period from week 25 to week 48. | |
| Reporting group title | Evobrutinib 25 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg QD (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Evobrutinib 75 mg BID (Period 1 and 2) |
| Reporting group description: Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Tecfidera (Period 1 and 2) |
| Reporting group description: Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period. | |
| Reporting group title | Placebo + Evobrutinib 25 mg QD (Period 3) |
| Reporting group description: Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period received Evobrutinib 25 mg orally, QD from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period. | |
| Reporting group title | Evobrutinib 25 mg QD (Period 3) |
| Reporting group description: Subjects received Evobrutinib 25 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period. | |
| Reporting group title | Evobrutinib 75 mg QD (Period 3) |

Reporting group description:

Subjects received Evobrutinib 75 mg QD orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Evobrutinib 75 mg BID (Period 3) |
|-----------------------|----------------------------------|

Reporting group description:

Subjects Evobrutinib 75 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|----------------------|
| Reporting group title | Tecfidera (Period 3) |
|-----------------------|----------------------|

Reporting group description:

Subjects received Tecfidera 120 mg BID orally from Week 48 of BE period (OLE period Day 1) to Week 336 in OLE period.

| | |
|----------------------------|---------|
| Subject analysis set title | Placebo |
|----------------------------|---------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Evobrutinib 25 mg QD |
|----------------------------|----------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Evobrutinib 75 mg QD |
|----------------------------|----------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Evobrutinib 75 mg BID |
|----------------------------|-----------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

| | |
|----------------------------|-----------|
| Subject analysis set title | Tecfidera |
|----------------------------|-----------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

Primary: Total Number of Gadolinium-Enhancing T1 Lesions

| | |
|-----------------|---|
| End point title | Total Number of Gadolinium-Enhancing T1 Lesions |
|-----------------|---|

End point description:

Analysis of T1-Gadolinium enhancing lesions was done using magnetic resonance imaging (MRI) scans. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. Modified Intent-To-Treat (mITT) analysis set included subjects who belong to both Intent To Treat (ITT, consisted all subjects who randomly allocated to a treatment, based on the intention to treat "as randomized" principle) and safety analysis sets (consisted all subjects who receive at least 1 dose of trial treatment), and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 12 to Week 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 3.85 (\pm 5.436) | 4.06 (\pm 8.024) | 1.69 (\pm 4.693) | 1.15 (\pm 3.702) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 4.78 (\pm 22.045) | | | |

Statistical analyses

| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
|---|--|
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2947 |
| Method | Negative Binomial model |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 2.91 |

| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
|---|---|
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0313 |
| Method | Negative Binomial model |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 0.44 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 0.93 |

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0015 |
| Method | Negative Binomial model |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 0.63 |

Secondary: Annualized relapse rate (ARR) at Week 24

| | |
|---|--|
| End point title | Annualized relapse rate (ARR) at Week 24 |
| End point description: | |
| A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 24 | |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|---|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.37 (0.17 to 0.70) | 0.57 (0.30 to 0.97) | 0.13 (0.03 to 0.38) | 0.08 (0.01 to 0.30) |

| | | | | |
|---|-------------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.20 (0.06 to 0.47) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2692 |
| Method | Negative Binomial model |
| Parameter estimate | Qualified relapse rate ratio |
| Point estimate | 1.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 4.09 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0633 |
| Method | Negative Binomial model |
| Parameter estimate | Qualified relapse rate ratio |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 1.09 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0896 |
| Method | Negative Binomial model |
| Parameter estimate | Qualified relapse rate ratio |
| Point estimate | 0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 1.2 |

Secondary: Qualified Relapse-Free Status at Week 24

| | |
|------------------------|--|
| End point title | Qualified Relapse-Free Status at Week 24 |
| End point description: | <p>A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. Percentage of subjects with qualified relapse-free status at week 24 were reported. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment.</p> |
| End point type | Secondary |
| End point timeframe: | |
| Week 24 | |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|----------------------------------|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 77.4 (63.8 to 87.7) | 74.0 (59.7 to 85.4) | 88.2 (76.1 to 95.6) | 86.8 (74.7 to 94.5) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|----------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 88.9 (77.4 to 95.8) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5609 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 1.95 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1767 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 5.99 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |

| | |
|---|-----------------|
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0689 |
| Method | Logistic model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 8.41 |

Secondary: Change From Baseline in Expanded Disability Status Scale (EDSS) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Expanded Disability Status Scale (EDSS) at Week 24 |
|-----------------|--|

End point description:

The EDSS is an ordinal clinical rating scale in half-point increments. It assesses the following eight functional systems, areas of the central nervous system that control bodily functions: Pyramidal (ability to walk), Cerebellar (coordination), Brain stem (speech and swallowing), Sensory (touch and pain), Bowel and bladder functions, Visual, Mental, Other (includes any other neurological findings due to Multiple Sclerosis [MS]). EDSS overall score ranging from 0 (normal) to 10 (death due to MS). As per planned analysis, Tecfidera treatment group was not included in inferential analysis. mITT analysis set was used.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.03 (± 0.301) | 0.02 (± 0.622) | -0.14 (± 0.664) | 0.04 (± 0.216) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.02 (± 0.274) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.407 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2732 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5829 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Death

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Death |
|-----------------|---|

End point description:

AE: any untoward medical occurrence in a subject which does not necessarily have a causal relationship with study drug. An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. SAE: AE that resulted in any of 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: any adverse event with a start date on or after the date of first dose and within 28 days after the date of last dose in the study. TEAEs included both Serious TEAEs and non-serious TEAEs. Safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Safety Follow-up (Week 52)

| End point values | Placebo (period 1) | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|-----------------------------|--------------------|--|---------------------------------------|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 49 | 52 | 53 |
| Units: subjects | | | | |
| TEAEs | 24 | 19 | 28 | 35 |
| Serious TEAEs | 2 | 0 | 2 | 2 |
| TEAEs Leading to Death | 0 | 0 | 0 | 0 |

| End point values | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) | | |
|-----------------------------|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 54 | | |

| | | | | |
|------------------------|----|----|--|--|
| Units: subjects | | | | |
| TEAEs | 34 | 35 | | |
| Serious TEAEs | 4 | 2 | | |
| TEAEs Leading to Death | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or Higher Hematology, Biochemistry and Urinalysis Values

| | |
|-----------------|--|
| End point title | Number of Subjects With Grade 3 or Higher Hematology, Biochemistry and Urinalysis Values |
|-----------------|--|

End point description:

Hematology, biochemistry, and urinalysis values were graded with National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 toxicity grades (where Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening and Grade 5 = death). For the hematology and biochemistry parameters, subjects with a value grade 3 or higher were reported. For the urinalysis parameters, subjects with a value grade 3 or higher, or a value ≥ 2 upper limit of normal (ULN), or a value classified as ++ Increasing urinalysis values (IUV) were reported. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Safety Follow-up (Week 52)

| End point values | Placebo (period 1) | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|---|--------------------|--|---------------------------------------|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 49 | 52 | 53 |
| Units: subjects | | | | |
| Grade ≥ 3 hematology values | 0 | 2 | 0 | 1 |
| Grade ≥ 3 biochemistry values | 2 | 8 | 6 | 9 |
| Grade ≥ 3 /value ≥ 2 ULN/++ IUV | 0 | 2 | 1 | 2 |

| End point values | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) | | |
|---|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 54 | | |
| Units: subjects | | | | |
| Grade ≥ 3 hematology values | 0 | 1 | | |
| Grade ≥ 3 biochemistry values | 16 | 9 | | |
| Grade ≥ 3 /value ≥ 2 ULN/++ IUV | 2 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs and Electrocardiograms (ECGs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs and Electrocardiograms (ECGs) |
|-----------------|---|

End point description:

Vital signs, including semi supine blood pressure, pulse rate, respiratory rate, weight, and oral temperature were assessed. ECG parameters included rhythm, ventricular rate, PR interval, QRS duration, and QT interval. Number of subjects with clinically significant change from baseline in vital signs and ECG were reported. Clinical Significance was decided by the investigator. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Safety Follow-up (Week 52)

| End point values | Placebo (period 1) | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) |
|-----------------------------|--------------------|--|---------------------------------------|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 49 | 52 | 53 |
| Units: subjects | | | | |
| Vital Sign Abnormalities | 0 | 0 | 0 | 0 |
| ECG Abnormalities | 0 | 0 | 0 | 0 |

| End point values | Evobrutinib 75 mg BID (Period 1 and 2) | Tecfidera (Period 1 and 2) | | |
|-----------------------------|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 54 | | |
| Units: subjects | | | | |
| Vital Sign Abnormalities | 0 | 0 | | |
| ECG Abnormalities | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) Levels (Active Treatment Period)

| | |
|-----------------|---|
| End point title | Absolute Concentrations of Immunoglobulin (Ig) Levels (Active Treatment Period) |
|-----------------|---|

End point description:

Absolute Concentrations serum levels of IgG, IgA, IgM were assessed. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 16, and 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|---------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 52 | 53 | 54 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Day 1: n = 54, 51, 53, 54, 54 | 1.99 (± 0.777) | 1.89 (± 0.764) | 1.90 (± 0.722) | 1.87 (± 0.675) |
| Ig A, Week 4: n = 54, 52, 53, 54, 54 | 1.98 (± 0.777) | 1.92 (± 0.770) | 1.93 (± 0.762) | 1.94 (± 0.748) |
| Ig A, Week 16: n = 53, 50, 49, 53, 52 | 2.07 (± 0.824) | 2.10 (± 0.813) | 2.13 (± 0.832) | 2.08 (± 0.753) |
| Ig A, Week 24: n = 50, 47, 49, 48, 52 | 1.99 (± 0.807) | 2.12 (± 0.833) | 2.09 (± 0.838) | 2.09 (± 0.793) |
| Ig G, Day 1: n = 54, 51, 53, 54, 54 | 9.61 (± 1.897) | 9.43 (± 2.126) | 9.81 (± 1.841) | 9.62 (± 1.960) |
| Ig G, Week 4: n = 54, 52, 53, 54, 54 | 9.64 (± 2.094) | 9.34 (± 1.972) | 9.79 (± 1.910) | 9.64 (± 1.987) |
| Ig G, Week 16: n = 53, 50, 49, 53, 52 | 9.68 (± 2.085) | 9.41 (± 2.077) | 9.70 (± 1.991) | 9.56 (± 2.129) |
| Ig G, Week 24: n = 50, 47, 49, 48, 52 | 9.66 (± 2.081) | 9.46 (± 2.123) | 9.62 (± 2.048) | 9.36 (± 1.988) |
| Ig M, Day 1: n = 54, 51, 53, 54, 54 | 1.42 (± 0.692) | 1.27 (± 0.542) | 1.44 (± 0.716) | 1.33 (± 0.684) |
| Ig M, Week 4: n = 54, 51, 53, 54, 54 | 1.40 (± 0.668) | 1.21 (± 0.526) | 1.32 (± 0.654) | 1.28 (± 0.656) |
| Ig M, Week 16: n = 53, 50, 49, 53, 52 | 1.43 (± 0.703) | 1.13 (± 0.558) | 1.24 (± 0.639) | 1.20 (± 0.689) |
| Ig M, Week 24: n = 49, 47, 49, 48, 52 | 1.44 (± 0.748) | 1.03 (± 0.499) | 1.20 (± 0.672) | 1.08 (± 0.494) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|---------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Day 1: n = 54, 51, 53, 54, 54 | 2.03 (± 0.763) | | | |
| Ig A, Week 4: n = 54, 52, 53, 54, 54 | 1.90 (± 0.699) | | | |
| Ig A, Week 16: n = 53, 50, 49, 53, 52 | 2.03 (± 0.752) | | | |
| Ig A, Week 24: n = 50, 47, 49, 48, 52 | 1.97 (± 0.757) | | | |
| Ig G, Day 1: n = 54, 51, 53, 54, 54 | 9.47 (± 1.839) | | | |
| Ig G, Week 4: n = 54, 52, 53, 54, 54 | 9.05 (± 1.922) | | | |
| Ig G, Week 16: n = 53, 50, 49, 53, 52 | 9.58 (± 1.850) | | | |
| Ig G, Week 24: n = 50, 47, 49, 48, 52 | 9.27 (± 1.866) | | | |

| | | | | |
|---------------------------------------|---------------------|--|--|--|
| Ig M, Day 1: n = 54, 51, 53, 54, 54 | 1.27 (\pm 0.589) | | | |
| Ig M, Week 4: n = 54, 51, 53, 54, 54 | 1.23 (\pm 0.603) | | | |
| Ig M, Week 16: n = 53, 50, 49, 53, 52 | 1.28 (\pm 0.678) | | | |
| Ig M, Week 24: n = 49, 47, 49, 48, 52 | 1.29 (\pm 0.667) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) Levels (Blinded Extension Period)

| | |
|-----------------|--|
| End point title | Absolute Concentrations of Immunoglobulin (Ig) Levels (Blinded Extension Period) |
|-----------------|--|

End point description:

Absolute Concentrations serum levels of IgG, IgA, IgM were assessed. The safety analysis set included of all subjects who received at least 1 dose evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint. Results reported are for BE period only and no participants took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48

| End point values | Tecfidera (Period 1 and 2) | Evobrutinib 25 mg QD | Evobrutinib 75 mg QD | Evobrutinib 75 mg BID |
|--------------------------------------|----------------------------|----------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 52 | 50 | 51 | 53 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| IgA | 2.06 (\pm 0.695) | 2.13 (\pm 0.807) | 2.18 (\pm 0.790) | 2.23 (\pm 0.838) |
| IgG | 9.60 (\pm 1.968) | 9.53 (\pm 2.070) | 9.74 (\pm 1.902) | 9.38 (\pm 2.189) |
| IgM | 1.28 (\pm 0.635) | 1.08 (\pm 0.557) | 1.13 (\pm 0.639) | 1.10 (\pm 0.692) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) Levels (Active Treatment Period)

| | |
|-----------------|--|
| End point title | Change From Baseline in Immunoglobulin (Ig) Levels (Active Treatment Period) |
|-----------------|--|

End point description:

Change in the serum levels of IgG, IgA, IgM were assessed. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 16, and 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|---------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54 | 50 | 53 | 54 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Week 4: n = 54, 50, 53, 54, 54 | -0.02 (± 0.201) | 0.02 (± 0.165) | 0.04 (± 0.169) | 0.07 (± 0.195) |
| Ig A, Week 16: n = 51, 48, 49, 53, 52 | 0.10 (± 0.188) | 0.18 (± 0.245) | 0.21 (± 0.313) | 0.22 (± 0.209) |
| Ig A, Week 24: n = 49, 44, 48, 48, 52 | 0.06 (± 0.250) | 0.21 (± 0.283) | 0.18 (± 0.416) | 0.22 (± 0.229) |
| Ig G, Week 4: n = 54, 50, 53, 54, 54 | 0.02 (± 0.758) | -0.10 (± 0.697) | -0.02 (± 0.688) | 0.02 (± 0.581) |
| Ig G, Week 16: n = 51, 48, 49, 53, 52 | 0.04 (± 0.747) | -0.07 (± 0.964) | -0.10 (± 1.068) | -0.05 (± 0.710) |
| Ig G, Week 24: n = 50, 45, 49, 48, 52 | 0.06 (± 0.682) | 0.00 (± 1.228) | -0.15 (± 1.058) | -0.28 (± 0.774) |
| Ig M, Week 4: n = 54, 50, 53, 54, 54 | -0.01 (± 0.210) | -0.06 (± 0.100) | -0.12 (± 0.233) | -0.05 (± 0.133) |
| Ig M, Week 16: n = 53, 48, 49, 53, 52 | 0.02 (± 0.177) | -0.12 (± 0.184) | -0.18 (± 0.244) | -0.14 (± 0.189) |
| Ig M, Week 24: n = 50, 45, 49, 48, 52 | 0.04 (± 0.163) | -0.14 (± 0.286) | -0.20 (± 0.289) | -0.21 (± 0.167) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|---------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Week 4: n = 54, 50, 53, 54, 54 | -0.13 (± 0.238) | | | |
| Ig A, Week 16: n = 51, 48, 49, 53, 52 | -0.02 (± 0.274) | | | |
| Ig A, Week 24: n = 49, 44, 48, 48, 52 | -0.06 (± 0.207) | | | |
| Ig G, Week 4: n = 54, 50, 53, 54, 54 | -0.42 (± 0.926) | | | |
| Ig G, Week 16: n = 51, 48, 49, 53, 52 | 0.07 (± 0.961) | | | |
| Ig G, Week 24: n = 50, 45, 49, 48, 52 | -0.23 (± 0.882) | | | |
| Ig M, Week 4: n = 54, 50, 53, 54, 54 | -0.04 (± 0.132) | | | |
| Ig M, Week 16: n = 53, 48, 49, 53, 52 | -0.00 (± 0.184) | | | |
| Ig M, Week 24: n = 50, 45, 49, 48, 52 | -0.00 (± 0.186) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) Levels (Blinded Extension Period)

| | |
|-----------------|---|
| End point title | Change From Baseline in Immunoglobulin (Ig) Levels (Blinded Extension Period) |
|-----------------|---|

End point description:

Change from baseline in the serum levels of IgG, IgA, IgM were assessed. The safety analysis set included of all subjects who received at least 1 dose evobrutinib or placebo or Tecfidera. Here, "Overall Number of subjects Analyzed" signifies those subjects who were evaluable for this endpoint. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint. Results reported are for BE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Week 25), Week 48

| End point values | Tecfidera (Period 1 and 2) | Evobrutinib 25 mg QD | Evobrutinib 75 mg QD | Evobrutinib 75 mg BID |
|--------------------------------------|----------------------------------|-------------------------|-------------------------|--------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 52 | 48 | 51 | 53 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| IgA | 0.03 (± 0.316) | 0.26 (± 0.248) | 0.28 (± 0.275) | 0.36 (± 0.320) |
| IgG | 0.10 (± 1.244) | 0.11 (± 1.024) | -0.08 (± 0.940) | 0.320 (± 0.883) |
| IgM | -0.01 (± 0.198) | -0.18 (± 0.211) | -0.27 (± 0.287) | -0.23 (± 0.218) |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Numbers of B Cells (Active Treatment Period)

| | |
|-----------------|---|
| End point title | Absolute Numbers of B Cells (Active Treatment Period) |
|-----------------|---|

End point description:

Absolute Numbers of B Cells are reported. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, and 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 52 | 53 | 53 |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: n = 52, 52, 49, 51, 48 | 242 (± 134.2) | 208 (± 117.5) | 247 (± 131.8) | 219 (± 113.7) |
| Week 4: n = 52, 50, 53, 53, 52 | 243 (± 130.8) | 220 (± 92.7) | 277 (± 156.2) | 270 (± 143.2) |
| Week 24: n = 49, 44, 49, 47, 52 | 264 (± 154.9) | 230 (± 119.7) | 235 (± 115.3) | 214 (± 105.0) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 52 | | | |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: n = 52, 52, 49, 51, 48 | 210 (± 97.4) | | | |
| Week 4: n = 52, 50, 53, 53, 52 | 201 (± 114.3) | | | |
| Week 24: n = 49, 44, 49, 47, 52 | 180 (± 114.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentration of B Cells (Blinded Extension Period)

| | |
|-----------------|--|
| End point title | Absolute Concentration of B Cells (Blinded Extension Period) |
|-----------------|--|

End point description:

Absolute Numbers of B Cells are reported. The safety analysis set included of all subjects who received at least 1 dose evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points. Here, "9999" = Based on pre-specified criteria and statistics perspective, it was not meaningful to calculate Mean and Standard Deviation when "n" is only 2. Results reported are for BE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48 and 52

| End point values | Tecfidera (Period 1 and 2) | Evobrutinib 25 mg QD | Evobrutinib 75 mg QD | Evobrutinib 75 mg BID |
|--------------------------------------|-------------------------------|-------------------------|-------------------------|--------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 47 | 49 | 51 | 53 |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48: n = 49, 51, 53, 47 | 181 (\pm 109.8) | 203 (\pm 111.9) | 222 (\pm 148.8) | 187 (\pm 87.1) |
| Week 52: n = 6, 7, 8, 2 | 9999 (\pm 9999) | 227 (\pm 93.7) | 206 (\pm 140.3) | 154 (\pm 73.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Absolute B cells (Active Treatment Period)

| | |
|------------------------|---|
| End point title | Change From Baseline in Absolute B cells (Active Treatment Period) |
| End point description: | Change from baseline in absolute B cells are reported. The safety analysis set included of all subjects who received at least 1 dose of evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points. |
| End point type | Secondary |
| End point timeframe: | Baseline (Day 1), Weeks 4 and 24 |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--------------------|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 52 | 50 | 53 | 53 |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: n = 52, 50, 53, 53, 52 | -5 (\pm 94.5) | 9 (\pm 112.2) | 31 (\pm 114.2) | 50 (\pm 86.7) |
| Week 24: n = 49, 44, 49, 47, 52 | 7 (\pm 135.8) | 13 (\pm 98.2) | -15 (\pm 128.5) | -9 (\pm 85.1) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 52 | | | |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: n = 52, 50, 53, 53, 52 | -3 (\pm 111.0) | | | |
| Week 24: n = 49, 44, 49, 47, 52 | -26 (\pm 113.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Absolute B cells (Blinded Extension Period)

| | |
|-----------------|---|
| End point title | Change From Baseline in Absolute B cells (Blinded Extension Period) |
|-----------------|---|

End point description:

Change from baseline in absolute B cells are reported. The safety analysis set included of all subjects who received at least 1 dose evobrutinib or placebo or Tecfidera. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points. . Here, "9999" = Based on pre-specified criteria and statistics perspective, it was not meaningful to calculate Mean and Standard Deviation when "n" is only 2. Results reported are for BE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Week 25), Weeks 48 and 52

| End point values | Tecfidera (Period 1 and 2) | Evobrutinib 25 mg QD | Evobrutinib 75 mg QD | Evobrutinib 75 mg BID |
|--------------------------------------|-------------------------------|-------------------------|-------------------------|--------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 47 | 49 | 51 | 53 |
| Units: cells per micro-liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48: n = 49, 51, 53, 47 | -15 (\pm 105.7) | -5 (\pm 116.1) | -30 (\pm 148.2) | -32 (\pm 97.9) |
| Week 52: n = 6, 7, 8, 2 | 9999 (\pm 9999) | -28 (\pm 209.8) | -25 (\pm 65.5) | -81 (\pm 119.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New gadolinium-positive (Gd+) T1 Lesions

| | |
|-----------------|--|
| End point title | Total Number of New gadolinium-positive (Gd+) T1 Lesions |
|-----------------|--|

End point description:

Analysis of Gadolinium-positive T1 lesions was done using magnetic resonance imaging (MRI) scans. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. Modified Intent-To-Treat (mITT) analysis set included subjects who belong to both Intent To Treat (ITT, consisted all subjects who randomly allocated to a treatment, based on the intention to treat "as randomized" principle) and safety analysis sets (consisted all subjects who received at least 1 dose of trial treatment), and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12 to 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 3.08 (\pm 4.371) | 3.44 (\pm 6.846) | 1.20 (\pm 3.499) | 0.98 (\pm 3.273) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 3.24 (\pm 15.320) | | | |

Statistical analyses

| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
|---|--|
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3676 |
| Method | Negative Binomial |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 2.65 |

| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
|----------------------------|---|
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0157 |
| Method | Negative Binomial |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.85 |

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0005 |
| Method | Negative Binomial |
| Parameter estimate | Lesion rate ratio |
| Point estimate | 0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 0.57 |

Secondary: Mean Per-scan Number of gadolinium-positive (Gd+) T1 lesions

| | |
|---|--|
| End point title | Mean Per-scan Number of gadolinium-positive (Gd+) T1 lesions |
| End point description: | |
| Analysis of Gadolinium-positive T1 lesions was done using magnetic resonance imaging (MRI) scans. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 to Week 24 | |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 1.02 (\pm 1.439) | 1.31 (\pm 3.130) | 0.42 (\pm 1.173) | 0.34 (\pm 0.960) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 1.45 (\pm 7.293) | | | |

Statistical analyses

| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
|---|--|
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9731 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.25 |
| upper limit | 0.25 |

| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
|---|---|
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | -0.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.75 |
| upper limit | -0.25 |

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0017 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 0 |

Secondary: Total Number of New or Enlarging T2 Lesions

| | |
|--|---|
| End point title | Total Number of New or Enlarging T2 Lesions |
| End point description: | |
| Analysis of New or Enlarging T2 lesions was done using magnetic resonance imaging (MRI) scans. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 to Week 24 | |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 5.96 (± 6.994) | 6.52 (± 11.569) | 3.41 (± 10.752) | 2.19 (± 4.719) |

| | | | | |
|------------------|-------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and | | | |
|------------------|-------------------------|--|--|--|

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| | 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 5.35 (\pm 16.667) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4807 |
| Method | Negative Binomial |
| Parameter estimate | Lesion Rate ratio |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.65 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0189 |
| Method | Negative Binomial |
| Parameter estimate | Lesion Rate ratio |
| Point estimate | 0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.87 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |

| | |
|---|-------------------|
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.062 |
| Method | Negative Binomial |
| Parameter estimate | Lesion Rate ratio |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.24 |
| upper limit | 1.04 |

Secondary: Change From Baseline in Volume of T2 Lesions at Week 24

| | |
|---|---|
| End point title | Change From Baseline in Volume of T2 Lesions at Week 24 |
| End point description: | |
| Analysis of volume of T2 lesions was done using magnetic resonance imaging (MRI) scans. Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24 | |

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 46 | 48 | 46 |
| Units: cubic centimeter (cc) | | | | |
| arithmetic mean (standard deviation) | 0.42 (± 1.009) | 0.93 (± 1.853) | -0.01 (± 0.562) | 0.09 (± 0.463) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: cubic centimeter (cc) | | | | |
| arithmetic mean (standard deviation) | 0.47 (± 2.964) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8776 |
| Method | Mixed Effect Model for Repeat Measures |
| Parameter estimate | Difference in least squares means |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 0.28 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0063 |
| Method | Mixed Effect Model for Repeat Measures |
| Parameter estimate | Difference in least squares means |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.62 |
| upper limit | -0.1 |

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0019 |
| Method | Mixed Effect Model for Repeat Measures |
| Parameter estimate | Difference in least squares means |
| Point estimate | -0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.66 |
| upper limit | -0.15 |

Secondary: Change From Baseline in Volume of gadolinium-positive (Gd+) T1 Lesions at Week 24

| | |
|-----------------|---|
| End point title | Change From Baseline in Volume of gadolinium-positive (Gd+) T1 Lesions at Week 24 |
|-----------------|---|

End point description:

Analysis of volume of Gd+ T1 lesions was done using magnetic resonance imaging (MRI) scans. As per planned analysis, Tecfidera treatment group was not included in inferential analysis. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 24

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|------------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | -0.023 (\pm 0.2220) | 0.057 (\pm 0.3479) | -0.111 (\pm 0.5416) | -0.051 (\pm 0.1032) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | -0.050 (\pm 0.4771) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 25 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 25 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9315 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.004 |
| upper limit | 0.009 |

| | |
|---|---|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg BID |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg BID (Period 1 and 2) |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0014 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | -0.018 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.042 |
| upper limit | 0 |

| | |
|---|--|
| Statistical analysis title | Placebo vs Evobrutinib 75 mg QD |
| Comparison groups | Placebo (period 1) v Evobrutinib 75 mg QD (Period 1 and 2) |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0008 |
| Method | Wilcoxon rank-sum test |
| Parameter estimate | Hodges-Lehmann estimate |
| Point estimate | -0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0 |

Secondary: Number of Gadolinium-positive (Gd+) T1 Lesions at Week 48

| | |
|--|---|
| End point title | Number of Gadolinium-positive (Gd+) T1 Lesions at Week 48 |
| End point description: | |
| Analysis of Gd+ T1 lesions was done using magnetic resonance imaging (MRI) scans. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period. | |
| End point type | Secondary |

End point timeframe:

Week 48

| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 1.00 (± 1.614) | 1.91 (± 4.296) | 0.85 (± 2.867) | 0.49 (± 1.218) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 0.42 (± 1.444) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of New Gadolinium-positive (Gd+) T1 Lesions at Week 48

| | |
|-----------------|---|
| End point title | Number of New Gadolinium-positive (Gd+) T1 Lesions at Week 48 |
|-----------------|---|

End point description:

Analysis of new Gd+ T1 lesions was done using magnetic resonance imaging (MRI) scans. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 48

| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 0.95 (± 1.569) | 1.84 (± 4.154) | 0.85 (± 2.867) | 0.49 (± 1.218) |

| | | | | |
|--------------------------------------|-------------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 0.42 (± 1.444) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Qualified Relapse-free Status

| | |
|-----------------|-------------------------------|
| End point title | Qualified Relapse-free Status |
|-----------------|-------------------------------|

End point description:

A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. Percentage of subjects with qualified relapse-free status were reported. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 25 to Week 48

| | | | | |
|-------------------------------|---|---|---|--|
| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 84.1 | 86.4 | 78.3 | 91.1 |

| | | | | |
|-------------------------------|-------------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 96.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized relapse rate (ARR)

| | |
|-----------------|-------------------------------|
| End point title | Annualized relapse rate (ARR) |
|-----------------|-------------------------------|

End point description:

A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 to Week 48

| End point values | Placebo (period 1) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|---|---------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 53 | 50 | 51 | 53 |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.37 (0.21 to 0.59) | 0.52 (0.33 to 0.78) | 0.25 (0.12 to 0.44) | 0.11 (0.04 to 0.25) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|---|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.14 (0.06 to 0.29) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Expanded Disability Status Scale (EDSS) at

Week 48

| | |
|-----------------|---|
| End point title | Change From Week 24 in Expanded Disability Status Scale (EDSS) at Week 48 |
|-----------------|---|

End point description:

The EDSS is an ordinal clinical rating scale in half-point increments. It assesses the following eight functional systems, areas of the central nervous system that control bodily functions: Pyramidal (ability to walk), Cerebellar (coordination), Brain stem (speech and swallowing), Sensory (touch and pain), Bowel and bladder functions, Visual, Mental, Other (includes any other neurological findings due to Multiple Sclerosis [MS]). EDSS overall score ranging from 0 (normal) to 10 (death due to MS). mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24, Week 48

| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.05 (\pm 0.260) | -0.10 (\pm 0.351) | -0.01 (\pm 0.619) | 0.00 (\pm 0.238) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.10 (\pm 0.404) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New or Enlarging T2 Lesions at Week 48 relative to Week 24

| | |
|-----------------|--|
| End point title | Total Number of New or Enlarging T2 Lesions at Week 48 relative to Week 24 |
|-----------------|--|

End point description:

Analysis of New or Enlarging T2 lesions was done using magnetic resonance imaging (MRI) scans. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24 to Week 48

| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 | 42 | 43 | 43 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 3.57 (\pm 4.346) | 5.86 (\pm 11.330) | 3.84 (\pm 10.083) | 1.60 (\pm 3.799) |

| End point values | Tecfidera (Period 1 and 2) | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | 1.88 (\pm 4.796) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Volume of T2 Lesions at Week 48

| | |
|-----------------|--|
| End point title | Change From Week 24 in Volume of T2 Lesions at Week 48 |
|-----------------|--|

End point description:

Analysis of volume of T2 lesions was done using magnetic resonance imaging (MRI) scans. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24, Week 48

| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | 0.53 (\pm 1.360) | 0.67 (\pm 1.865) | 0.35 (\pm 1.083) | -0.03 (\pm 1.031) |

| | | | | |
|--------------------------------------|-------------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | -0.57 (\pm 2.699) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Volume of gadolinium-positive (Gd+) T1 Lesions at Week 48

| | |
|------------------------|--|
| End point title | Change From Week 24 in Volume of gadolinium-positive (Gd+) T1 Lesions at Week 48 |
| End point description: | Analysis of volume of Gd+ T1 lesions was done using magnetic resonance imaging (MRI) scans. mITT BE analysis set included all subjects who belonged to the mITT analysis set with an MRI assessment during the 24-week blinded extension period. |
| End point type | Secondary |
| End point timeframe: | Week 24, Week 48 |

| | | | | |
|--------------------------------------|--|---------------------------------------|---------------------------------------|--|
| End point values | Placebo Then Evobrutinib 25 mg QD (Period 2) | Evobrutinib 25 mg QD (Period 1 and 2) | Evobrutinib 75 mg QD (Period 1 and 2) | Evobrutinib 75 mg BID (Period 1 and 2) |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 44 | 46 | 45 |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | 0.092 (\pm 0.4626) | 0.088 (\pm 0.4006) | 0.045 (\pm 0.2285) | 0.024 (\pm 0.1981) |

| | | | | |
|--------------------------------------|-------------------------------|--|--|--|
| End point values | Tecfidera (Period 1 and 2) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: cc | | | | |
| arithmetic mean (standard deviation) | -0.203 (\pm 1.1073) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Total Number of Gadolinium-Enhancing T1 Lesions

| | |
|-----------------|---|
| End point title | OLE Period: Total Number of Gadolinium-Enhancing T1 Lesions |
|-----------------|---|

End point description:

Analysis of T1-Gadolinium enhancing lesions was done using magnetic resonance imaging (MRI) scans. modified ITT OLE Analysis Set (mITT-OLE) Analysis Set: subjects randomly allocated to a treatment who belong to Safety OLE Analysis Set, and who have at least 1 Magnetic Resonance Imaging (MRI) assessment on or after OLE Week 0. Here, "Overall Number of Subjects Analyzed" = subjects evaluable for this endpoint and "n" = subjects who were evaluable for the specified category. Results reported are for OLE period only and no participants took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48), OLE Weeks 96, 144, 192, 240, 288 and 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|--|---|---------------------------------|---------------------------------|----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 34 | 35 | 37 | 44 |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline(BE period Week 48): n =34, 35, 37, 44, 37 | 0.82 (± 2.668) | 1.74 (± 4.395) | 1.46 (± 4.519) | 1.16 (± 3.050) |
| Week 96: n = 31, 27, 35, 36, 36 | 0.13 (± 0.341) | 0.63 (± 1.822) | 0.49 (± 1.121) | 0.69 (± 1.411) |
| Week 144: n = 29, 27, 34, 35, 31 | 0.76 (± 2.294) | 0.41 (± 1.217) | 0.82 (± 3.512) | 0.54 (± 1.146) |
| Week 192: n = 28, 25, 32, 32, 26 | 1.00 (± 3.367) | 0.64 (± 1.890) | 0.81 (± 2.206) | 0.84 (± 1.798) |
| Week 240: n = 25, 24, 30, 30, 26 | 1.68 (± 5.800) | 0.63 (± 1.996) | 0.37 (± 1.189) | 0.77 (± 2.417) |
| Week 288: n = 20, 17, 28, 26, 23 | 0.35 (± 0.671) | 0.35 (± 0.786) | 0.32 (± 1.090) | 1.04 (± 2.946) |
| Week 336: n = 6, 7, 6, 7, 15 | 0.83 (± 1.602) | 3.00 (± 5.745) | 1.17 (± 2.858) | 0.29 (± 0.756) |

| End point values | Tecfidera (Period 3) | | | |
|--|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 | | | |
| Units: Lesions | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline(BE period Week 48): n =34, 35, 37, 44, 37 | 2.03 (± 11.829) | | | |
| Week 96: n = 31, 27, 35, 36, 36 | 0.67 (± 2.255) | | | |

| | | | | |
|----------------------------------|-----------------|--|--|--|
| Week 144: n = 29, 27, 34, 35, 31 | 1.29 (± 5.940) | | | |
| Week 192: n = 28, 25, 32, 32, 26 | 0.96 (± 3.130) | | | |
| Week 240: n = 25, 24, 30, 30, 26 | 0.88 (± 3.204) | | | |
| Week 288: n = 20, 17, 28, 26, 23 | 0.35 (± 1.265) | | | |
| Week 336: n = 6, 7, 6, 7, 15 | 5.60 (± 18.310) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Annualized relapse rate (ARR)

| | |
|-----------------|---|
| End point title | OLE Period: Annualized relapse rate (ARR) |
|-----------------|---|

End point description:

A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. modified ITT OLE Analysis Set (mITT-OLE) Analysis Set: subjects randomly allocated to a treatment who belong to Safety OLE Analysis Set, and who have at least 1 Magnetic Resonance Imaging (MRI) assessment on or after OLE Week 0. Here, "n" = subjects who were evaluable for the specified category. Results reported are for OLE period only and no participants took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48), OLE Weeks 96, 144, 192, 240, 288 and 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|--|---|---------------------------------|---------------------------------|----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 38 | 42 | 44 |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Baseline(BE period Week 48): n =39, 38, 42, 44, 48 | 0.29 (0.14 to 0.53) | 0.18 (0.06 to 0.38) | 0.14 (0.04 to 0.32) | 0.17 (0.07 to 0.36) |
| Week 96: n = 37, 36, 37, 44, 40 | 0.16 (0.05 to 0.37) | 0.13 (0.04 to 0.34) | 0.09 (0.02 to 0.26) | 0.08 (0.02 to 0.22) |
| Week 144: n = 33, 30, 37, 40, 36 | 0.07 (0.01 to 0.25) | 0.11 (0.02 to 0.33) | 0.03 (0.00 to 0.17) | 0.15 (0.05 to 0.34) |
| Week 192: n = 31, 27, 35, 35, 33 | 0.04 (0.00 to 0.20) | 0.08 (0.01 to 0.29) | 0.22 (0.09 to 0.45) | 0.16 (0.05 to 0.38) |
| Week 240: n = 30, 27, 34, 33, 30 | 0.16 (0.04 to 0.41) | 0.04 (0.00 to 0.23) | 0.10 (0.02 to 0.28) | 0.13 (0.04 to 0.34) |
| Week 288: n = 25, 24, 32, 32, 26 | 0.13 (0.13 to 0.38) | 0.05 (0.00 to 0.25) | 0.07 (0.01 to 0.25) | 0.00 (0.00 to 0.13) |
| Week 336: n = 24, 22, 26, 29, 7 | 0.00 (0.00 to 1.75) | 0.00 (0.00 to 1.55) | 0.31 (0.01 to 1.70) | 0.00 (0.00 to 1.27) |

| End point values | Tecfidera (Period 3) | | | |
|--|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 48 | | | |
| Units: relapses per year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Baseline(BE period Week 48): n =39, 38, 42, 44, 48 | 0.12 (0.04 to 0.28) | | | |
| Week 96: n = 37, 36, 37, 44, 40 | 0.03 (0.00 to 0.16) | | | |
| Week 144: n = 33, 30, 37, 40, 36 | 0.16 (0.05 to 0.37) | | | |
| Week 192: n = 31, 27, 35, 35, 33 | 0.04 (0.00 to 0.20) | | | |
| Week 240: n = 30, 27, 34, 33, 30 | 0.00 (0.00 to 0.15) | | | |
| Week 288: n = 25, 24, 32, 32, 26 | 0.04 (0.00 to 0.24) | | | |
| Week 336: n = 24, 22, 26, 29, 7 | 0.00 (0.00 to 7.97) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Percentage of Subjects with Qualified Relapse-Free Status

| | |
|-----------------|---|
| End point title | OLE Period: Percentage of Subjects with Qualified Relapse-Free Status |
|-----------------|---|

End point description:

A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to Multiple Sclerosis (MS) that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. Percentage of subjects with qualified relapse-free status from OLE Baseline (BE period Week 48) up to Week 336 were reported. The modified ITT (mITT) analysis set consists of all subjects who belong to both the ITT and safety analysis sets, and who have at least one baseline and one post-baseline magnetic resonance imaging (MRI) assessment. results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48) up to OLE Week 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|-------------------------------|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 38 | 42 | 44 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 66.7 | 68.4 | 71.4 | 65.9 |

| | | | | |
|-------------------------------|-------------------------|--|--|--|
| End point values | Tecfidera (Period 3) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 48 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 83.3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Change from Baseline in Expanded Disability Status Scale (EDSS) at Week 96, 144, 192, 240, 288 and 336

| | |
|-----------------|--|
| End point title | OLE Period: Change from Baseline in Expanded Disability Status Scale (EDSS) at Week 96, 144, 192, 240, 288 and 336 |
|-----------------|--|

End point description:

The EDSS is an ordinal clinical rating scale in half-point increments. It assesses the following eight functional systems, areas of the central nervous system that control bodily functions: Pyramidal (ability to walk), Cerebellar (coordination), Brain stem (speech and swallowing), Sensory (touch and pain), Bowel and bladder functions, Visual, Mental, Other (includes any other neurological findings due to Multiple Sclerosis [MS]). EDSS overall score ranging from 0 (normal) to 10 (death due to MS). modified ITT OLE Analysis Set (mITT-OLE) Analysis Set: subjects randomly allocated to a treatment who belong to Safety OLE Analysis Set, and who have at least 1 Magnetic Resonance Imaging (MRI) assessment on or after OLE Week 0. Here, "Overall Number of Subjects Analyzed" = subjects evaluable for this endpoint and "n" = subjects who were evaluable for the specified category. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48), OLE Weeks 96, 144, 192, 240, 288 and 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|--|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 37 | 35 | 28 | 44 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline(BE period Week 48): n =37, 35, 28, 44, 40 | 0.1 (± 0.39) | 0.0 (± 0.69) | 0.1 (± 0.46) | 0.0 (± 0.27) |
| Week 96: n = 34, 30, 35, 38, 36 | 0.1 (± 0.40) | 0.1 (± 0.46) | 0.2 (± 0.71) | 0.0 (± 0.42) |
| Week 144: n = 31, 27, 36, 35, 32 | 0.1 (± 0.79) | 0.1 (± 0.61) | 0.2 (± 0.79) | 0.0 (± 0.44) |
| Week 192: n = 28, 26, 34, 33, 28 | 0.2 (± 0.64) | 0.1 (± 0.61) | 0.2 (± 0.35) | 0.2 (± 0.72) |
| Week 240: n = 25, 25, 32, 32, 26 | 0.3 (± 0.72) | 0.3 (± 0.50) | 0.2 (± 0.46) | 0.2 (± 0.93) |
| Week 288: n = 25, 23, 29, 29, 25 | 0.4 (± 0.80) | 0.1 (± 0.87) | 0.4 (± 0.58) | 0.4 (± 0.81) |
| Week 336: n = 11, 10, 10, 7, 15 | 0.0 (± 0.52) | 0.5 (± 1.36) | 0.7 (± 1.38) | -0.2 (± 0.57) |

| | | | | |
|---|-------------------------|--|--|--|
| End point values | Tecfidera (Period 3) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline(BE period Week 48): n = 37, 35, 28, 44, 40 | 0.0 (± 0.34) | | | |
| Week 96: n = 34, 30, 35, 38, 36 | 0.0 (± 0.32) | | | |
| Week 144: n = 31, 27, 36, 35, 32 | 0.0 (± 0.28) | | | |
| Week 192: n = 28, 26, 34, 33, 28 | 0.0 (± 0.29) | | | |
| Week 240: n = 25, 25, 32, 32, 26 | 0.1 (± 0.40) | | | |
| Week 288: n = 25, 23, 29, 29, 25 | 0.2 (± 0.45) | | | |
| Week 336: n = 11, 10, 10, 7, 15 | 0.0 (± 0.52) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | OLE Period: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

AE: any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study drug. SAE: 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: adverse event with a start date on or after the date of first dose and within 28 days after the date of last dose in the study. TEAEs included both Serious TEAEs and non-serious TEAEs. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48) up to OLE Week 336

| | | | | |
|-----------------------------|--|---------------------------------------|---------------------------------------|--|
| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 39 | 42 | 44 |
| Units: subjects | 35 | 29 | 41 | 40 |

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | Tecfidera (Period 3) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: subjects | 37 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs

| | |
|--|---|
| End point title | OLE Period: Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs |
| End point description: Vital signs, including semi supine blood pressure, pulse rate, respiratory rate, weight, and oral temperature were assessed. Number of subjects with clinically significant change from baseline in vital signs were reported. Clinical Significance was decided by the investigator. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Results reported are for OLE period only and no subjects took placebo during this period. | |
| End point type | Secondary |
| End point timeframe: OLE Baseline (BE period Week 48) up to OLE Week 336 | |

| | | | | |
|-----------------------------|--|---------------------------------------|---------------------------------------|--|
| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 39 | 42 | 44 |
| Units: subjects | 0 | 0 | 0 | 0 |

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | Tecfidera (Period 3) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: subjects | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects With Clinically Significant Changes From Baseline in Laboratory Parameters

| | | | | |
|-----------------|--|--|--|--|
| End point title | OLE Period: Number of Subjects With Clinically Significant | | | |
|-----------------|--|--|--|--|

End point description:

Laboratory parameters included hematology, biochemistry, and urinalysis. Number of subjects with clinically significant change from baseline in laboratory parameters were reported. Clinical Significance was decided by the investigator. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48) up to OLE Week 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|-----------------------------|---|---------------------------------|---------------------------------|----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 39 | 42 | 44 |
| Units: subjects | 0 | 0 | 0 | 0 |

| End point values | Tecfidera (Period 3) | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: subjects | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Absolute Concentrations of Immunoglobulin (Ig) Levels

| | |
|-----------------|---|
| End point title | OLE Period: Absolute Concentrations of Immunoglobulin (Ig) Levels |
|-----------------|---|

End point description:

Absolute Concentrations serum levels of IgG, IgA, IgM were assessed. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Here, "Overall Number of Subjects Analyzed" = subjects evaluable for this endpoint and "n" = subjects who were evaluable for the specified category. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48), OLE Weeks 96, 144, 192, 240 and 288

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|--|--|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 37 | 37 | 37 | 44 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A,Baseline (Week 48):n = 37, 37, 37, 44, 40 | 2.31 (± 0.966) | 2.44 (± 0.897) | 2.49 (± 0.953) | 2.52 (± 0.970) |
| Ig A, Week 96: n = 32, 30, 36, 39, 38 | 2.42 (± 1.173) | 2.69 (± 1.026) | 2.91 (± 1.181) | 2.82 (± 1.113) |
| Ig A, Week 144: n = 30, 27, 36, 35, 33 | 2.57 (± 1.274) | 2.73 (± 0.918) | 2.82 (± 1.326) | 2.91 (± 1.233) |
| IgA, Week 192: n = 29, 26, 33, 32, 26 | 2.60 (± 1.242) | 2.71 (± 0.987) | 2.86 (± 1.255) | 3.15 (± 1.185) |
| IgA, Week 240: n = 24,22, 33, 28, 23 | 2.71 (± 1.280) | 2.85 (± 1.095) | 3.05 (± 1.314) | 3.13 (± 1.269) |
| IgA, Week 288: n = 37, 20, 26, 27, 17 | 2.68 (± 1.305) | 3.08 (± 1.276) | 3.12 (± 1.306) | 3.30 (± 1.347) |
| Ig G, Baseline(Week 48): n = 37, 37, 37, 44, 40 | 9.75 (± 2.253) | 10.37 (± 2.512) | 10.73 (± 2.479) | 10.44 (± 2.291) |
| Ig G, Week 96: n = 32, 30, 36, 39, 38 | 9.46 (± 2.490) | 10.10 (± 2.461) | 10.76 (± 2.413) | 10.29 (± 2.172) |
| Ig G, Week 144: n = 30, 27, 36, 35, 33 | 9.48 (± 2.294) | 10.43 (± 2.304) | 10.38 (± 2.638) | 10.21 (± 2.552) |
| IgG, Week 192: n = 29, 26, 33, 32, 26 | 9.37 (± 2.156) | 9.99 (± 2.197) | 10.36 (± 2.548) | 10.46 (± 2.135) |
| IgG, Week 240: n = 24,22, 33, 28, 23 | 9.28 (± 2.081) | 10.33 (± 2.422) | 2.422 (± 2.562) | 10.47 (± 2.562) |
| IgG, Week 288: n = 25, 20, 26, 27, 17 | 9.46 (± 2.068) | 10.48 (± 2.541) | 10.64 (± 2.566) | 10.36 (± 2.273) |
| Ig M, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 1.06 (± 0.550) | 0.89 (± 0.403) | 1.08 (± 0.680) | 0.92 (± 0.422) |
| Ig M, Week 96: n = 32, 30, 36, 39, 38 | 1.01 (± 0.556) | 0.87 (± 0.413) | 1.05 (± 0.747) | 0.92 (± 0.460) |
| Ig M, Week 144: n = 30, 27, 36, 35, 33 | 0.88 (± 0.463) | 0.88 (± 0.468) | 0.94 (± 0.614) | 0.89 (± 0.377) |
| Ig M, Week 192: n = 28, 26, 33, 32, 26 | 0.89 (± 0.492) | 0.87 (± 0.461) | 0.90 (± 0.462) | 0.84 (± 0.320) |
| Ig M, Week 240: n = 24,22, 33, 28, 23 | 0.85 (± 0.420) | 0.83 (± 0.419) | 0.87 (± 0.468) | 0.88 (± 0.369) |
| Ig M, Week 288: n = 25, 22, 27, 28, 18 | 0.85 (± 0.405) | 0.90 (± 0.490) | 0.94 (± 0.544) | 0.87 (± 0.397) |

| End point values | Tecfidera (Period 3) | | | |
|---|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A,Baseline (Week 48):n = 37, 37, 37, 44, 40 | 2.31 (± 0.906) | | | |
| Ig A, Week 96: n = 32, 30, 36, 39, 38 | 2.62 (± 1.072) | | | |
| Ig A, Week 144: n = 30, 27, 36, 35, 33 | 2.57 (± 1.025) | | | |
| IgA, Week 192: n = 29, 26, 33, 32, 26 | 2.70 (± 1.055) | | | |
| IgA, Week 240: n = 24,22, 33, 28, 23 | 2.65 (± 0.984) | | | |
| IgA, Week 288: n = 37, 20, 26, 27, 17 | 2.92 (± 1.108) | | | |
| Ig G, Baseline(Week 48): n = 37, 37, 37, 44, 40 | 9.65 (± 2.165) | | | |
| Ig G, Week 96: n = 32, 30, 36, 39, 38 | 9.93 (± 2.285) | | | |
| Ig G, Week 144: n = 30, 27, 36, 35, 33 | 9.32 (± 2.115) | | | |
| IgG, Week 192: n = 29, 26, 33, 32, 26 | 9.56 (± 2.094) | | | |
| IgG, Week 240: n = 24,22, 33, 28, 23 | 9.58 (± 2.245) | | | |

| | | | | |
|--|----------------|--|--|--|
| IgG, Week 288: n = 25, 20, 26, 27, 17 | 9.72 (± 2.700) | | | |
| Ig M, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 0.99 (± 0.586) | | | |
| Ig M, Week 96: n = 32, 30, 36, 39, 38 | 0.91 (± 0.525) | | | |
| Ig M, Week 144: n = 30, 27, 36, 35, 33 | 0.90 (± 0.519) | | | |
| Ig M, Week 192: n = 28, 26, 33, 32, 26 | 0.90 (± 0.585) | | | |
| Ig M, Week 240: n = 24, 22, 33, 28, 23 | 0.87 (± 0.611) | | | |
| Ig M, Week 288: n = 25, 22, 27, 28, 18 | 1.03 (± 0.568) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Number of Subjects With Clinically Significant Changes From Baseline in Electrocardiograms (ECGs)

| | |
|-----------------|---|
| End point title | OLE Period: Number of Subjects With Clinically Significant Changes From Baseline in Electrocardiograms (ECGs) |
|-----------------|---|

End point description:

ECG parameters included rhythm, ventricular rate, PR interval, QRS duration, and QT interval. Number of subjects with clinically significant change from baseline in ECG were reported. Clinical Significance was decided by the investigator. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48) up to OLE Week 336

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|-----------------------------|---|---------------------------------|---------------------------------|----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 39 | 39 | 42 | 44 |
| Units: subjects | 0 | 0 | 0 | 0 |

| End point values | Tecfidera (Period 3) | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: subjects | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Period: Change from Baseline in Immunoglobulin (Ig) Levels

| | |
|-----------------|--|
| End point title | OLE Period: Change from Baseline in Immunoglobulin (Ig) Levels |
|-----------------|--|

End point description:

Change from baseline in the serum levels of IgG, IgA, IgM were assessed. The Safety OLE Analysis Set included all subjects who receive at least 1 dose of Evobrutinib during the OLE. Here, "Overall Number of Subjects Analyzed" = subjects evaluable for this endpoint and "n" = subjects who were evaluable for the specified category. Results reported are for OLE period only and no subjects took placebo during this period.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OLE Baseline (BE period Week 48), OLE Weeks 96, 144, 192, 240 and 288

| End point values | Placebo + Evobrutinib 25 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 75 mg BID (Period 3) |
|--|---|---------------------------------|---------------------------------|----------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 37 | 37 | 37 | 44 |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 0.26 (± 0.237) | 0.17 (± 0.333) | 0.19 (± 0.283) | 0.26 (± 0.291) |
| Ig A, Week 96: n = 32, 30, 36, 39, 38 | 0.44 (± 0.491) | 0.45 (± 0.407) | 0.58 (± 0.485) | 0.54 (± 0.446) |
| Ig A, Week 144: n = 30, 27, 36, 35, 33 | 0.58 (± 0.594) | 0.41 (± 0.347) | 0.50 (± 0.670) | 0.57 (± 0.589) |
| IgA, Week 192: n = 29, 26, 33, 32, 36 | 0.60 (± 0.597) | 0.38 (± 0.443) | 0.55 (± 0.667) | 0.82 (± 0.530) |
| IgA, Week 240: n = 24, 22, 33, 28, 23 | 0.67 (± 0.605) | 0.55 (± 0.471) | 0.74 (± 0.682) | 0.78 (± 0.621) |
| IgA, Week 288: n = 25, 20, 26, 27, 17 | 0.68 (± 0.934) | 0.75 (± 0.680) | 0.91 (± 0.915) | 1.02 (± 0.637) |
| Ig G, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 0.39 (± 0.960) | 0.54 (± 1.463) | 0.69 (± 1.147) | 1.11 (± 1.150) |
| Ig G, Week 96: n = 32, 30, 36, 39, 38 | 0.17 (± 1.359) | 0.18 (± 1.228) | 0.64 (± 1.178) | 0.84 (± 1.073) |
| Ig G, Week 144: n = 30, 27, 36, 35, 33 | 0.35 (± 1.367) | 0.17 (± 1.451) | 0.31 (± 1.356) | 0.68 (± 1.458) |
| IgG, Week 192: n = 29, 26, 33, 32, 26 | 0.14 (± 1.227) | -0.13 (± 1.141) | 0.18 (± 1.625) | 0.84 (± 1.384) |
| IgG, Week 240: n = 24, 22, 33, 28, 23 | -0.01 (± 1.336) | 0.10 (± 1.557) | 0.37 (± 1.596) | 0.75 (± 1.362) |
| IgG, Week 288: n = 25, 20, 26, 27, 17 | 0.18 (± 1.492) | 0.48 (± 1.465) | 0.37 (± 2.203) | 1.01 (± 1.570) |
| Ig M, Baseline (Week 48): n = 37, 37, 37, 44, 40 | -0.18 (± 0.152) | -0.10 (± 0.120) | -0.09 (± 0.122) | -0.05 (± 0.099) |
| IgM, Week 96: n = 32, 30, 36, 39, 38 | -0.23 (± 0.146) | -0.13 (± 0.141) | -0.09 (± 0.199) | -0.08 (± 0.127) |
| IgM, Week 144: n = 30, 27, 36, 35, 33 | -0.28 (± 0.323) | -0.14 (± 0.195) | -0.17 (± 0.174) | -0.11 (± 0.149) |
| IgM, Week 192: n = 28, 26, 33, 32, 26 | -0.28 (± 0.254) | -0.16 (± 0.204) | -0.19 (± 0.186) | -0.18 (± 0.197) |
| IgM, Week 240: n = 24, 22, 33, 28, 23 | -0.29 (± 0.282) | -0.20 (± 0.187) | -0.19 (± 0.205) | -0.16 (± 0.254) |
| IgM, Week 288: n = 25, 22, 27, 28, 18 | -0.29 (± 0.284) | -0.11 (± 0.313) | -0.15 (± 0.315) | -0.17 (± 0.178) |

| | | | | |
|------------------|----------------------|--|--|--|
| End point values | Tecfidera (Period 3) | | | |
|------------------|----------------------|--|--|--|

| | | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: Gram per Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ig A, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 0.28 (± 0.355) | | | |
| Ig A, Week 96: n = 32, 30, 36, 39, 38 | 0.59 (± 0.545) | | | |
| Ig A, Week 144: n = 30, 27, 36, 35, 33 | 0.54 (± 0.452) | | | |
| IgA, Week 192: n = 29, 26, 33, 32, 36 | 0.67 (± 0.492) | | | |
| IgA, Week 240: n = 24, 22, 33, 28, 23 | 0.68 (± 0.520) | | | |
| IgA, Week 288: n = 25, 20, 26, 27, 17 | 0.93 (± 0.724) | | | |
| Ig G, Baseline (Week 48): n = 37, 37, 37, 44, 40 | 0.23 (± 1.216) | | | |
| Ig G, Week 96: n = 32, 30, 36, 39, 38 | 0.47 (± 1.355) | | | |
| Ig G, Week 144: n = 30, 27, 36, 35, 33 | -0.09 (± 1.176) | | | |
| IgG, Week 192: n = 29, 26, 33, 32, 26 | 0.09 (± 1.324) | | | |
| IgG, Week 240: n = 24, 22, 33, 28, 23 | 0.19 (± 1.314) | | | |
| IgG, Week 288: n = 25, 20, 26, 27, 17 | 0.36 (± 1.440) | | | |
| Ig M, Baseline (Week 48): n = 37, 37, 37, 44, 40 | -0.28 (± 0.280) | | | |
| IgM, Week 96: n = 32, 30, 36, 39, 38 | -0.35 (± 0.301) | | | |
| IgM, Week 144: n = 30, 27, 36, 35, 33 | -0.40 (± 0.327) | | | |
| IgM, Week 192: n = 28, 26, 33, 32, 26 | -0.46 (± 0.330) | | | |
| IgM, Week 240: n = 24, 22, 33, 28, 23 | -0.53 (± 0.348) | | | |
| IgM, Week 288: n = 25, 22, 27, 28, 18 | -0.39 (± 0.472) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Safety Follow up of blinded extension period (Week 52); OLE Baseline (BE period Week 48) up to OLE Week 336

Adverse event reporting additional description:

Active treatment period and BE period: MedDRA version 21.0; OLE Period: MedDRA version 26.1

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----------|
| Dictionary version | 21.026.1 |
|--------------------|----------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Evobrutinib 25 mg QD (Period 1 and Period 2) |
|-----------------------|--|

Reporting group description:

Subjects received Evobrutinib 25 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1.

| | |
|-----------------------|---|
| Reporting group title | Evobrutinib 75 mg BID (Period 1 and Period 2) |
|-----------------------|---|

Reporting group description:

Subjects received Evobrutinib 75 mg orally, twice daily (BID) up to Week 48 in active treatment period 1 and BE period.

| | |
|-----------------------|--|
| Reporting group title | Evobrutinib 75 mg QD (Period 1 and Period 2) |
|-----------------------|--|

Reporting group description:

Subjects received Evobrutinib 75 mg orally, QD up to Week 48 in active treatment period 1 and BE period.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Evobrutinib 75 mg BID (Period 3) |
|-----------------------|----------------------------------|

Reporting group description:

Subjects received Evobrutinib 75 mg BID orally from Week 48 of main period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|----------------------|
| Reporting group title | Tecfidera (period 3) |
|-----------------------|----------------------|

Reporting group description:

Subjects received Tecfidera 120 mg BID orally from Week 48 of main period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Evobrutinib 75 mg QD (Period 3) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received Evobrutinib 75 mg QD orally from Week 48 of main period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Evobrutinib 25 mg QD (Period 3) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received Evobrutinib 25 mg QD orally from Week 48 of main period (OLE period Day 1) to Week 336 in OLE period.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo Then Evobrutinib 25 mg QD |
|-----------------------|-----------------------------------|

Reporting group description:

Participants who received placebo matched to Evobrutinib tablet orally for 24 weeks in active treatment period 1 received Evobrutinib 25 milligram (mg) orally, once daily (QD) in blinded extension (BE) period from week 25 to week 48.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Tecfidera (Period 1 and Period 2) |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects received Tecfidera 120 mg twice daily (BID) for first 7 days followed by 240 mg orally, BID up to Week 48 in active treatment period 1 and BE period.

| | |
|---|---|
| Reporting group title | Placebo + Evobrutinib 25 mg QD (Period 3) |
| Reporting group description: | |
| Subjects who received placebo matched to Evobrutinib tablet orally for 24 weeks in main treatment period were switched to receive Evobrutinib 25 mg orally, QD up to 301 weeks in OLE period. | |

| Serious adverse events | Evobrutinib 25 mg QD (Period 1 and Period 2) | Placebo | Evobrutinib 75 mg BID (Period 1 and Period 2) |
|---|--|----------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 54 (3.70%) | 4 / 54 (7.41%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 54 (1.85%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilloma | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral embolism | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 54 (1.85%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical dysplasia | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cervix stenosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar ischaemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis pseudo relapse | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar artery dissection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Keratoconus | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 54 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder hypertrophy | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 54 (1.85%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometritis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serratia infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Haemochromatosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Evobrutinib 75 mg QD (Period 1 and Period 2) | Evobrutinib 75 mg BID (Period 3) | Tecfidera (period 3) |
|---|--|----------------------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 5 / 44 (11.36%) | 10 / 49 (20.41%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilloma | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cervix stenosis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Transaminases increased | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Epilepsy | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis pseudo relapse | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar artery dissection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo CNS origin | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Keratoconus | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder hypertrophy | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture pain | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 2 / 49 (4.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| COVID-19 | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometritis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serratia infection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Haemochromatosis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Placebo Then Evobrutinib 25 mg QD |
|---|---------------------------------|---------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 42 (19.05%) | 12 / 39 (30.77%) | 0 / 49 (0.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilloma | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cervix stenosis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mood disorder due to a general medical condition | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Head injury | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis pseudo relapse | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebrobasilar artery dissection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Keratoconus | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Bladder hypertrophy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 39 (5.13%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Appendicitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serratia infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Haemochromatosis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Tecfidera (Period 1 and Period 2) | Placebo + Evobrutinib 25 mg QD (Period 3) | |
|---|-----------------------------------|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 54 (3.70%) | 7 / 39 (17.95%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papilloma | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Pregnancy | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Heavy menstrual bleeding | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cervix stenosis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |

| | | | |
|--|----------------|----------------|--|
| Confusional state | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple sclerosis pseudo relapse | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar artery dissection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Keratoconus | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Hepatitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Bladder hypertrophy | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture pain | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Lyme disease | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervicitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometritis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Serratia infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Haemochromatosis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 25 mg QD (Period 1 and Period 2) | Placebo | Evobrutinib 75 mg BID (Period 1 and Period 2) |
|---|--|------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 52 (36.54%) | 14 / 54 (25.93%) | 20 / 54 (37.04%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaccination site pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 54 (0.00%) | 0 / 54 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Investigations | | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 3 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 54 (1.85%) 1 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 1 / 54 (1.85%) 1 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 3 / 54 (5.56%) 3 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 54 (1.85%) 1 | 4 / 54 (7.41%) 4 |
| Lipase increased subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | 2 / 54 (3.70%) 2 | 5 / 54 (9.26%) 5 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 3 / 54 (5.56%) 3 | 5 / 54 (9.26%) 5 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 3 / 54 (5.56%) 3 | 0 / 54 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Immunisation reaction subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 2 / 54 (3.70%) 2 | 1 / 54 (1.85%) 1 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Muscle spasticity subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 1 / 54 (1.85%) 1 | 0 / 54 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | 0 / 54 (0.00%) 0 | 1 / 54 (1.85%) 1 |

| | | | |
|---|----------------------|---------------------|----------------------|
| Vomiting subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | 1 / 54 (1.85%) 1 | 0 / 54 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 9 / 52 (17.31%) 9 | 5 / 54 (9.26%) 5 | 7 / 54 (12.96%) 7 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 54 (0.00%) 0 | 1 / 54 (1.85%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | 3 / 54 (5.56%) 3 | 0 / 54 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Laryngitis subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| COVID-19 subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |
| Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | 0 / 54 (0.00%) 0 | 0 / 54 (0.00%) 0 |

| Non-serious adverse events | Evobrutinib 75 mg QD (Period 1 and Period 2) | Evobrutinib 75 mg BID (Period 3) | Tecfidera (period 3) |
|--|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 19 / 53 (35.85%) | 31 / 44 (70.45%) | 26 / 49 (53.06%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Uterine leiomyoma subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 1 / 49 (2.04%) 1 |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 2 / 44 (4.55%) 2 | 0 / 49 (0.00%) 0 2 / 49 (4.08%) 2 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Vaccination site pain | 0 / 53 (0.00%) 0 0 | 1 / 44 (2.27%) 1 | 0 / 49 (0.00%) 0 |

| | | | |
|---|---|---|---|
| subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 1 / 49 (2.04%) 1 |
| Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 2 / 44 (4.55%) 2 | 1 / 49 (2.04%) 1 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 1 / 44 (2.27%) 1 | 2 / 49 (4.08%) 2 0 / 49 (0.00%) 0 |
| Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Lipase increased | 1 / 53 (1.89%) 1 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 3 / 53 (5.66%) 3 2 / 53 (3.77%) 2 | 0 / 44 (0.00%) 0 0 / 44 (0.00%) 0 1 / 44 (2.27%) 1 3 / 44 (6.82%) 3 0 / 44 (0.00%) 0 | 3 / 49 (6.12%) 3 0 / 49 (0.00%) 0 2 / 49 (4.08%) 2 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 53 (9.43%) | 8 / 44 (18.18%) | 5 / 49 (10.20%) |
| occurrences (all) | 5 | 8 | 5 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 0 / 44 (0.00%) | 5 / 49 (10.20%) |
| occurrences (all) | 6 | 0 | 5 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 1 / 49 (2.04%) |
| occurrences (all) | 0 | 1 | 1 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 4 / 49 (8.16%) |
| occurrences (all) | 0 | 0 | 4 |
| Injury, poisoning and procedural complications | | | |
| Immunisation reaction | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 3 / 49 (6.12%) |
| occurrences (all) | 0 | 1 | 3 |
| Fall | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 4 / 44 (9.09%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 6 / 44 (13.64%) | 4 / 49 (8.16%) |
| occurrences (all) | 2 | 6 | 4 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 2 / 44 (4.55%) | 1 / 49 (2.04%) |
| occurrences (all) | 0 | 2 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 1 / 49 (2.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasticity | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Blood and lymphatic system disorders Microcytic anaemia subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 1 / 49 (2.04%) 1 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 3 / 49 (6.12%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 3 / 49 (6.12%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 3 / 49 (6.12%) 3 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 44 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 2 / 44 (4.55%) 2 | 2 / 49 (4.08%) 2 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 1 / 44 (2.27%) 1 | 3 / 49 (6.12%) 3 |
| Back pain | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 3 / 44 (6.82%) 3 | 0 / 49 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 9 / 44 (20.45%) | 4 / 49 (8.16%) |
| occurrences (all) | 3 | 9 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 4 / 44 (9.09%) | 3 / 49 (6.12%) |
| occurrences (all) | 1 | 4 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 5 / 44 (11.36%) | 3 / 49 (6.12%) |
| occurrences (all) | 1 | 5 | 3 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 44 (2.27%) | 1 / 49 (2.04%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 2 / 44 (4.55%) | 2 / 49 (4.08%) |
| occurrences (all) | 0 | 2 | 2 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 6 / 44 (13.64%) | 7 / 49 (14.29%) |
| occurrences (all) | 0 | 6 | 7 |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 44 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------------|------------------------------------|------------------------------------|---|
| Non-serious adverse events | Evobrutinib 75 mg QD (Period 3) | Evobrutinib 25 mg QD (Period 3) | Placebo Then Evobrutinib 25 mg QD |
|-----------------------------------|------------------------------------|------------------------------------|---|

| | | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 34 / 42 (80.95%) | 26 / 39 (66.67%) | 9 / 49 (18.37%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Uterine leiomyoma subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 39 (5.13%) 2 | 0 / 49 (0.00%) 0 |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 2 / 42 (4.76%) 2 | 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Vaccination site pain subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 2 / 42 (4.76%) 2 | 2 / 39 (5.13%) 2 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 1 / 39 (2.56%) 1 | 0 / 49 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 3 / 42 (7.14%) 3 | 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Investigations | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 39 (5.13%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 6 / 39 (15.38%) | 3 / 49 (6.12%) |
| occurrences (all) | 6 | 6 | 3 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 39 (2.56%) | 1 / 49 (2.04%) |
| occurrences (all) | 0 | 1 | 1 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 39 (5.13%) | 3 / 49 (6.12%) |
| occurrences (all) | 1 | 2 | 3 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Immunisation reaction | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 39 (5.13%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Fall | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 39 (2.56%) 1 | 0 / 49 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 2 / 39 (5.13%) | 0 / 49 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 39 (7.69%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 39 (5.13%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Muscle spasticity | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 4 / 39 (10.26%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 39 (2.56%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 39 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------------|----------------------|---------------------|
| Erythema subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 2 / 39 (5.13%) 2 | 0 / 49 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 39 (7.69%) 3 | 0 / 49 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 4 / 39 (10.26%) 4 | 0 / 49 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 9 / 42 (21.43%) 9 | 5 / 39 (12.82%) 5 | 0 / 49 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 42 (19.05%) 8 | 7 / 39 (17.95%) 7 | 1 / 49 (2.04%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 6 | 2 / 39 (5.13%) 2 | 0 / 49 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 7 | 5 / 39 (12.82%) 5 | 0 / 49 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 39 (0.00%) 0 | 3 / 49 (6.12%) 3 |
| Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Laryngitis subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 39 (5.13%) 2 | 0 / 49 (0.00%) 0 |
| Respiratory tract infection | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 4 | 1 / 39 (2.56%) 1 | 0 / 49 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 1 / 39 (2.56%) 1 | 0 / 49 (0.00%) 0 |
| COVID-19 subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 8 / 39 (20.51%) 8 | 0 / 49 (0.00%) 0 |
| Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 1 / 39 (2.56%) 1 | 0 / 49 (0.00%) 0 |

| Non-serious adverse events | Tecfidera (Period 1 and Period 2) | Placebo + Evobrutinib 25 mg QD (Period 3) | |
|---|--------------------------------------|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 30 / 54 (55.56%) | 30 / 39 (76.92%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Uterine leiomyoma subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 0 / 39 (0.00%) 0 | |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) | 12 / 54 (22.22%) 12 | 0 / 39 (0.00%) 0 | |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 | |
| Vaccination site pain subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|--|---|--|
| Menstruation irregular subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 1 / 39 (2.56%) 1 | |
| Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Lipase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased | 1 / 54 (1.85%) 1 3 / 54 (5.56%) 3 5 / 54 (9.26%) 5 1 / 54 (1.85%) 1 2 / 54 (3.70%) 2 3 / 54 (5.56%) 3 | 2 / 39 (5.13%) 2 0 / 39 (0.00%) 0 1 / 39 (2.56%) 1 2 / 39 (5.13%) 2 0 / 39 (0.00%) 0 5 / 39 (12.82%) 5 | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | 1 / 39 (2.56%) 1 | |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 | |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 0 / 39 (0.00%) 0 | |
| Injury, poisoning and procedural complications Immunisation reaction subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Fall subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 3 / 39 (7.69%) 3 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 | |
| Muscle spasticity subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 0 / 39 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|--|--|
| Microcytic anaemia subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 0 / 39 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 39 (5.13%) 2 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 3 / 54 (5.56%) 3 0 / 54 (0.00%) 0 | 1 / 39 (2.56%) 1 3 / 39 (7.69%) 3 1 / 39 (2.56%) 1 | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 7 / 54 (12.96%) 7 0 / 54 (0.00%) 0 | 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 0 / 54 (0.00%) 0 0 / 54 (0.00%) 0 | 5 / 39 (12.82%) 5 2 / 39 (5.13%) 2 1 / 39 (2.56%) 1 | |
| Infections and infestations | | | |

| | | | |
|------------------------------------|----------------|-----------------|--|
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 54 (3.70%) | 7 / 39 (17.95%) | |
| occurrences (all) | 2 | 7 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | 5 / 39 (12.82%) | |
| occurrences (all) | 3 | 5 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 7 / 39 (17.95%) | |
| occurrences (all) | 0 | 7 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 2 / 39 (5.13%) | |
| occurrences (all) | 0 | 2 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 0 / 39 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 1 / 39 (2.56%) | |
| occurrences (all) | 0 | 1 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 6 / 39 (15.38%) | |
| occurrences (all) | 0 | 6 | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 54 (0.00%) | 2 / 39 (5.13%) | |
| occurrences (all) | 0 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 28 November 2017 | <ul style="list-style-type: none">• Addition of 2-week safety visits for chemistry monitoring (including ALT, AST, alkaline phosphatase, GGT, and bilirubin) until the IDMC determines the optimum monitoring interval for participant randomized to the M2951/placebo arm;• Addition of a comprehensive hepatic panel for participants randomized to the M2951/placebo arm for whom withdrawal criteria are met or who permanently discontinue dosing because of elevated transaminases;• Addition of blood tests (ESR, hsCRP, and fibrinogen) for all participants at any 1 point during the trial;• Addition of Open-label extension period, with modifications to planned trial period, addition of objective and endpoints, addition of statistical analyses and analysis set, addition of informed consent prior to participation, and clarification that there will be a second clinical trial report;• Addition of pharmacokinetic endpoints and statistical analyses• Clarification of pharmacodynamics endpoints• Clarification that separate informed consent will be collected for the MRI dummy run;• Clarification that soluble factors may be measured from pharmacokinetic blood samples if there is sufficient volume;• Clarification that blood pressure will be collected in a semisupine position; |
| 29 May 2018 | <ul style="list-style-type: none">• Update exploratory endpoints;• Remove Futility analyses (also referred to as interim analyses)• Remove 2-week additional safety visits after Week 16 and update to a monthly (4-week) schedule;• Clarify that phone calls for confirmation of home pregnancy testing is required only if urine pregnancy tests are completed at home;• Include monthly urine pregnancy tests for all sites in all countries during the main study and OLE period;• Clarify the schedule of collection of additional PK samples; |
| 08 August 2018 | To include recommendations from the Czech Republic Regulatory Authority on reinitiating IMP following increase in AST, ALT, or bilirubin to Grade 2. |
| 21 November 2018 | <ul style="list-style-type: none">• Based on the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily.• Increased liver monitoring was added following an urgent safety measure.• Provide direction to sites to consult with Medical Monitor regarding potential withdrawal, continued participation in study, additional monitoring, and retesting.• Updated liver enzyme stopping criteria to ensure the safety of the patients within the study. |
| 08 November 2019 | To extend the optional open-label extension period of the study by 5 years (60 months), to allow patients continued access to study treatment and long-term characterization of the study drug in patients with relapsing multiple sclerosis. The Sponsor evaluated the duration of the extension on an annual basis. |
| 02 December 2022 | To include an opportunity for participants who completed their treatment under the current protocol to transition into the long-term follow-up study under a new protocol allowing continued access to study treatment. Additionally, the prohibited medicines section was revised to include an additional concomitant therapeutic option, as well as other prohibited medications. |

| | |
|--------------|---|
| 06 July 2023 | <ul style="list-style-type: none"> • To reflect the recent update to the risk profile of evobrutinib (i.e., important identified risk of drug-induced liver injury) by adapting monitoring and discontinuation criteria, as well as language on tolerability and safety of evobrutinib across the protocol. • To extend the OLE period by up to one additional year to allow an opportunity for participants to transition into the long-term follow-up study under a new protocol. |
|--------------|---|

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.

| |
|--|
| Reported p values are not adjusted for multiple testing. |
|--|

Notes: