



## 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           | 2018-004700-19 |
| Trial protocol           | BG             |
| Global end of trial date | 20 May 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_0074 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04032171 |
| 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                       | 20 May 2020 |
| Is this the analysis of the primary completion data? | No          |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 20 May 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 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                          | 10 September 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: 1 |
| Worldwide total number of subjects   | 1                |
| 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)                      | 1 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 950 subjects were planned to be included however, only 1 subject was enrolled in Evobrutinib + Avonex® matched Placebo and no subject was enrolled in Avonex® + Evobrutinib matched Placebo (no results reported in the draft) due to early termination of study.

### Pre-assignment

Screening details:

Study was conducted in 2 periods; double blind period and open label extension (OLE) period. However, due to early termination of study, sponsor decided not to conduct the OLE period. Total of 950 subjects were planned to be included in 1:1 to treatment with evobrutinib or Avonex, however only 1 subject was enrolled in evobrutinib.

### 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                | Investigator, Carer, Assessor, Subject |

### Arms

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | 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 | 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.

|                                        |                         |
|----------------------------------------|-------------------------|
| 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.

| Number of subjects in period 1 | Evobrutinib + Avonex® matched Placebo |
|--------------------------------|---------------------------------------|
| Started                        | 1                                     |
| Completed                      | 0                                     |
| Not completed                  | 1                                     |
| Study Termination              | 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 values                    | Evobrutinib + Avonex® matched Placebo | Total |  |
|-------------------------------------------|---------------------------------------|-------|--|
| Number of subjects                        | 1                                     | 1     |  |
| Age Categorical                           |                                       |       |  |
| Units: Subjects                           |                                       |       |  |
| <=18 years                                | 0                                     | 0     |  |
| Between 18 and 65 years                   | 1                                     | 1     |  |
| >=65 years                                | 0                                     | 0     |  |
| Sex: Female, Male                         |                                       |       |  |
| Units: Subjects                           |                                       |       |  |
| Female                                    | 0                                     | 0     |  |
| Male                                      | 1                                     | 1     |  |
| Race (NIH/OMB)                            |                                       |       |  |
| Units: Subjects                           |                                       |       |  |
| American Indian or Alaska Native          | 0                                     | 0     |  |
| Asian                                     | 0                                     | 0     |  |
| Native Hawaiian or Other Pacific Islander | 0                                     | 0     |  |
| Black or African American                 | 0                                     | 0     |  |
| White                                     | 1                                     | 1     |  |
| More than one race                        | 0                                     | 0     |  |
| Unknown or Not Reported                   | 0                                     | 0     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                       |                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Reporting group title                                                                                                                                                                                                                 | Evobrutinib + Avonex® matched Placebo |
| Reporting group description:<br>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. |                                       |

### Primary: Annualized Relapse Rate (ARR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Annualized Relapse Rate (ARR) <sup>[1]</sup> |
| End point description:<br>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 MS200527-0074. 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:<br>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 |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup>                      |  |  |  |
| Units: per year                      |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[2] - 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:<br>EDSS is an ordinal scale in half-point increments that measures disability in participants 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 MS200527-0074. 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 |           |

|                                  |                                       |  |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>          | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type               | Reporting group                       |  |  |  |
| Number of subjects analysed      | 0 <sup>[3]</sup>                      |  |  |  |
| Units: Weeks                     |                                       |  |  |  |
| median (confidence interval 95%) | ( to )                                |  |  |  |

Notes:

[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 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 participants 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 MS200527-0074. 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 |           |

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[4]</sup>                      |  |  |  |
| Units: Months                        |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[4] - 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:

PROMIS Physical function outcome measure assesses various aspects related to a subject's participation in physical activity. The PROMIS measure has 10 items that parents rate on a 5-point likert scale, where 5 indicates "Without any difficulty" and 1 indicates "Unable to do". Responses were summed and converted to standardized T-Scores where higher scores indicates higher PF. 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 MS200527-0074. 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

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[5]</sup>                      |  |  |  |
| Units: T-Score                       |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[5] - 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) Fatigue Short Form Score at Week 96

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

End point description:

The PROMIS Fatigue item bank includes 95 items assessing the experience (frequency, duration, and intensity) as well as the impacts of fatigue on physical, mental and social activities. An 8-item short-form specific to MS was used each measured on a 5-point Likert scale with question (example: How often did you feel tired?) where, 1=never, 2=rarely, 3=sometimes, 4=often, 5=always. Measures from



the fatigue item bank were scored on a T-score metric where, higher scores indicates higher fatigue. 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 MS200527-0074. 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    |           |

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[6]</sup>                      |  |  |  |
| Units: T-Score                       |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[6] - 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 MS200527-0074. 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 |           |

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[7]</sup>                      |  |  |  |
| Units: Lesions                       |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[7] - 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 MS200527-0074. 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

|                                      |                                       |  |  |  |
|--------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>              | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                   | Reporting group                       |  |  |  |
| Number of subjects analysed          | 0 <sup>[8]</sup>                      |  |  |  |
| Units: Lesions                       |                                       |  |  |  |
| arithmetic mean (standard deviation) | ( )                                   |  |  |  |

Notes:

[8] - 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, Serious TEAEs and Adverse Events of Special Interest (AESIs)

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

End point description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an 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 investigational medicinal product (IMP), or resulted in death, discontinuation, interruption or reduction of study therapy. TEAEs included both serious and non-serious TEAEs. AESIs included liver AEs (possible drug-induced, non-infectious, non-alcoholic and immune-mediated)

infections (serious and opportunistic infections), lipase and amylase elevation, and seizure. 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 |           |

|                             |                                       |  |  |  |
|-----------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>     | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type          | Reporting group                       |  |  |  |
| Number of subjects analysed | 1                                     |  |  |  |
| Units: Subjects             |                                       |  |  |  |
| Subjects With AESIs         | 0                                     |  |  |  |
| Subjects with TEAEs         | 1                                     |  |  |  |
| Subjects with Serious TEAEs | 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:

Adverse event (AE) was defined as any untoward medical occurrence in a subject, which does not necessarily have causal relationship with treatment. Serious AE was defined as an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in subject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs included both serious TEAEs and non-serious TEAEs. 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 subject with TEAEs based on severity were reported. Safety analysis set (SAF) 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 +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|-----------------------------|------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                |  |  |  |
| Number of subjects analysed | 1                                              |  |  |  |
| Units: Subjects             |                                                |  |  |  |
| Grade 1                     | 1                                              |  |  |  |
| Grade 2                     | 0                                              |  |  |  |
| Grade 3                     | 0                                              |  |  |  |
| Grade 4                     | 0                                              |  |  |  |
| Grade 5                     | 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 participants at indicated time points. 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 +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|--------------------------------------|------------------------------------------------|--|--|--|
| Subject group type                   | Reporting group                                |  |  |  |
| Number of subjects analysed          | 1                                              |  |  |  |
| Units: Millimeters of mercury (mmHg) |                                                |  |  |  |
| number (not applicable)              |                                                |  |  |  |
| DBP: Day 1 (n=1, 0)                  | 72                                             |  |  |  |
| DBP: Week 2 unscheduled 1 (n=1, 0)   | 68                                             |  |  |  |
| DBP: Week 12 (n=1, 0)                | 76                                             |  |  |  |
| DBP: Week 96/ED (n=1, 0)             | 84                                             |  |  |  |
| SBP: Day 1(n=1, 0)                   | 124                                            |  |  |  |
| SBP: Week 2 unscheduled 1 (n=1, 0)   | 119                                            |  |  |  |
| SBP: Week 12 (n=1, 0)                | 130                                            |  |  |  |
| SBP: Week 96/ED (n=1, 0)             | 140                                            |  |  |  |

## 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 participants at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention.

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

End point timeframe:

At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation)

| End point values                                | Evobrutinib +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|-------------------------------------------------|------------------------------------------------|--|--|--|
| Subject group type                              | Reporting group                                |  |  |  |
| Number of subjects analysed                     | 1                                              |  |  |  |
| Units: breaths/minute                           |                                                |  |  |  |
| number (not applicable)                         |                                                |  |  |  |
| Pulse rate: Day 1 (n=1, 0)                      | 71                                             |  |  |  |
| Pulse rate: Week 2 unscheduled 1 (n=1, 0)       | 77                                             |  |  |  |
| Pulse rate: Week 12 (n=1, 0)                    | 75                                             |  |  |  |
| Pulse rate: Week 96/ED (n=1, 0)                 | 80                                             |  |  |  |
| Respiratory rate: Day 1 (n=1, 0)                | 12                                             |  |  |  |
| Respiratory rate: Week 2 unscheduled 1 (n=1, 0) | 18                                             |  |  |  |
| Respiratory rate: Week 12 (n=1, 0)              | 12                                             |  |  |  |
| Respiratory rate: Week 96/ED (n=1, 0)           | 14                                             |  |  |  |

## 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 participants who were administered any dose of any study intervention.

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

End point timeframe:

At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation)

| End point values              | Evobrutinib + Avonex® matched Placebo |  |  |  |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type            | Reporting group                       |  |  |  |
| Number of subjects analysed   | 1                                     |  |  |  |
| Units: Degree Celsius         |                                       |  |  |  |
| number (not applicable)       |                                       |  |  |  |
| Day 1 (n=1, 0)                | 36.4                                  |  |  |  |
| Week 2 unscheduled 1 (n=1, 0) | 36.7                                  |  |  |  |
| Week 12 (n=1, 0)              | 36.9                                  |  |  |  |
| Week 96/ED (n=1, 0)           | 36.7                                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Vital Signs: Weight

|                                                                                                                                |                     |
|--------------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                                                | Vital Signs: Weight |
| End point description:<br>SAF analysis set included all participants who were administered any dose of any study intervention. |                     |
| End point type                                                                                                                 | Secondary           |
| End point timeframe:<br>At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation).                        |                     |

| End point values              | Evobrutinib + Avonex® matched Placebo |  |  |  |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type            | Reporting group                       |  |  |  |
| Number of subjects analysed   | 1                                     |  |  |  |
| Units: kilogram (kg)          |                                       |  |  |  |
| number (not applicable)       |                                       |  |  |  |
| Day 1 (n=1, 0)                | 91.4                                  |  |  |  |
| Week 2 unscheduled 1 (n=1, 0) | 92.3                                  |  |  |  |
| Week 12 (n=1, 0)              | 92.6                                  |  |  |  |
| Week 96/ED (n=1, 0)           | 95.5                                  |  |  |  |

### 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 laboratory parameters included hematology, coagulation, biochemistry and urinalysis. Clinical meaningful was determined by the investigator. Number of subjects with any clinically meaningful change from baseline in laboratory parameters were reported. SAF included all subjects who were administered any dose of any study intervention.

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

End point timeframe:

Baseline up to weeks 108

|                             |                                       |  |  |  |
|-----------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>     | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type          | Reporting group                       |  |  |  |
| Number of subjects analysed | 1                                     |  |  |  |
| Units: Subjects             | 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. Number of subjects with clinically meaningful change from baseline in 12-lead ECG were reported. SAF included all subjects who were administered any dose of any study intervention.

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

End point timeframe:

Baseline up to week 108

|                             |                                       |  |  |  |
|-----------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>     | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type          | Reporting group                       |  |  |  |
| Number of subjects analysed | 1                                     |  |  |  |
| Units: Subjects             | 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:

Absolute concentrations of Immunoglobulin (Ig) A was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

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

End point timeframe:

At Day 1 and Day 92

| End point values            | Evobrutinib +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|-----------------------------|------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                |  |  |  |
| Number of subjects analysed | 1                                              |  |  |  |
| Units: gram per liter (g/L) |                                                |  |  |  |
| number (not applicable)     |                                                |  |  |  |
| Day 1 (n=1, 0)              | 0.8                                            |  |  |  |
| Day 92 (n=1, 0)             | 0.92                                           |  |  |  |

## 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) E was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

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

End point timeframe:

At Day 1 and Day 92

| End point values             | Evobrutinib +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|------------------------------|------------------------------------------------|--|--|--|
| Subject group type           | Reporting group                                |  |  |  |
| Number of subjects analysed  | 1                                              |  |  |  |
| Units: grams per liter (g/L) |                                                |  |  |  |
| number (not applicable)      |                                                |  |  |  |
| Day 1 (n=1, 0)               | 5.54                                           |  |  |  |



|                 |      |  |  |  |
|-----------------|------|--|--|--|
| Day 92 (n=1, 0) | 6.11 |  |  |  |
|-----------------|------|--|--|--|

## 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:<br>Absolute concentrations of Immunoglobulin (Ig) M was reported. SAF analysis set included all participants who were administered any dose of any study intervention. |                                                        |
| End point type                                                                                                                                                                                | Secondary                                              |
| End point timeframe:<br>At Day 1 and Day 92                                                                                                                                                   |                                                        |

| End point values             | Evobrutinib +<br>Avonex®<br>matched<br>Placebo |  |  |  |
|------------------------------|------------------------------------------------|--|--|--|
| Subject group type           | Reporting group                                |  |  |  |
| Number of subjects analysed  | 1                                              |  |  |  |
| Units: grams per liter (g/L) |                                                |  |  |  |
| number (not applicable)      |                                                |  |  |  |
| Day 1 (n=1, 0)               | 0.29                                           |  |  |  |
| Day 92 (n=1, 0)              | 0.25                                           |  |  |  |

## 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:<br>Absolute concentration of IGE level was reported. SAF analysis set included all participants who were administered any dose of any study intervention. |                                                        |
| End point type                                                                                                                                                                   | Secondary                                              |
| End point timeframe:<br>At Day 1 and Day 92                                                                                                                                      |                                                        |

|                                           |                                       |  |  |  |
|-------------------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>                   | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type                        | Reporting group                       |  |  |  |
| Number of subjects analysed               | 1                                     |  |  |  |
| Units: International units per milliliter |                                       |  |  |  |
| number (not applicable)                   |                                       |  |  |  |
| Day 1 (n=1, 0)                            | 14.1                                  |  |  |  |
| Day 92 (n=1, 0)                           | 16.7                                  |  |  |  |

## 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:<br>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. |                                                     |
| End point type                                                                                                                                                                                   | Secondary                                           |
| End point timeframe:<br>At Day 1 and Day 92                                                                                                                                                      |                                                     |

|                             |                                       |  |  |  |
|-----------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>     | Evobrutinib + Avonex® matched Placebo |  |  |  |
| Subject group type          | Reporting group                       |  |  |  |
| Number of subjects analysed | 1 <sup>[9]</sup>                      |  |  |  |
| Units: gram per liter (g/L) |                                       |  |  |  |
| number (not applicable)     | 1                                     |  |  |  |

Notes:

[9] - 0.12

## 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:<br>SAF analysis set included all participants who were administered any dose of any study intervention. |                                                      |
| End point type                                                                                                                 | Secondary                                            |
| End point timeframe:<br>At Day 1 and Day 92                                                                                    |                                                      |

| End point values                          | Evobrutinib + Avonex® matched Placebo |  |  |  |
|-------------------------------------------|---------------------------------------|--|--|--|
| Subject group type                        | Reporting group                       |  |  |  |
| Number of subjects analysed               | 1 <sup>[10]</sup>                     |  |  |  |
| Units: International units per milliliter |                                       |  |  |  |
| number (not applicable)                   | 1                                     |  |  |  |

Notes:

[10] - 2.6

## 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:<br>Change from baseline in immunoglobulin (Ig) G level was reported. SAF analysis set included all participants who were administered any dose of any study intervention. |                                                     |
| End point type                                                                                                                                                                                   | Secondary                                           |
| End point timeframe:<br>At Day 1 and Day 92                                                                                                                                                      |                                                     |

| End point values             | Evobrutinib + Avonex® matched Placebo |  |  |  |
|------------------------------|---------------------------------------|--|--|--|
| Subject group type           | Reporting group                       |  |  |  |
| Number of subjects analysed  | 1 <sup>[11]</sup>                     |  |  |  |
| Units: grams per liter (g/L) |                                       |  |  |  |
| number (not applicable)      | 1                                     |  |  |  |

Notes:

[11] - 0.57

## 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:<br>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. |                                                     |
| End point type                                                                                                                                                                                   | Secondary                                           |

---

End point timeframe:  
At Day 1 and Day 92

---

|                              |                                                |  |  |  |
|------------------------------|------------------------------------------------|--|--|--|
| <b>End point values</b>      | Evobrutinib +<br>Avonex®<br>matched<br>Placebo |  |  |  |
| Subject group type           | Reporting group                                |  |  |  |
| Number of subjects analysed  | 1 <sup>[12]</sup>                              |  |  |  |
| Units: grams per liter (g/L) |                                                |  |  |  |
| number (not applicable)      | 1                                              |  |  |  |

Notes:

[12] - -0.04

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 108 Weeks

|                 |                |
|-----------------|----------------|
| 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.

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

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

| Non-serious adverse events                               | Evobrutinib +<br>Avonex® matched<br>Placebo |  |  |
|----------------------------------------------------------|---------------------------------------------|--|--|
| Total subjects affected by non-serious<br>adverse events |                                             |  |  |
| subjects affected / exposed                              | 1 / 1 (100.00%)                             |  |  |
| Nervous system disorders                                 |                                             |  |  |
| Peripheral edema                                         |                                             |  |  |
| subjects affected / exposed                              | 1 / 1 (100.00%)                             |  |  |
| occurrences (all)                                        | 1                                           |  |  |
| Eye disorders                                            |                                             |  |  |
| Dry eye                                                  |                                             |  |  |
| subjects affected / exposed                              | 1 / 1 (100.00%)                             |  |  |
| occurrences (all)                                        | 1                                           |  |  |
| Hepatobiliary disorders                                  |                                             |  |  |

|                                                                          |                      |  |  |
|--------------------------------------------------------------------------|----------------------|--|--|
| Hypercholesterolemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 1 (100.00%)<br>1 |  |  |
|--------------------------------------------------------------------------|----------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05 September 2019 | <ul style="list-style-type: none"><li>- Restructured text on discontinuation of Study Intervention</li><li>- Clarified role of Sponsor's Medical Monitor</li><li>- Clarified statistical approach towards primary and secondary endpoints</li><li>- Adjusted Exclusion Criteria</li><li>- Clarified use of concomitant therapy</li></ul> |

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 MS200527-0074. Consequently, this trial terminated early.

Notes: