Clinical trial results:
A Randomized, Double - Blind, Placebo-Controlled Study to Investigate the Efficacy of Fenebrutinib in Relapsing Multiple Sclerosis

Summary

EudraCT number	2021-003772-14
Trial protocol	CZ SK HR
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	30 May 2024
First version publication date	12 April 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GN43271

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05119569
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse, 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	29 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The study aims to evaluate the efficacy of fenebrutinib compared with placebo on the total number of new gadolinium (Gd) - enhancing T1 magnetic resonance imaging (MRI) lesions in participants with relapsing multiple sclerosis (RMS).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2022
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	Bosnia and Herzegovina: 12
Country: Number of subjects enrolled	Czechia: 46
Country: Number of subjects enrolled	Croatia: 19
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	109
EEA total number of subjects	67

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	109
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled across 18 sites in 6 countries (Bosnia and Herzegovina, Croatia, Czech Republic, Serbia, Slovakia and the United States). This study is still ongoing.

Pre-assignment

Screening details:

This study consists of two parts: Double-blind treatment (DBT) phase and an optional Open-label extension (OLE) phase. A total of 129 participants were screened, of which 109 were randomized into the fenebrutinib arm and placebo arm in a 2:1 ratio.

Period 1

Period 1 title	Double Blind Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DBT Phase: Fenebrutinib

Arm description:

Participants received fenebrutinib, 200 milligrams (mg), orally, twice daily (BID) for 12 weeks during the DBT phase.

Arm type	Experimental
Investigational medicinal product name	Fenebrutinib
Investigational medicinal product code	RO7010939
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered two 100 mg tablets, orally, BID for a total dose of 400 mg of fenebrutinib every day.

Arm title	DBT Phase: Placebo

Arm description:

Participants received fenebrutinib matching placebo, orally, BID, for 12 weeks during the DBT phase.

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:

Participants were administered two tablets of placebo orally, BID.

Number of subjects in period 1	DBT Phase: Fenebrutinib	DBT Phase: Placebo
Started	73	36
Completed	65	34
Not completed	8	2
Consent withdrawn by subject	2	2
Adverse event, non-fatal	6	-

Period 2

Period 2 title	Open Label Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	OLE Phase: Fenebrutinib from Fenebrutinib

Arm description:

Participants who received fenebrutinib in the DBT phase were given an option to receive fenebrutinib, 200 mg, orally, BID up to a maximum of 192 weeks in the OLE phase.

Arm type	Experimental
Investigational medicinal product name	Fenebrutinib
Investigational medicinal product code	RO7010939
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered two 100 mg tablets orally BID for a total dose of 400 mg of fenebrutinib every day.

Arm title	OLE Phase: Fenebrutinib from Placebo

Arm description:

Participants who received fenebrutinib matching placebo in the DBT phase were given an option to receive fenebrutinib, 200 mg, orally, BID up to a maximum of 192 weeks in the OLE phase.

Arm type	Experimental
Investigational medicinal product name	Fenebrutinib
Investigational medicinal product code	RO7010939
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered two 100 mg tablets, orally, BID for a total dose of 400 mg of fenbrutinib everyday.

Number of subjects in period 2	OLE Phase: Fenebrutinib from Fenebrutinib	OLE Phase: Fenebrutinib from Placebo
Started	65	34
Completed	0	0
Not completed	65	34
Ongoing in the study	65	34

Baseline characteristics

Reporting groups	
Reporting group title	DBT Phase: Fenebrutinib
Reporting group description:	
Participants received fenebrutinib, 200 milligrams (mg), orally, twice daily (BID) for 12 weeks during the DBT phase.	
Reporting group title	DBT Phase: Placebo
Reporting group description:	
Participants received fenebrutinib matching placebo, orally, BID, for 12 weeks during the DBT phase.	

Reporting group values	DBT Phase: Fenebrutinib	DBT Phase: Placebo	Total
Number of subjects	73	36	109
Age categorical Units:			
Age Continuous Units: years			
arithmetic mean	38.6	39.8	
standard deviation	± 8.5	± 7.7	-
Sex: Female, Male Units: participants			
Female	52	26	78
Male	21	10	31
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	72	36	108
Unknown or Not Reported	1	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	73	36	109
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	DBT Phase: Fenebrutinib
Reporting group description:	
Participants received fenebrutinib, 200 milligrams (mg), orally, twice daily (BID) for 12 weeks during the DBT phase.	
Reporting group title	DBT Phase: Placebo
Reporting group description:	
Participants received fenebrutinib matching placebo, orally, BID, for 12 weeks during the DBT phase.	
Reporting group title	OLE Phase: Fenebrutinib from Fenebrutinib
Reporting group description:	
Participants who received fenebrutinib in the DBT phase were given an option to receive fenebrutinib, 200 mg, orally, BID up to a maximum of 192 weeks in the OLE phase.	
Reporting group title	OLE Phase: Fenebrutinib from Placebo
Reporting group description:	
Participants who received fenebrutinib matching placebo in the DBT phase were given an option to receive fenebrutinib, 200 mg, orally, BID up to a maximum of 192 weeks in the OLE phase.	

Primary: DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scans of the Brain Over 12 Weeks

End point title	DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scans of the Brain Over 12 Weeks
End point description:	
Radiologic evaluation for Gd enhancing T1 lesion rate was performed using a standardized MRI protocol at screening, and at Weeks 4, 8, and 12. All MRI scans were read by a centralized reading center for efficacy endpoints. The total number of new Gd-enhancing T1 lesions were calculated as the sum of the individual number of new lesions observed at Weeks 4, 8 and 12. The lesion rate (new lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an "offset" variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.	
End point type	Primary
End point timeframe:	
MRI scans performed at Weeks 4, 8 and 12	

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.077 (0.043 to 0.135)	0.245 (0.144 to 0.418)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0022
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.313
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.658

Secondary: DBT Phase: Proportion of Participants Free From any New Gd - Enhancing T1 Lesions and New or Enlarging T2 - Weighted Lesions Observed on MRI Scans of the Brain Over 12 Weeks

End point title	DBT Phase: Proportion of Participants Free From any New Gd - Enhancing T1 Lesions and New or Enlarging T2 - Weighted Lesions Observed on MRI Scans of the Brain Over 12 Weeks

End point description:

Radiologic evaluation for new Gd - enhancing T1 lesions and new or enlarging T2 - weighted lesions were performed using a standardized MRI protocol at screening, and at Weeks 4, 8, and 12. All MRI scans were read by a centralized reading center for efficacy endpoints. The total number of new Gd-enhancing T1 lesions and new or enlarging T2 - weighted lesions were calculated as the sum of the individual number of lesions observed at Weeks 4, 8 and 12. Analysis was performed using a logistic regression model performed on the status of both new T1 Gd+ lesion and new or enlarging T2-weighted lesions post-baseline (present or not) adjusted for the stratification factor(s) presence or absence of T1 Gd+ lesions on the screening MRI. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Secondary

End point timeframe:

MRI scans performed at Weeks 4, 8 and 12

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: proportion of participants				
number (not applicable)	72.9	50.0		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0117
Method	Logistic Regression Model
Parameter estimate	Odds ratio (OR)
Point estimate	4.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.317
upper limit	13.078

Secondary: DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scans of the Brain Over 12 Weeks

End point title	DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scans of the Brain Over 12 Weeks

End point description:

Radiologic evaluation for new or enlarging T2-weighted lesion rate was performed using a standardized MRI protocol at screening, and at Weeks 4, 8, and 12. All MRI scans were read by a centralized reading center for efficacy endpoints. Total number of new or enlarging T2-weighted lesions were calculated as the sum of the individual number of new or enlarging lesions at Weeks 4, 8, 12. The lesion rate (new/enlarging lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an "offset" variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Secondary

End point timeframe:

MRI scans performed at Weeks 4, 8 and 12

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.168 (0.102 to 0.277)	0.634 (0.375 to 1.071)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0004
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.265
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	0.55

Secondary: DBT Phase: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	DBT Phase: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability or incapacity, is a congenital anomaly or birth defect. Safety population included all participants who received any study drug.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	36		
Units: participants				
AEs	28	12		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Fenebrutinib

End point title	Plasma Concentrations of Fenebrutinib

End point description:

Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion

Date.

End point type	Secondary

End point timeframe:

Up to Week 192

End point values	OLE Phase: Fenebrutinib from Fenebrutinib	OLE Phase: Fenebrutinib from Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[1] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[2] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Post-baseline Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants With Post-baseline Suicidal Ideation or Suicidal Behavior as Measured Using Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS=assessment tool used to assess lifetime suicidality of a participant (at baseline) as well as any new instances of suicidality (C-SSRS since last visit). Structured interview prompts recollection of suicidal ideation, including intensity of ideation, behavior, & attempts with actual/potential lethality. Categories have binary responses (yes/no) & include Wish to be Dead; Non-specific Active Suicidal Thoughts; Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act; Active Suicidal Ideation with Some Intent to Act, without Specific Plan; Active Suicidal Ideation with Specific Plan and Intent, Preparatory Acts and Behavior; Aborted Attempt; Interrupted Attempt; Actual Attempt (non-fatal); Completed Suicide. Score of 0 is assigned if no suicide risk is present. Score of 1 or higher= suicidal ideation or behavior. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to Week 192

End point values	OLE Phase: Fenebrutinib from Fenebrutinib	OLE Phase: Fenebrutinib from Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: participants				
number (not applicable)				

Notes:

[3] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[4] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: OLE Phase: Number of Participants with AEs and SAEs

End point title	OLE Phase: Number of Participants with AEs and SAEs

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability or incapacity, is a congenital anomaly or birth defect. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

OLE Baseline (DBT Week 12) up to Week 192

End point values	OLE Phase: Fenebrutinib from Fenebrutinib	OLE Phase: Fenebrutinib from Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: participants				

Notes:

[5] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[6] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 4

End point title	DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 4

End point description:

Radiologic evaluation for Gd enhancing T1 lesion rate was performed using a standardized MRI protocol at screening, and at Week 4. All MRI scans were read by a centralized reading center for efficacy endpoints. The lesion rate (new lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate ‘presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 4

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.210 (0.115 to 0.382)	0.269 (0.128 to 0.565)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5889
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.316
upper limit	1.922

Other pre-specified: DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 8

End point title	DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 8

End point description:

Radiologic evaluation for Gd enhancing T1 lesion rate was performed using a standardized MRI protocol at screening, and at Week 8. All MRI scans were read by a centralized reading center for efficacy endpoints. The lesion rate (new lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate ‘presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 8

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	34		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.025 (0.006 to 0.101)	0.325 (0.150 to 0.702)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.355

Other pre-specified: DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 12

End point title	DBT Phase: New Gd - Enhancing T1 Lesion Rate Observed on MRI Scan of the Brain at Week 12

End point description:

Radiologic evaluation for Gd enhancing T1 lesion rate was performed using a standardized MRI protocol at screening, and at Week 12. All MRI scans were read by a centralized reading center for efficacy endpoints. The lesion rate (new lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 12

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.007 (0.001 to 0.052)	0.066 (0.013 to 0.324)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.481

Other pre-specified: DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scans of the Brain at Week 4

End point title	DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scans of the Brain at Week 4

End point description:

Radiologic evaluation for new or enlarging T2-weighted lesion rate was performed using a standardized MRI protocol at screening, and at Week 4. All MRI scans were read by a centralized reading center for efficacy endpoints. The lesion rate (new/enlarging lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 4

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.456 (0.274 to 0.757)	0.891 (0.490 to 1.620)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0958
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.512
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.233
upper limit	1.126

Other pre-specified: DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scan of the Brain at Week 8

End point title	DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scan of the Brain at Week 8

End point description:

Radiologic evaluation for new or enlarging T2-weighted lesion rate was performed using a standardized MRI protocol at screening, and at Week 8. All MRI scans were read by a centralized reading center for efficacy endpoints. The lesion rate (new/enlarging lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 8

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	34		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.058 (0.023 to 0.144)	0.549 (0.314 to 0.958)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.283

Other pre-specified: DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scan of the Brain at Week 12

End point title	DBT Phase: New or Enlarging T2-Weighted Lesion Rate Observed on MRI Scan of the Brain at Week 12

End point description:

Radiologic evaluation for new or enlarging T2-weighted lesion rate was performed using a standardized MRI protocol at screening, and at Week 12. All MRI scans were read by a centralized reading center for efficacy endpoints.The lesion rate (new/enlarging lesions per scan) was estimated from a negative binomial regression model for the total number of events and was adjusted for the covariate 'presence or absence of T1 Gd+ lesions on the screening MRI'. Log-transformed number of scans were included in the negative binomial model as an “offset” variable to account for different number of scans. All Randomized Participants set included all randomized participants grouped by treatment as assigned by randomization. Overall number analyzed is the number of participants with evaluable post-baseline MRI scans.

End point type	Other pre-specified

End point timeframe:

MRI scan performed at Week 12

End point values	DBT Phase: Fenebrutinib	DBT Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: adjusted number of new lesions per scan				
number (confidence interval 95%)	0.015 (0.003 to 0.068)	0.282 (0.135 to 0.586)		

Statistical analyses

Statistical analysis title	Fenebrutinib vs Placebo
Comparison groups	DBT Phase: Fenebrutinib v DBT Phase: Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.233

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 12

Adverse event reporting additional description:

Safety population included all participants who received any study drug. Data collected up to the primary completion date is reported here. Adverse events section will be updated one year after the study completion date.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	DBT Phase: Placebo

Reporting group description:

Participants received fenebrutinib matching placebo, orally, BID, for 12 weeks during the DBT phase.

Reporting group title	DBT Phase: Fenebrutinib

Reporting group description:

Participants received fenebrutinib, 200 mg, orally, BID for 12 weeks during the DBT phase.

Serious adverse events	DBT Phase: Placebo	DBT Phase: Fenebrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 73 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	DBT Phase: Placebo	DBT Phase: Fenebrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 36 (11.11%)	8 / 73 (10.96%)	
Investigations			
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 36 (0.00%)	4 / 73 (5.48%)	
occurrences (all)	0	4	
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 73 (0.00%) 0	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 36 (5.56%) 2	 4 / 73 (5.48%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2021	1. Changes were made to clarify reporting procedures for increase in transaminase. 2. The pharmacokinetic and biomarker samples and collection timepoints were updated. 3. COVID-19 vaccines administration details were added. 4. The exclusion criterion regarding white blood cell count was updated. 5. The eligibility requirement on disease modifying therapy washout periods prior to study entry was amended to unify across different drug labels/countries. 6. Platelet count ranges for adverse event management of thrombocytopenia were updated.
15 December 2022	1. Per recommendations from the independent Data Monitoring Committee (iDMC), additional monitoring visits for liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], total and direct bilirubin) were added to the Schedule of Activities. 2. Guidance was provided for management of participants with abnormal liver function tests. 3. The duration of the optional OLE phase was extended from 96 weeks up to a maximum of 192 weeks. 4. Language was updated for the Week 12 lumbar puncture, addition of primary and secondary efficacy estimands, inclusion of biotin as a prohibited concomitant medication, clarifications to exclusion criteria, and updates to discontinuation criteria in relation to thrombocytopenia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported