Clinical trial results:
A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety

Summary

EudraCT number	2018-004701-11
Trial protocol	BG
Global end of trial date	16 April 2020

Results information

Result version number	v1
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	MS200527_0073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04032158
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 Center, Merck Healthcare KGaA, Darmstadt Germany, +49 6151 72 5200, service@merckgroup.com
Scientific contact	Communication Center, 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	16 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the the efficacy and safety of evobrutinib administered orally twice daily versus Interferon-beta-1a (Avonex®), once a week intramuscularly in subjects with Relapsing Multiple Sclerosis (RMS).

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	26 August 2019
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	United States: 3
Worldwide total number of subjects	3
EEA total number of subjects	0

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was to be conducted in 2 periods; double blind period and open label extension period. However, due to early termination of the study, sponsor decided not to conduct the open label extension period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Evobrutinib + Avonex® matched Placebo

Arm description:

Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Avonex® matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subject received IM injection of placebo matched to Avonex® once a week

Investigational medicinal product name	Evobrutinib
Investigational medicinal product code	M2951
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received active evobrutinib BID

Arm title	Avonex® + Evobrutinib matched Placebo

Arm description:

Subjects received IM injection of active Avonex® once a week along with concomitant placebo matched to evobrutinib BID. Treatment period was planned to be of 96 weeks.

Arm type	Active comparator
Investigational medicinal product name	Avonex®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received IM injection of active Avonex® once a week.

Investigational medicinal product name	Evobrutinib matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subject received placebo matched to evobrutinib BID.

Number of subjects in period 1	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo
Started	2	1
Completed	0	0
Not completed	2	1
Study Termination	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Evobrutinib + Avonex® matched Placebo
Reporting group description:	
Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.	
Reporting group title	Avonex® + Evobrutinib matched Placebo
Reporting group description:	
Subjects received IM injection of active Avonex® once a week along with concomitant placebo matched to evobrutinib BID. Treatment period was planned to be of 96 weeks.	

Reporting group values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo	Total
Number of subjects	2	1	3
Age Categorical Units: Years			
<=18 years	0	0	0
Between 18 and 65 years	2	1	3
>=65 years	0	0	0
Sex: Female, Male Units: Subjects			
Female	1	1	2
Male	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	1	1
White	2	0	2
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Evobrutinib + Avonex® matched Placebo

Reporting group description:

Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.

Reporting group title	Avonex® + Evobrutinib matched Placebo

Reporting group description:

Subjects received IM injection of active Avonex® once a week along with concomitant placebo matched to evobrutinib BID. Treatment period was planned to be of 96 weeks.

Primary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR)[1]

End point description:

The annualized relapse rate at 96 weeks was to be calculated based on qualified relapses. A qualifying relapse is the occurrence of new or worsening neurological symptoms attributable to MS. The relapse should be accompanied by an increase of 0.5 points or more on Expanded Disability Status Scale (EDSS), or 2 points increase on one of the Functional System Scores (FSS), or 1 point increase on at least two of the FSS. The increase in FSS scores must be related to the neurological symptoms which were reported as new or worsening. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Primary

End point timeframe:

At Week 96

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for efficacy analysis was not collected and evaluated due to early termination of study.

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: per year				

Notes:

[2] - As per Statistical Analysis Plan, efficacy data were not reported.

[3] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of 12-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point title	Time to First Occurrence of 12-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point description:

EDSS is an ordinal scale in half-point increments that measures disability in subjects with MS. EDSS progression is defined as an increase of 1 point or more from Baseline EDSS score when the Baseline score is 5.0 or less, and an increase of 0.5 points or more when the Baseline score is 5.5 or greater. Time to first occurrence of 12-week confirmed EDSS progression is defined as the time from randomization to the first EDSS progression event that was confirmed at a regularly scheduled visit at least 12 weeks later. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline up to 96 weeks

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Weeks				
median (confidence interval 95%)	(to)	(to)		

Notes:

[4] - As per Statistical Analysis Plan, efficacy data were not reported.

[5] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of 24-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point title	Time to First Occurrence of 24-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point description:

EDSS is an ordinal scale in half-point increments that measures disability in subjects with MS. EDSS progression is defined as an increase of 1 point or more from Baseline EDSS score when the Baseline score is 5.0 or less, and an increase of 0.5 points or more when the Baseline score is 5.5 or greater. Time to first occurrence of 24-week confirmed EDSS progression is defined as the time from randomization to the first EDSS progression event that was confirmed at a regularly scheduled visit at least 24 weeks later. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline up to 96 weeks

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Weeks				
median (confidence interval 95%)	(to)	(to)		

Notes:

[6] - As per Statistical Analysis Plan, efficacy data were not reported.

[7] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Short Form Score at Week 96

End point title	Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Short Form Score at Week 96

End point description:

The PROMIS PF Short Form is specific to measuring the physical function domain of MS patients, with each item on the form scored on a T-score metric. Higher scores indicate higher PF. Change from baseline at Week 96 is the difference between the PROMIS PF scores at 96 weeks and at baseline. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: T-score				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - As per Statistical Analysis Plan, efficacy data were not reported.

[9] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) MS Fatigue Score at Week 96

End point title	Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) MS Fatigue Score at Week 96

End point description:

The PROMIS Fatigue Short Form is specific to measuring the fatigue domain of MS patients, with each item on the form scored on a T-score metric. Higher scores indicate higher fatigue. Change from baseline at Week 96 is the difference between the PROMIS Fatigue scores at 96 weeks and at baseline. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: T-score				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - As per Statistical Analysis Plan, efficacy data were not reported.

[11] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Gadolinium-Enhancing (Gd+) Time Constant 1 (T1) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point title	Total Number of Gadolinium-Enhancing (Gd+) Time Constant 1 (T1) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point description:

Total number of Gd+ T1 lesions was to be assessed using magnetic resonance imaging (MRI). Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

At Week 24, 48 and 96

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Lesion				
arithmetic mean (standard deviation)	()	()		

Notes:

[12] - As per Statistical Analysis Plan, efficacy data were not reported.

[13] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New or Enlarging Time Constant 2 (T2) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point title	Total Number of New or Enlarging Time Constant 2 (T2) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point description:

Total number of new or enlarging T2 lesions was to be assessed using magnetic resonance imaging (MRI). Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527-0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

At Week 24, 48 and 96

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Lesion				
arithmetic mean (standard deviation)	()	()		

Notes:

[14] - As per Statistical Analysis Plan, efficacy data were not reported.

[15] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs)

End point description:

AE is any untoward medical occurrence in subject administered a pharmaceutical product, regardless of causal relationship with treatment. Therefore, AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product. TEAE is an AE that started after study drug treatment or if the event was continuous from baseline & was serious, related to study drug, or resulted in death, discontinuation, interruption or reduction of study therapy. TEAEs includes both serious TEAEs & non-serious TEAEs. AESIs included liver AEs (possible drug-induced, non-infectious,

non-alcoholic and immune-mediated) infections (serious and opportunistic infection), lipase and amylase elevation, & seizure. Number of subjects with AESIs are reported.

End point type	Secondary

End point timeframe:

Baseline up to week 108

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Subjects				
Subjects with AESIs	0	0		
Subjects with TEAEs	2	1		
Subjects with Serious TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point description:

TEAE is an AE that started after study drug treatment; or if the event was continuous from baseline and was serious, related to IMP, or resulted in death, discontinuation, interruption or reduction of study therapy. Severity of TEAEs were graded using NCI-CTCAE v4.03 toxicity grades, as follows: Grade 1= Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. Number of subjects with TEAEs based on severity were reported. SAF analysis set included all subjects who were administered any dose of any study intervention. SAF analysis set included all subjects who were administered any dose of any study intervention

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Subjects				
Grade 1	2	0		

Grade 2	0	1		
Grade 3	0	0		
Grade 4	0	0		
Grade 5	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)

End point title	Vital Signs: Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)

End point description:

DBP and SBP were measured in semi-supine position after 5 minutes rest for the subjects at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Millimeters of mercury (mmHg)				
number (not applicable)				
Subject 1 - DBP: Day 1	0	82		
Subject 1 - DBP: Day 83	0	87		
Subject 1 - DBP: Day 125	0	80		
Subject 1 - DBP: Day 155	0	75		
Subject 1 - SBP: Day 1	0	112		
Subject 1 - SBP: Day 83	0	120		
Subject 1 - SBP: Day 125	0	118		
Subject 1 - SBP: Day 155	0	109		
Subject 2 - DBP: Day 1	84	0		
Subject 2 - DBP: Day 83	77	0		
Subject 2 - DBP: Day 125	84	0		
Subject 2 - DBP: Day 155	90	0		
Subject 2 - SBP: Day 1	124	0		
Subject 2 - SBP: Day 83	133	0		
Subject 2 - SBP: Day 125	138	0		
Subject 2 - SBP: Day 155	137	0		

Subject 3 - DBP: Day 1	65	0		
Subject 3 - DBP: Day 83	76	0		
Subject 3 - SBP: Day 1	101	0		
Subject 3 - SBP: Day 83	117	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Pulse Rate and Respiratory Rate

End point title	Vital Signs: Pulse Rate and Respiratory Rate

End point description:

Pulse rate and Respiration rate was measured in semi-supine position after 5 minutes rest for the subjects at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: breaths/minute				
number (not applicable)				
Subject 1 - Pulse rate: Day 1	0	71		
Subject 1 - Pulse rate: Day 83	0	69		
Subject 1 - Pulse rate: Day 125	0	72		
Subject 1 - Pulse rate: Day 155	0	75		
Subject 1 - Respiratory rate: Day 1	0	20		
Subject 1 - Respiratory rate: Day 83	0	18		
Subject 1 - Respiratory rate: Day 125	0	18		
Subject 1 - Respiratory rate: Day 155	0	20		
Subject 2 - Pulse rate: Day 1	71	0		
Subject 2 - Pulse rate: Day 83	66	0		
Subject 2 - Pulse rate: Day 125	82	0		
Subject 2 - Pulse rate: Day 155	82	0		
Subject 2 - Respiratory rate: Day 1	18	0		
Subject 2 - Respiratory rate: Day 83	20	0		
Subject 2 - Respiratory rate: Day 125	18	0		
Subject 2 - Respiratory rate: Day 155	20	0		
Subject 3 - Pulse rate: Day 1	76	0		
Subject 3 - Pulse rate: Day 83	75	0		

Subject 3 - Respiratory rate: Day 1	18	0		
Subject 3 - Respiratory rate: Day 83	18	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Temperature

End point title	Vital Signs: Temperature

End point description:

Temperature was measured in semi-supine position after 5 minutes rest for the participants at indicated time points. SAF analysis set included all subjects who were administered any dose of any study intervention. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Degree Celsius				
number (not applicable)				
Subject 1: Day 1	0	35.7		
Subject 1: Day 83	0	36.4		
Subject 1: Day 125	0	36.9		
Subject 1: Day 155	0	36.4		
Subject 2: Day 1	36.9	0		
Subject 2: Day 83	36.7	0		
Subject 2: Day 125	36.9	0		
Subject 2: Day 155	36.8	0		
Subject 3: Day 1	36.5	0		
Subject 3: Day 83	37.0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Weight

End point title	Vital Signs: Weight

End point description:

SAF analysis set included all subjects who were administered any dose of any study intervention. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527-0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: kilogram (kg)				
number (not applicable)				
Subject 1: Day 1	0	75.7		
Subject 1: Day 83	0	74.9		
Subject 1: Day 125	0	77.3		
Subject 1: Day 155	0	77.2		
Subject 2: Day 1	89.0	0		
Subject 2: Day 83	89.0	0		
Subject 2: Day 125	92.2	0		
Subject 2: Day 155	92.1	0		
Subject 3: Day 1	40.8	0		
Subject 3: Day 83	40.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Abnormal Lab Values

End point title	Number of Subjects with Abnormal Lab Values

End point description:

The total number of subjects with laboratory test abnormalities was assessed. Clinical laboratory tests included hematology, coagulation, biochemistry and urinalysis. SAF analysis set included all subjects who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects with Clinically Significant Electrocardiogram (ECG) Abnormalities

End point description:

ECG parameters included heart rhythm, heart rate, QRS intervals, QT intervals, RR intervals and corrected QT (QTc) intervals. Clinical meaningful was determined by the investigator. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) A Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) A Level

End point description:

SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527-0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 1	0	2.09		
Subject 1: Day 83	0	2.64		
Subject 1: Day 125	0	2.64		
Subject 1: Day 155	0	2.78		
Subject 2: Day 1	1.64	0		
Subject 2: Day 83	1.85	0		
Subject 2: Day 125	2.2	0		
Subject 2: Day 155	2.15	0		
Subject 3: Day 1	2.09	0		
Subject 3: Day 125	1.84	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) E Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) E Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) E was reported. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: International unit per milliliter(IU/mL)				
number (not applicable)				
Subject 1: Day 1	0	61		

Subject 1: Day 83	0	108		
Subject 1: Day 125	0	55.2		
Subject 1: Day 155	0	71.9		
Subject 2: Day 1	10.7	0		
Subject 2: Day 83	12.3	0		
Subject 2: Day 125	14.9	0		
Subject 2: Day 155	11.4	0		
Subject 3: Day 1	27.6	0		
Subject 3: Day 125	23.5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) G Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) G Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) G was reported. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 1	0	16.49		
Subject 1: Day 83	0	21.77		
Subject 1: Day 125	0	19.34		
Subject 1: Day 155	0	19.62		
Subject 2: Day 1	9.46	0		
Subject 2: Day 83	10.26	0		
Subject 2: Day 125	11.23	0		
Subject 2: Day 155	11.18	0		
Subject 3: Day 1	12.52	0		
Subject 3: Day 125	11.41	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) M Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) M Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) M was reported. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 1	0	0.97		
Subject 1: Day 83	0	1.47		
Subject 1: Day 125	0	1.35		
Subject 1: Day 155	0	1.43		
Subject 2: Day 1	1.08	0		
Subject 2: Day 83	0.84	0		
Subject 2: Day 125	0.78	0		
Subject 2: Day 155	1	0		
Subject 3: Day 1	2.22	0		
Subject 3: Day 125	1.91	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) A Level

End point title	Change From Baseline in Immunoglobulin (Ig) A Level

End point description:

Change from baseline in immunoglobulin (Ig) A level was reported. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 83	0	0.55		
Subject 1: Day 125	0	0.55		
Subject 1: Day 155	0	0.69		
Subject 2: Day 83	0.21	0		
Subject 2: Day 125	0.56	0		
Subject 2: Subject 155	0.51	0		
Subject 3: Day 125	-0.25	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) E Level

End point title	Change From Baseline in Immunoglobulin (Ig) E Level

End point description:

Change from baseline in immunoglobulin (Ig) E level was reported. SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: International unit per milliliter(IU/mL)				
number (not applicable)				
Subject 1: Day 83	0	47		
Subject 1: Day 125	0	-5.8		

Subject 1: Day 155	0	10.9		
Subject 2: Day 83	1.6	0		
Subject 2: Day 125	4.2	0		
Subject 2: Day 155	0.7	0		
Subject 3: Day 125	-4.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) G Level

End point title	Change From Baseline in Immunoglobulin (Ig) G Level

End point description:

SAF analysis set included all participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527-0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 83	0	5.28		
Subject 1: Day 125	0	2.85		
Subject 1: Day 155	0	3.13		
Subject 2: Day 83	0.8	0		
Subject 2: Day 125	1.77	0		
Subject 2: Day 155	1.72	0		
Subject 3: Day 125	-1.11	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) M Level

End point title	Change From Baseline in Immunoglobulin (Ig) M Level

End point description:

Change from baseline in immunoglobulin (Ig) M level was reported. SAF analysis set included all

participants who were administered any dose of any study intervention. No summary analysis was done. Following analysis of OLE data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early. Therefore, participant wise data reported and number analyzed= specific participant evaluated in respective arm at specified timepoint.

End point type	Secondary

End point timeframe:

At Day 1, 83, 125 and 155

End point values	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: grams per liter (g/L)				
number (not applicable)				
Subject 1: Day 83	0	0.5		
Subject 1: Day 125	0	0.38		
Subject 1: Day 155	0	0.46		
Subject 2: Day 83	-0.24	0		
Subject 2: Day 125	-0.3	0		
Subject 2: Day 155	-0.08	0		
Subject 3: Day 125	-0.31	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 108	
Adverse event reporting additional description:	
SAF analysis set included all subjects who were administered any dose of any study intervention.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Evobrutinib + Avonex® matched Placebo
Reporting group description:	
Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.	
Reporting group title	Avonex® + Evobrutinib matched Placebo
Reporting group description:	
Subjects received IM injection of active Avonex® once a week along with concomitant placebo matched to evobrutinib BID. Treatment period was planned to be of 96 weeks.	

Serious adverse events	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Evobrutinib + Avonex® matched Placebo	Avonex® + Evobrutinib matched Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 1 (100.00%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Nervous system disorders			

Tension headache			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Drug eruption			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Tinea cruris			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2019	-Restructured text on discontinuation of Study Intervention -Clarified the statistical approach towards primary and secondary endpoints -Adjusted Exclusion Criteria -Clarified the use of concomitant therapy

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.

Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0073. Consequently, this trial terminated early.

Notes: