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 tecfidera 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 (± 5.436)	4.06 (± 8.024)	1.69 (± 4.693)	1.15 (± 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 (± 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:

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.

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>=2ULN/++ 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>=2ULN/++ 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 (± 0.589)			
Ig M, Week 4: n = 54, 51, 53, 54, 54	1.23 (± 0.603)			
Ig M, Week 16: n = 53, 50, 49, 53, 52	1.28 (± 0.678)			
Ig M, Week 24: n = 49, 47, 49, 48, 52	1.29 (± 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 (± 0.695)	2.13 (± 0.807)	2.18 (± 0.790)	2.23 (± 0.838)
IgG	9.60 (± 1.968)	9.53 (± 2.070)	9.74 (± 1.902)	9.38 (± 2.189)
IgM	1.28 (± 0.635)	1.08 (± 0.557)	1.13 (± 0.639)	1.10 (± 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 (± 109.8)	203 (± 111.9)	222 (± 148.8)	187 (± 87.1)
Week 52: n = 6, 7, 8, 2	9999 (± 9999)	227 (± 93.7)	206 (± 140.3)	154 (± 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 (± 94.5)	9 (± 112.2)	31 (± 114.2)	50 (± 86.7)
Week 24: n = 49, 44, 49, 47, 52	7 (± 135.8)	13 (± 98.2)	-15 (± 128.5)	-9 (± 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 (± 111.0)			
Week 24: n = 49, 44, 49, 47, 52	-26 (± 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 (± 105.7)	-5 (± 116.1)	-30 (± 148.2)	-32 (± 97.9)
Week 52: n = 6, 7, 8, 2	9999 (± 9999)	-28 (± 209.8)	-25 (± 65.5)	-81 (± 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 (± 4.371)	3.44 (± 6.846)	1.20 (± 3.499)	0.98 (± 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 (± 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 (± 1.439)	1.31 (± 3.130)	0.42 (± 1.173)	0.34 (± 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 (± 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 (± 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 (± 0.2220)	0.057 (± 0.3479)	-0.111 (± 0.5416)	-0.051 (± 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 (± 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 (± 0.260)	-0.10 (± 0.351)	-0.01 (± 0.619)	0.00 (± 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 (± 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 (± 4.346)	5.86 (± 11.330)	3.84 (± 10.083)	1.60 (± 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 (± 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 (± 1.360)	0.67 (± 1.865)	0.35 (± 1.083)	-0.03 (± 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 (± 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 (± 0.4626)	0.088 (± 0.4006)	0.045 (± 0.2285)	0.024 (± 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 (± 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. esults 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

	Changes From Baseline in Laboratory Parameters

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

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

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

Laryngitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	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	0 / 53 (0.00%)	0 / 44 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 53 (0.00%)	0 / 44 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 53 (0.00%)	2 / 44 (4.55%)	2 / 49 (4.08%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 44 (2.27%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Vaccination site pain			

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

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

subjects affected / exposed	0 / 53 (0.00%)	3 / 44 (6.82%)	0 / 49 (0.00%)
occurrences (all)	0	3	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)	0 / 42 (0.00%) 0	0 / 39 (0.00%) 0	0 / 49 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	0 / 39 (0.00%) 0	0 / 49 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	2 / 39 (5.13%) 2	0 / 49 (0.00%) 0
Vaccination site pain subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	0 / 39 (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)	2 / 42 (4.76%) 2	0 / 39 (0.00%) 0	0 / 49 (0.00%) 0
Depressed mood subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	0 / 39 (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	0 / 42 (0.00%)	1 / 39 (2.56%)	0 / 49 (0.00%)
occurrences (all)	0	1	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	0 / 42 (0.00%)	0 / 39 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 42 (7.14%)	2 / 39 (5.13%)	0 / 49 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 42 (2.38%)	3 / 39 (7.69%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Pain in extremity			
subjects affected / exposed	3 / 42 (7.14%)	4 / 39 (10.26%)	0 / 49 (0.00%)
occurrences (all)	3	4	0
Back pain			
subjects affected / exposed	9 / 42 (21.43%)	5 / 39 (12.82%)	0 / 49 (0.00%)
occurrences (all)	9	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 42 (19.05%)	7 / 39 (17.95%)	1 / 49 (2.04%)
occurrences (all)	8	7	1
Upper respiratory tract infection			
subjects affected / exposed	6 / 42 (14.29%)	2 / 39 (5.13%)	0 / 49 (0.00%)
occurrences (all)	6	2	0
Urinary tract infection			
subjects affected / exposed	7 / 42 (16.67%)	5 / 39 (12.82%)	0 / 49 (0.00%)
occurrences (all)	7	5	0
Cystitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 39 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	3
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 39 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			

subjects affected / exposed	4 / 42 (9.52%)	1 / 39 (2.56%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Pharyngitis			
subjects affected / exposed	3 / 42 (7.14%)	1 / 39 (2.56%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
COVID-19			
subjects affected / exposed	3 / 42 (7.14%)	8 / 39 (20.51%)	0 / 49 (0.00%)
occurrences (all)	3	8	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 39 (2.56%)	0 / 49 (0.00%)
occurrences (all)	1	1	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	0 / 54 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	12 / 54 (22.22%)	0 / 39 (0.00%)	
occurrences (all)	12	0	
Hypertension			
subjects affected / exposed	0 / 54 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vaccination site pain			
subjects affected / exposed	0 / 54 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			

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

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